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Review

Druggable Metabolic Vulnerabilities Are Exposed and Masked during Progression to Castration Resistant Prostate Cancer

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Abstract: There is an urgent need for exploring new actionable targets other than androgen receptor to improve outcome from lethal castration-resistant prostate cancer. Tumor metabolism has reemerged as a hallmark of cancer that drives and supports oncogenesis. In this regard, it is important to understand the relationship between distinctive metabolic features, androgen receptor signaling, genetic drivers in prostate cancer, and the tumor microenvironment (symbiotic and competitive metabolic interactions) to identify metabolic vulnerabilities. We explore the links between metabolism and gene regulation, and thus the unique metabolic signatures that define the malignant phenotypes at given stages of prostate tumor progression. We also provide an overview of current metabolism-based pharmacological strategies to be developed or repurposed for metabolism-based therapeutics for castration-resistant prostate cancer.

Keywords: androgen receptor; cancer metabolism; prostate cancer; Warburg's effect; lactate; fatty acids; drug resistance

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1. Introduction

Prostate cancer (PCa) is the second most common cancer and the second leading cause of cancer death in American men. In 2022, 268,490 new cases will be diagnosed, and there will be an associated 34,500 deaths [1]. The major challenge in PCa therapy is to improve the outcome from lethal castration-resistant prostate cancer (CRPC), which almost inevitably emerges following anti-androgen therapy of advanced PCa [2–5]. Progression to CRPC and resistance to androgen receptor (AR) targeting therapies such as androgen synthesis inhibitors (abiraterone) and AR-ligand inhibitors (enzalutamide, apalutamide, and darolutamide) is often associated with persistent AR signaling due to multiple mechanisms such as increased AR copy number, activating point mutations, and constitutively active splice variants (AR-Vs) [3,5–8]. Tumor plasticity driven by continual stepwise targeting of AR has garnered recent attention and may lead to AR negative cells driven by fibroblast growth factor (FGF) or neuroendocrine transdifferentiation mechanisms [9–12]. The AR domains outside of the ligand-binding domain are attractive sties for pharmacological interference [12–16]. However, the compound EPI-7386 targeting the AR-N-terminal transactivation domain is still in Phase 1 trial, and degrading agents proteolysis targeting

chimeras (PROTACs) against AR-Vs are still in preclinical development [17–20]. Much effort has been made to therapeutically target PCa-specific cell surface receptors such as prostate-specific membrane antigen (PSMA) [21–24], DNA damage and repair (DDR) pathways [25,26], and bone metastasis niches [27,28]. However, results from clinical trials indicate that these treatments continue to have issues including but not limited to the targeting of specific patient populations and resistance mechanisms, and tumor heterogeneity [29,30].

One hundred years have passed since Otto Warburg's pioneering work to report aerobic glycolysis in tumors [31–33]. Nevertheless, antiglycolytic agents such as 2-deoxyglucose (2-DG) had never been clinically translated [34,35]. On the other hand, Sidney Farber successfully introduced antifolic agents in 1948 [36], which became the basis for many of the most widely used chemotherapies [37]. Early studies focused on exploiting cancer metabolism proved to be an effective strategy for some cancers. However, serial discoveries of genetic drivers such as tumor suppressors and oncogenes moved the focus of therapeutic strategies away from metabolism, which was often thought to be a mere passenger event [35,38–40]. The situation drastically changed when the link between oncogenic drivers and metabolic reprogramming began to be appreciated in the early 2000s [39–43]. Altered metabolism not only supports and maintains tumor phenotypes by meeting their energetic and metabolic demands, it also allows for further progression to metastases [44,45]. Metabolic reprogramming is now firmly established as a hallmark of cancer and is attractive because it represents unique vulnerabilities that can be therapeutically targeted [39,41]. Indeed, promising and innovative therapeutic strategies are emerging owing to the resurgent appreciation of cancer metabolism [35,46]. Their antitumor effects may simply reflect the promotion of energy consumption and subsequent starvation-induced cell death, or, more ideally, be related to active tumoricidal activities [42].

There is an urgent need for exploring new actionable targets other than AR to improve outcome from lethal CRPC [47–49]. In this regard, it is important to understand the relationship between distinctive metabolic features, AR signaling, genetic drivers in PCa, and the tumor microenvironment (TME) to identify metabolic vulnerabilities [50–54]. A one-size-fits-all approach has not been successful in anti-CRPC therapy [5,8,48]. Therefore, in this article, we will discuss whether therapeutic targeting of tumor metabolism can arise as precision medicine to give patients a "tailor-made" therapy based on their metabolic phenotypes [55]. To this end, we will provide an overview of the current knowledge of cell autonomous metabolic alterations and metabolic interactions in the TME during tumor initiation and progression, and introduce potential therapeutic targets that emerge from unique metabolic perspectives in PCa.

2. Metabolic Reprogramming during Progression to CRPC

2.1. Zinc-Driven Metabolism

In benign prostate epithelial cells, the zinc transporter ZIP1 facilitates the intracellular accumulation of zinc ions. This leads to the inhibition of m-aconitase (ACO2) in mitochondria and truncates the tricarboxylic acid (TCA) cycle to accumulate and release citrate into the prostatic fluid [56,57]. Androgen signaling is critical in supporting continuous citrate production. Because of the increase in zinc, the citrate synthase substrate oxaloacetate (OAA) is not derived from the TCA cycle but is generated by the action of mitochondrial aspartate aminotransferase (GOT2) on aspartate, which in turn is imported into the cells through the excitatory amino acid transporter EAAC1 (SLC1A1) [58,59]. Another substrate in mitochondria, acetyl-CoA, is supplied in association with an increased expression of pyruvate dehydrogenase E1 component subunit alpha (PDHE1α) [60]. Depletion of ZIP1 represents an essential early event in the development of PCa malignancy, whereby lower intracellular zinc levels relieve ACO2 to establish a complete TCA cycle [61] (Figure 1). Contrary to other types of cancer cells, malignant transformation in PCa involves the conversion from "aerobic glycolytic" benign cells to "oxidative" cancerous cells [50,51,62]. These bioen-

ergetic alterations are reflected by the general low avidity of ^{18}F-fluorodeoxyglucose (FDG) in primary PCa [50,51,62–64].

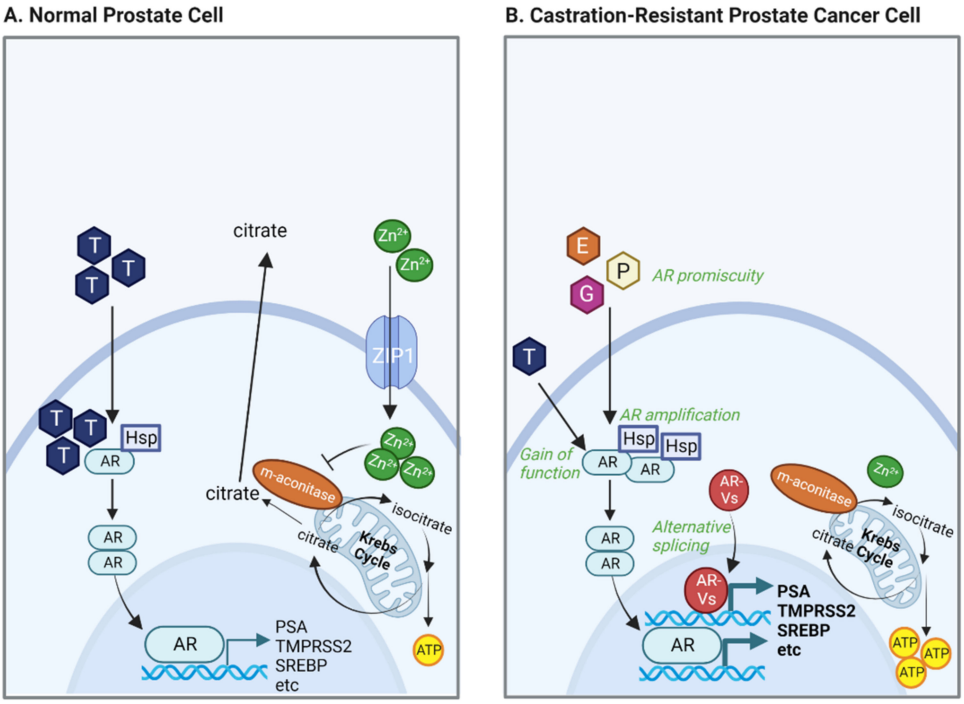

Figure 1. Metabolic reprogramming involved in PCa progression to CRPC. Alterations in Zinc-driven metabolism and AR pathway are observed as prostate cancer progresses to CRPC. Mechanisms of androgen resistance include AR promiscuity, amplification, gain of function and alternative splicing (Created with BioRender.com). T—testosterone; E—estrogen; P—progesterone; G—glucocorticoids.

2.2. AR Alterations

Localized PCa is treated primarily by radical prostatectomy or radiotherapy, while recurrent disease requires androgen deprivation therapy (ADT). PCa progression towards late-stage disease is primarily driven by alterations in the AR signaling pathway (Figure 1), but tumors will inevitably bypass androgen dependence and develop resistance to ADT. Metastatic CRPC (mCRPC) was shown to have multiple genomic alterations related to the AR, including gene amplification and mutations [65,66]. The first leads to increased levels of AR expression [67], while mutated AR can show gain-of-function and enhanced activity [65]. Certain AR mutations can also affect receptor specificity, allowing other steroid hormones such as estrogen, progesterone and glucocorticoids to bind to AR and induce transcription of its target genes [68]. Proteins that interact with AR, such as chromatin remodelers and cofactors, also present genomic aberrations [69], confirming the pivotal role of the AR pathway in prostate carcinogenesis. Alternative RNA splicing is also observed, which gives rise to constitutively active AR-variants (AR-V) [70], of which AR-V7 is considered the most critical driver of resistance to ADT [71].

Second-generation AR antagonists such as enzalutamide [72] and apalutamide [73] can impair ligand-dependent AR-mediated transcription and helped improve survival of mCRPC patients [74,75]; ultimately, however, patients will progress to lethal disease. Neuroendocrine prostate cancer (NEPC) is mainly characterized by the lack of expression of both AR and AR downstream targets, and by the expression of neuroendocrine differentiation markers. It can develop de novo or, more prevalently, can be induced by AR-mediated therapy as treatment-emergent NEPC (t-NEPC) [76,77]. Molecularly, these types of PCa are marked by *TP53* and *RB1* loss, and by *AURKA* and *MYCN* amplification [78]. The emergence of tumors that lack both AR and neuroendocrine markers, known as double-negative PCa (DNPC) [11], is also related to anti-AR therapies. Regardless of the mechanism by

which cells can achieve androgen independence, they represent a therapeutic hurdle that requires alternative strategies to improve patient survival. Platinum-based chemotherapy is commonly used for these patients, and several clinical trials have investigated the efficacy of combination therapies, such as docetaxel and cisplatin [79], and etoposide and carboplatin [80]; however, these studies report unfavorable toxicity profiles. Other studies have shown promising data when targeting alternative signaling pathways in advanced, androgen-indifferent settings: FGF/mitogen-activated protein kinase (MAPK) blockade was shown to be effective in impairing tumor growth in preclinical models of DNPC [11]. Delta-like protein 3 (DLL3)-directed therapy showed promising results in NE-like patient-derived xenograft (PDX) models [81]. Inhibition of both Aurora kinase A (AURKA) and poly (ADP-ribose) polymerase (PARP) in preclinical models of DDR-defective NEPC was also able to suppress tumor growth [82].

A better understanding of the cell biology in advanced PCa settings can help the development of newer and directed therapies; particularly, metabolic adaptations during PCa progression can be exploited. Hanahan and Weinberg defined the hallmarks of cancer as acquired cellular alterations that can sustain growth and allow cells to proliferate [38,39]. Six physiologic changes that are fundamental for tumorigenesis were initially established: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis. Recently, the concept has been expanded to eight hallmarks that include: sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction [41]. The inclusion of metabolic reprograming as a core hallmark of cancer reflects the abundant literature in the field that has shown the key role of metabolic adaptations in tumor growth. AR is known to play a role in tumor cell metabolic reprogramming during PCa progression. For example, metabolic signatures associated with AR-V7 have shown a decrease in citrate levels with a concomitant increase in glycolysis and dependence on the reductive carboxylation of glutamine [83]. Sterol response element-binding proteins (SREBPs), the transcription factors controlling the expression of lipid metabolism genes, are also androgen regulated [84]. Up-regulation of SREBPs and lipogenic genes contributes to CRPC progression [85]. Fatty acid synthase (FASN), the principal enzyme in de novo lipogenesis and an SREBP target gene, is overexpressed in CRPC [86,87]. In fact, PCa displays differential metabolic phenotypes depending on the stages of tumor progression [50,51]. Tumor imaging with positron emission tomography (PET) radiotracers helps determine what bioenergetic phenotype dominates in PCa tumors (glycolytic, lipogenic, or oxidative) [88,89]. Tumor uptake of ^{11}C-acetate is indicative of a lipogenic phenotype, while high avidity to ^{18}F-FDG is supportive of a glycolytic gene signature in advanced adeno-PCa, NEPC and DNPC [90–96]. Mitochondrial membrane potential ($\Delta\Psi m$) drives uptake of the agent 4-[^{18}F]fluorobenzyl triphenylphosphonium (^{18}FBnTP), which reflects oxidative tumors [97]. Next, we will discuss the major metabolic alterations observed throughout PCa progression.

3. Major Bioenergetic Sources

Due to their highly proliferative behavior, tumor cells need to rewire their metabolism to sustain a higher energetic demand [42,46,98]. The major examples are the altered utilization of glucose and endogenous and exogenous fatty acids (FAs). In addition, several other nutrients such as glutamine, acetate, and fructose are used by cancer cells to fuel their growth.

3.1. Glucose Metabolism

The quintessential example of altered cancer metabolism involves the aberrant utilization of glucose for increased lactic acid production. As a phenomenon first observed a century ago by Otto Warburg [99–101], it is traditionally described as an overreliance on the

glycolysis pathway even in the presence of abundant oxygen (termed "aerobic glycolysis" or the "Warburg effect"). Rather than fully catabolizing glucose into carbon dioxide through glycolysis in conjunction with the TCA cycle and oxidative phosphorylation (OXPHOS), many cancer cells truncate this process at the end of glycolysis, diverting pyruvate towards lactic acid production instead. This is evidenced by the in vivo conversion of [1-^{13}C] pyruvate to [1-^{13}C] lactate based on hyperpolarized ^{13}C magnetic resonance spectroscopic imaging (MRSI) [102]. The accompanied increase in glucose consumption and lactic acid secretion is widely observed across multiple cancer types. More significantly, this metabolic reprogramming is commonly associated with poor prognosis and increased aggressiveness in an extensive spectrum of cancers, including breast, lung, prostate, kidney, head and neck, colorectal, and liver cancer, to name a few [103–107].

Altered glucose metabolism is unique in the PCa context because, as discussed above, normal prostate epithelium has a distinct baseline metabolic profile. Due to the tissue-specific truncation of the TCA cycle for citrate production, the metabolic alteration that signals prostate carcinogenesis is, paradoxically, a reversion to "normal" glucose metabolism (transition from energy inefficient glycolytic metabolism to energy efficient oxidative metabolism) [108]. Nevertheless, elevated glucose consumption and lactic acid secretion remains a relevant metabolic alteration as the disease progresses towards more treatment-resistant and aggressive phenotypes [50]. This is exemplified by the fact that, while FDG-PET is not a useful diagnostic tool for imagining early PCa, it regains utility for the assessment of metastatic nodules and for the more aggressive NEPC [93,95]. As such, altered glucose metabolism is an important characteristic associated with PCa development and progression, even if it is slightly more nuanced than traditionally conceived.

Since glucose remains a key energy source in PCa metabolism, whether as fuel for adenosine triphosphate (ATP) production or as a precursor for biomolecule synthesis, multiple components of its import and catabolism can be deregulated as PCa progresses towards more advanced stages (Figure 2). AR signaling governs PCa metabolism by regulating components in the glycolytic pathway (glucose transporter GLUT1, hexokinase HK1, HK2, and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase PFK2/PFKFB) and in pyruvate flux into mitochondria (PDH and mitochondrial pyruvate carrier MPC2). At the top of the glycolytic pathway is the cell's ability to import glucose from the external environment. Expression of glucose transporters can become elevated to facilitate increased glycolytic flux. For example, GLUT1 (SLC2A1) is the primary glucose transporter implicated in tumorigenic transformation and is frequently considered a general therapeutic target in many advanced cancers [109–111]. Various studies have demonstrated that GLUT1 expression is correlated with poor prognosis and adverse outcomes in PCa [90,112]. Functionally, increased expression of GLUT1 can promote a more aggressive and glycolytic phenotype in PCa, especially in response to increased AR signaling [50,113–115]. While GLUT1 remains the most-studied glucose transporter, other family members such as GLUT3 (SLC2A3) and GLUT4 (SLC2A4) may also play a role in facilitating increased glucose uptake in advanced, treatment-resistant PCa [114,116–118].

Many other components of the glucose metabolic pathway are tightly associated with increased glucose uptake and are often assessed together as part of an overall glycolytic profile [90,119–121]. The immediate next steps following glucose uptake are considered critical regulatory junctions that determine glucose commitment towards glycolysis. Unsurprisingly, increased expression and altered functionalities of the relevant enzymes have been reported in the PCa context. For example, both the hyperactivation and mitochondrial localization of HK2, which supports Warburg-type tumors, facilitate PCa tumorigenesis and aggressiveness. This is especially prominent in a phosphatase and tensin homologue (PTEN)-deficient context, which results in constitutive activation of phosphatidyl inositol 3-kinase (PI3K)/AKT signaling [122–124]. The fact that HK2 functions as a regulatory nexus and is a downstream target of PI3K/AKT signaling makes it an attractive therapeutic target for CRPC [125–127]. Another critical component of the glycolysis pathway, phosphofructokinase (PFK), is also upregulated during PCa progression. The rate-limiting

glycolytic enzyme PFK1 converts fructose-6-phosphate to fructose-1,6-bisphosphate (1,6-FBP), which is then converted to glyceraldehyde-3-phosphate and dihydroxyacetone-3-phosphate [128,129]. PFK1 is allosterically regulated by the negative regulator citrate and the positive regulator 2,6-fructose bisphosphate (2,6-FBP). 2,6-FBP is produced by the PFK2 family of enzymes, which control intracellular 2,6-FBP levels through their dual kinase and phosphatase activities [128,129]. Increases in PFK1 and PFK2/PFKFB2 can all contribute to higher rates of glucose utilization and greater cancer cell survival in advanced PCa [130,131]. Conversely, activation of PFKBP4 leads to PFK1 inhibition, which directs glucose 6-phosphate (G6P) from glycolysis to the pentose phosphate pathway (PPP) for generation of nicotinamide adenine dinucleotide phosphate (NADPH) and nucleotide precursors. Relatedly, other glycolytic enzymes in the ten-step pathway can also help maintain increased glycolytic flux, with increases in aldolase expression being one contributor to PCa proliferation [132].

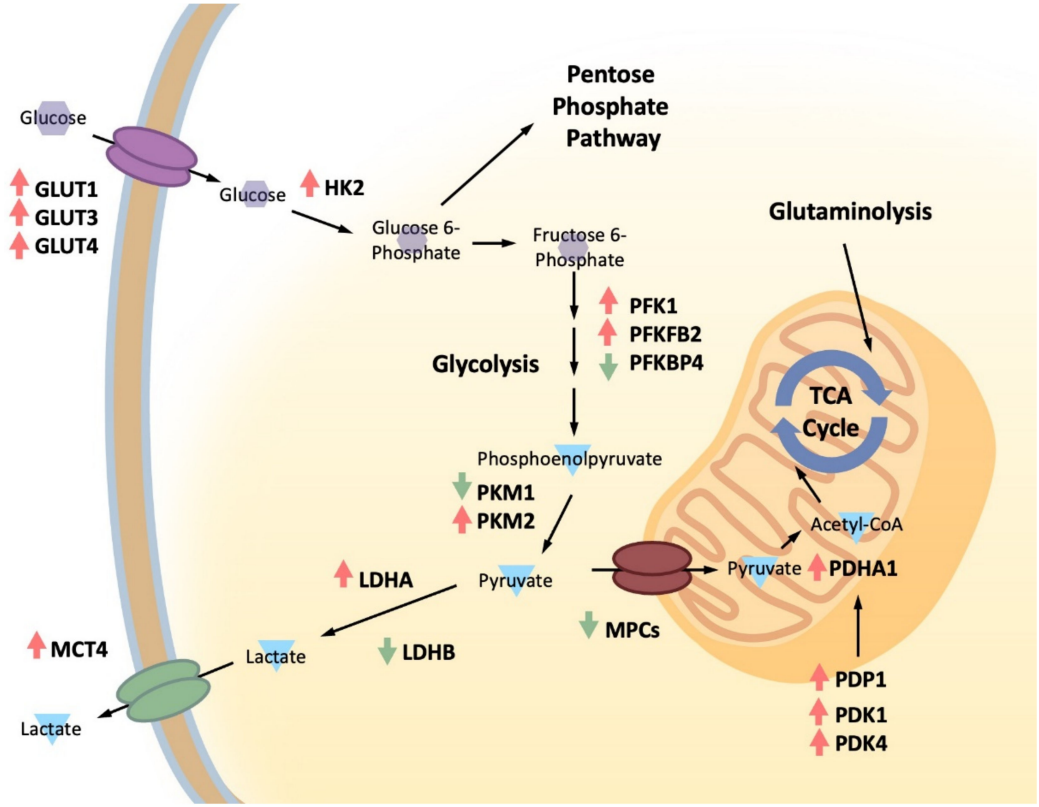

Figure 2. Altered glucose metabolism and the reported aberrations that help facilitate an increased glycolytic phenotype in aggressive PCa cells.

The end of the glycolysis pathway represents another major regulatory junction in glucose metabolism. Pyruvate is a central hub, integrating cellular energetics from different metabolic compartments. Many important enzymes regulate the final conversion of phosphoenolpyruvate into pyruvate and determine its ultimate trajectory either towards lactic acid production or into mitochondria for the TCA cycle. Pyruvate kinase is one such enzyme that plays a critical regulatory role in PCa progression, depending on the predominant isoform present in the cell. It has a liver and red blood cell isozyme (PKLR) and a muscle isozyme with two alternatively spliced forms, PKM1 and PKM2 [133]. PKM1 is a constitutively active tetrameric enzyme, while the allosteric binding of 1,6-FBP to PKM2 promotes its tetrameric formation from the less active dimer. An abundance of PKM1 suppresses PCa development by promoting more complete glucose catabolism, thereby limiting glucose entry into the PPP and reducing the production of nucleotides necessary for proliferation [134]. Alternatively, PKM2 functions as a more typical oncogene, and its

overexpression is implicated in multiple cancer types [135,136]. Metabolically, PKM2 has reduced enzymatic activity and slows down pyruvate production, allowing more upstream biomolecules to be available for other biosynthetic processes [137]. A recent report suggests that deoxyribonucleic acid (DNA)-dependent protein kinase (DNA-PK) may play a role in regulating increased glycolytic flux by phosphorylating aldolase and PKM2 to increase their enzymatic activities [138]. Interestingly, PKM2 also possess non-metabolic kinase activity and can function as a transcription factor, thereby promoting metastasis and regulating responses to hypoxia in PCa [139–143].

Glycolysis persists with pyruvate reduction to lactate in the cytosol. Alternatively, pyruvate flux into mitochondria is the first step of TCA-driven glucose oxidation and is mediated by MPC, which is a hetero-oligomer composed of MPC1 and MPC2 [144–146]. Changes to regulators that determine pyruvate's metabolic fate also contribute significantly to PCa progression. AR positively regulates MPC activity by increasing expression of MPC2 to support mitochondrial pyruvate oxidation in AR-driven PCa [147]. MPC inhibition resulted in activating transcription factor 4 (ATF4)-mediated activation of "integrated stress response" and delayed cell cycle progression [147]. Furthermore, it reduces AR-dependent PCa growth by decreasing the amount of pyruvate entering mitochondria, thereby restricting important TCA outputs such as acetyl-CoA for lipogenesis and other intermediates for OXPHOS [147]. Pharmacological inhibition of MPC also promotes metabolic alterations that rely on differential mitochondrial substrate utilizations, including using glutamine and branched chain amino acids for anaplerotic reactions to replenish TCA cycle intermediates and support OXPHOS [146,148,149]. Indeed, simultaneous inhibition of MPC and anaplerotic pathways exhibits drastic antitumor activities [148,149]. Intriguingly, reductions in MPC expression can increase PCa aggressiveness by promoting lineage reprogramming into AR-independent NEPC [150]. Moreover, MPC overexpression reverses NEPC differentiation and helps adeno-PCa regain sensitivity to enzalutamide [150]. Beyond MPCs, the metabolic switch between glycolysis and mitochondrial oxidation is facilitated by the pyruvate dehydrogenase complex, its inhibitory phosphorylation by associated kinases, and opposing phosphatases (i.e., pyruvate dehydrogenase kinases [PDKs] and pyruvate dehydrogenase phosphatase catalytic subunit 1 [PDP1]) [151]. They are implicated during PCa progression and play a critical role in modulating acetyl-CoA production [152–155]. Increased PDHA1 and PDP1 activities have been shown to enhance PDK activity, lipogenesis, and glutamine dependence in PCa [156,157]. Similarly, PDK1 can regulate PCa progression and local invasion [158,159], while increased expression of PDK4 is correlated with poor prognosis in PCa [160].

Lactate dehydrogenases (LDHs) catalyze pyruvate conversion into lactic acid with regeneration of nicotinamide adenine dinucleotide (NAD^+). LDHA has a higher affinity for lactate production from pyruvate, while LDHB possesses a higher affinity for lactate reconversion to pyruvate. Multiple reports have indicated that increased LDHA expression can confer treatment resistance and helps PCa adapt a more glycolytic and aggressive phenotype [161–164]. Furthermore, fibroblast growth factor receptor 1 (FGFR1) can mediate the balance between LDH isoforms, increasing the stability of LDHA and reducing the expression of LDHB, thereby tipping the metabolic flux in favor of increased lactic acid production [165]. Finally, increased lactic acid production also engenders increased lactic acid efflux in PCa cells. Changes to monocarboxylate transporter (MCT) expression help facilitate the final excretion of lactate into the TME. This primarily involves the increased expression of the proton symporter MCT4 (SLC16A3), which has been shown to promote CRPC and NEPC aggressiveness and suppress anticancer immunity [105,121]. Alternatively, co-expression of MCT1 (SLC16A1) and MCT4, especially MCT1 in PCa cells and MCT4 in the stromal compartment, also contribute to a more aggressive PCa phenotype [166,167]. It is well established that increased lactic acid secretion by cancer cells plays a critically important role in promoting many downstream cancer hallmark characteristics, including angiogenesis, metastasis, resistance to hypoxia and weak-base therapeutics, and the suppression of anticancer immunity [168,169].

3.2. Fructose

Fructose plays an important metabolic role in prostate cells [170]. Seminal fluid is rich in fructose, which is endogenously generated from glucose by the sequential actions of sorbitol dehydrogenase and aldose reductase [171]. The former is an AR-driven gene that is expressed in the seminal vesicles and in malignant PCa [172]. Moreover, emerging evidence suggests that dietary fructose or seminal fructose can be incorporated for energy and integrated into the glycolytic pathway by highly expressing the main fructose transporter GLUT5 (SLC2A5), suggesting that PCa possibly utilizes hexoses other than glucose [173,174]. This is another explanation for why clinical applicability of FDG-PET is limited in PCa diagnostics [114,170].

3.3. Amino Acid Metabolism

While glucose metabolism is considered the typical pathway for maintaining cellular energetic requirements, alterations to amino acid utilization also contribute significantly to PCa development. These changes generally facilitate anabolic processes, and they play a more fundamental role in producing biomolecule precursors for proliferation than in generating "energy" per se (for example, increased nitrogen catabolism for pyrimidine synthesis) [175]. Changes to the metabolism of many amino acids have been observed in PCa, ranging from glutamine and glycine to phenylalanine and sarcosine [176]. Indeed, when considering altered cancer metabolism more broadly beyond glucose, changes to the metabolic landscape may involve multiple interrelated pathways that collectively contribute to disease progression and aggressiveness [52]. A selection of the more prominent amino acid pathways is reviewed here.

3.3.1. Glutamine Metabolism

Glutaminolysis is another key pillar of altered cancer metabolism. Most practically, this phenomenon is understood as the need to supplement glutamine into cell culture media to cultivate in vitro cancer cell growth [175,177]. On a more mechanistic level, it is traditionally described as the import of glutamine that is then converted into glutamate, which is further metabolized into alpha-ketoglutarate (α-KG) as it enters the TCA cycle. This pathway can help replenish TCA cycle intermediates, especially if OXPHOS is to be maintained. Furthermore, various anabolic processes can be fueled by this pathway as metabolic intermediates exit the TCA cycle. Malate can be converted into pyruvate for lactic acid production or gluconeogenesis. OAA can be converted into aspartate for nucleotide synthesis. Citrate and acetyl-CoA can also be redirected towards FA production [178]. Similar to other pathways involved in PCa development, alterations to glutamine metabolism can also be androgen regulated [179,180].

The increased utilization of glutamine is facilitated by increased expressions of amino acid transporters such as alanine serine cysteine transporter 2 (ASCT2; SLC1A5) and L-type amino acid transporter 1 (LAT1; SLC7A5). Both are associated with PCa progression and treatment resistance [181–184]. Downstream of glutamine transport are two forms of glutaminase (GLS) encoded by distinct genes, designated GLS1 and GLS2. GLS1 has two splicing isoforms, kidney-type glutaminase (KGA) and the more active isoform glutaminase C (GAC) [185]. Increases in amino acid transporter expressions often coincide with increases to these other glutaminolytic enzymes [157,175,186–189]. More specifically, the overexpression of GLS for the first-step conversion of glutamine to glutamate in PCa cells can be MYC-driven and is associated with the maintenance of a cellular redox state that confers radioresistance [190]. GLS1 overexpression can also more generically promote PCa cell growth and facilitate metastasis [191,192]. Alternatively, resistance to ADT is also reportedly facilitated by a switch to the androgen-independent isoform GAC [180]. Finally, either transaminase or glutamate dehydrogenase (GDH) converts glutamate into α-KG when PCa cells enter an energy-restricted state, especially if typical glycolysis becomes unavailable [157]. Mitochondrial catabolism of the branched chain amino acids leucine,

isoleucine, and valine is also critical as a major source of cellular energy via generation of acetyl-CoA and succinyl-CoA [193].

In relation to glutamine metabolism, reliance on glutamine-derived carbon and precursor molecules for biosynthesis is also important in cancers that harbor mitochondrial defects or OXPHOS mutations. When typical TCA cycle becomes hampered by these deficiencies, glutaminolysis allows cancer cells to maintain the necessary pool of TCA cycle intermediates for various biosynthetic processes [194]. This can become especially pertinent in situations where altered electron transport chain (ETC) capacities factor into PCa disease progression [195]. Alternatively, altered glutamine metabolism can be associated with changes to proline biosynthesis, even if proline metabolism itself is a double-edged sword that both promotes and suppresses tumorigenesis [196–198]. In the PCa context, it has been shown that increased proline biosynthesis and reduced proline degradation is associated with reduced biochemical disease-free survival and can be regulated by C-MYC [189,199].

3.3.2. One-Carbon Metabolism

Another prominent aspect of amino acid metabolism involves serine, glycine, and methionine in relation to the cellular availability of methyl groups and precursor molecules [200]. 3-Phosphoglycerate (3-PG) is a glycolytic intermediate and a precursor of serine biosynthesis. 3-PG is converted into serine by three sequential enzymatic reactions mediated by phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT1), and 1-3-phosphoserine phosphatase (PSPH) [200–202]. The mutual conversion of serine and glycine is coupled with the folate cycle. Folate metabolism involves a set of paralogous enzymes which catalyze similar reactions in mitochondria and in the cytoplasm [200,201]. Cytosolic serine hydroxymethyltransferase (SHMT1) acts on glycine to generate serine. The mitochondrial isozyme SHMT2 facilitates the synthesis of glycine from serine along with the interconversion of tetrahydrofolate (THF) and 5,10-methylene-THF. In the cytosol, a single trifunctional protein MTHFD1 contains 5,10-methylene-THF dehydrogenase, 5,10-methenyl-THF cyclohydrolase, and 10-formyl-THF synthetase activity. On the other hand, dehydrogenase and cyclohydrolase activity is attributed to the bifunctional protein MTHFD2 (MTHFD2L), while MTHFD1L is a 10-formylt-THF synthetase.

Exogenous serine and glycine both provide important building blocks for protein, nucleic acid, and lipids synthesis [203,204]. Many enzymes involved in one-carbon metabolism is AR- or MYC-regulated [205,206], and an overall upregulation in this metabolic pathway plays a crucial role in facilitating PCa progression [199]. Furthermore, ATF4 has been shown to selectively activate the mitochondrial components of one-carbon metabolism, leading to enhanced cell growth and survival [207]. Alternatively, increased serine biosynthesis and one-carbon metabolism can be caused by PKCλ/ι deficiency in NEPC in an mTORC1/ATF4-driven manner [208]. Finally, there is evidence suggesting that increased levels of the glycine-derivative sarcosine as synthesized by glycine N-methyltransferase (GNMT) can promote PCa invasion and aggressiveness [209]. These new studies help develop game-changing therapeutic strategies, even though we still take advantage of a 75-year-old invention in the form of antifolate therapies [35,210].

One-carbon metabolism can be further linked to cysteine and sulfur metabolism, cellular redox balance, and histone methylation [200,205]. More specifically, it is linked to the polyamine biosynthetic pathway through the S-adenosyl-methionine (SAM)-dependent transfer of methyl groups [211]. In PCa, polyamine metabolism is frequently dysregulated. AR drives the expression of two key enzymes, ornithine decarboxylase (ODC1) and the SAM-decarboxylase AMD1, thus elevating polyamine to levels necessary for transformation and tumor progression [212,213]. ODC1 catalyzes the conversion of ornithine to putrescine. The further reactions to generate spermidine and spermine require decarboxylated SAM (dcSAM), which is obtained from the decarboxylation of SAM by AMD1 [211]. mTORC1 phosphorylates and activates AMD1 to integrate growth factor signaling to polyamine metabolism [213]. Increased polyamine metabolism is sustained via the methionine sal-

vage pathway by methylthioadenosine phosphorylase (MTAP) to recycle SAM [211,214]. Targeting this dependency on MTAP is an attractive translatable therapeutic approach.

3.4. Lipid Metabolism

FAs play an important role in cell proliferation as they are the building blocks for cell and organelle membrane synthesis [215,216] (Figure 3). FAs are also a vital source of energy and can modulate signaling pathways through post-translational modifications. FAs can be endogenously synthesized through de novo lipogenesis (DNL) or exogenously acquired from the environment [215,216]. FASN, the principal enzyme in DNL, is a homodimeric enzyme composed of seven catalytic domains (β-ketoacyl synthase, malonyl/acetyl transferase, dehydrase, enoyl reductase, β-ketoacyl reductase, acyl carrier protein, and thioesterase) that promote the synthesis of palmitate from acetyl-CoA and malonyl-CoA [217]. The FASN substrate acetyl-CoA is mainly generated upon cleavage of citrate, which is derived from the TCA cycle or from reductive carboxylation in the cytosol. Alternatively, acetyl-CoA is directly synthesized by the action of cytosolic acetyl-CoA synthetase 2 (ACSS2) on acetate [218,219]. Acetate uptake is increased concomitantly with elevated FASN activity and serves as a basis for powerful PET imaging [92,220]. FASN is the only eukaryotic enzyme that is able to produce palmitate in humans, and its expression is mostly restricted to adipocyte and liver cells. Other tissues have low to undetectable DNL rates [221,222]. Palmitate can be further elongated and desaturated to generate the diverse spectrum of saturated and monounsaturated FAs (SFA and MUFA) in mammalian cells. Palmitate and its derivatives can support membrane synthesis, be utilized for energy production to sustain increased proliferation, be stored as an energy reservoir, trigger signaling of major oncogenic pathways, and be used as substrates for oncogenic post-translational modifications [223]. FASN expression is upregulated in several types of cancer and correlates with poor prognosis, such as colorectal cancer [224], endometrial carcinoma [225], mantle cell lymphoma [226], B-cell non-Hodgkin lymphoma [227], multiple myeloma [228], ovarian cancer [229], breast cancer [230], and PCa [231,232].

The intracellular uptake of exogenous FAs can happen through a protein-mediated process involving FA transporters such as the cluster of differentiation 36 (CD36). CD36 is a glycoprotein responsible for the transport of long-chain FAs into the cells [233] and for cellular signal transduction [234,235]. It is expressed on the surface of several human cell types. CD36 expression and activity can be modulated by several ligands in response to fat supply. It was shown that a high-fat diet can upregulate CD36 transcription through hyper-O-GlcNAcylation and activation of the NF-κB pathway. It can also modify CD36 amino acid residues to promote increased FA uptake [236]. The peroxisome proliferator-activated receptor gamma (PPARγ) can also modulate CD36 expression levels [237]. Post-translational modification of CD36 through palmitoylation of its cytoplasmic tails is observed and can increased receptor activity [238,239]. As metabolic rewiring plays a role in the survival of tumor cells, different studies have implicated CD36 in carcinogenesis. Leukemic stem cells expressing CD36 can increase FA uptake from adipose tissue and fuel FA oxidation (FAO) to meet energetic demands for survival [240]. Increased FA uptake through upregulation of CD36 was observed in breast cancer resistant to anti-HER2 therapy [241]. In addition to providing FA as fuel for cell growth, CD36 was shown to support the formation of blood vessels in melanoma cancer cells by interaction with extracellular matrix components [242]. In PCa, both FA uptake and CD36 levels are upregulated in human malignant tissue, while genetic ablation of the receptor in Pten-deficient mouse models can impair tumor burden [243]. CD36 seems to also play a role in metastasis, as it is transcriptionally upregulated in lung metastatic CRPC [244]. The crosstalk between endogenous synthesis and exogenous uptake of lipids is of therapeutic relevance. It has been shown that tumor cells upregulate the rate of DNL to favor saturated membranes over polyunsaturated ones, as highly unsaturated FA acyl chains can render membranes more susceptible to oxidative damage [245]. Interestingly, DNL rates were observed to increase in the prostate of *Pten*$^{-/-}$ *Cd36*$^{-/-}$ mice as cells try to compensate for the FA deficiency caused by uptake block-

ade [243]. Enhanced antitumorigenic effects by inhibiting both DNL and CD36 activity has been observed in preclinical models of PCa [243,246].

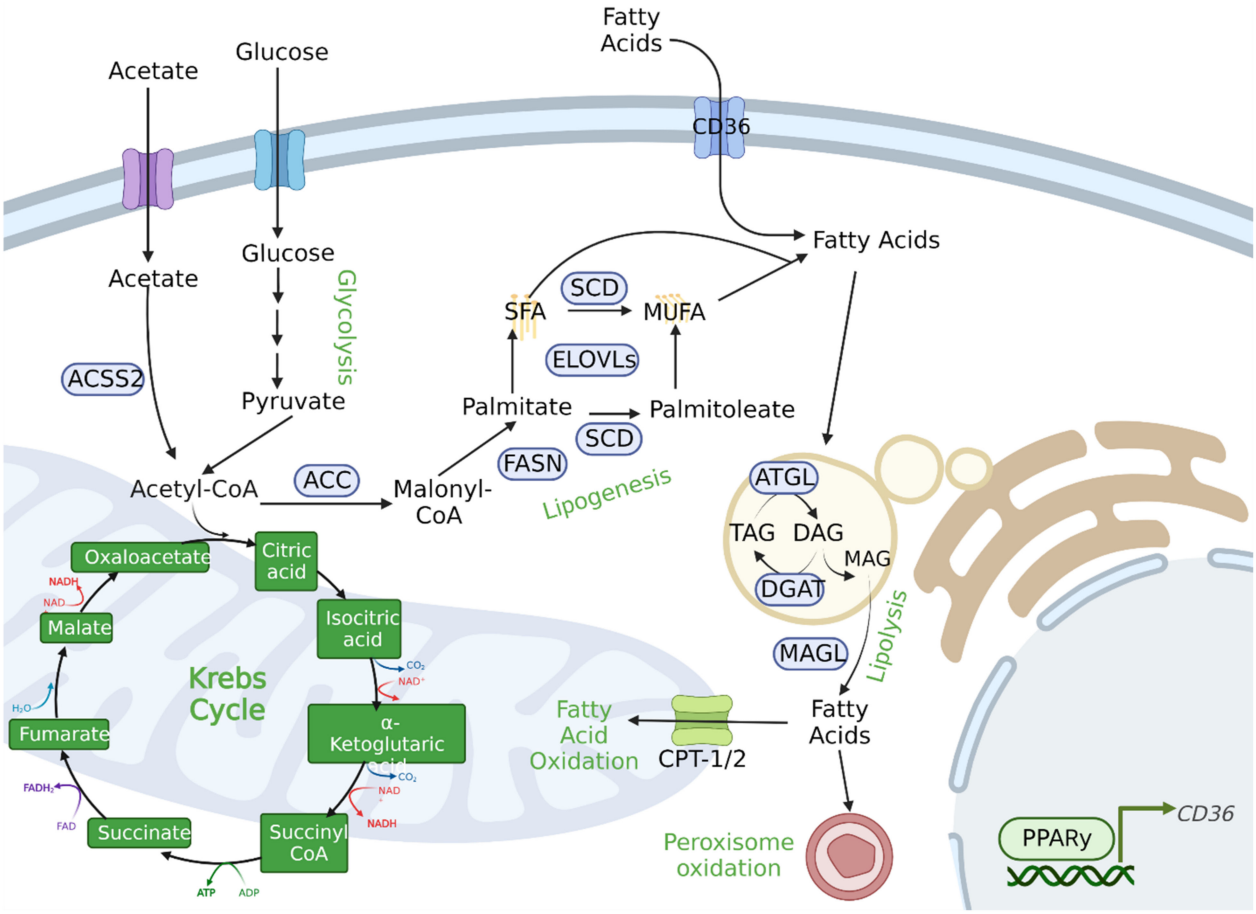

Figure 3. Major lipid metabolism enzymes and metabolites that are modulated on PCa cells. Several alterations are observed during prostate carcinogenesis, including increased rates of de novo lipogenesis, increased fatty acid uptake, lipolysis and fatty acid oxidation (Created with BioRender.com).

FA Storage and Utilization

As cancer cells upregulated uptake and synthesis of FA, they must also modulate storage and utilization of lipids (Figure 3). FA can be stored in lipid droplets. Lipid droplets are intracellular organelles that consist of a phospholipid monolayer within which neutral lipids can be stored. This is a process mediated by budding from the endoplasmic reticulum (ER) membrane, and subsequent growth is facilitated by the transferal of triacylglycerol (TAG) and cholesterol esters [247]. Cancer cells can upregulate lipolysis to utilize stored FAs. TAG can be hydrolyzed to diacylglycerol (DAG) and free FAs by the action of adipose triglyceride lipase (ATGL). DAG can then be converted to monoacylglycerol (MAG) and free FAs by hormone-sensitive lipase (HSL). Cells can obtain glycerol and free FAs by monoacylglycerol lipase (MAGL) activity [248]. All these steps are crucial for tumor cells that have high energetic demands; MAGL, for example, was shown to be upregulated in both advanced cancer cells and primary tumors, increasing free FA levels and modulating migration and tumor growth [249].

In addition to lipolysis, cancer cells also rely on the oxidation of FAs. Oxidation of FAs is observed in both mitochondria and peroxisomes, and is a major metabolic energy source. While peroxisomal FAO does not generate energy per se, very long and branched chain FAs cannot be processed directly in the mitochondria and need to be initially broken down in peroxisomes [250]. Peroxisomal FAO is increased in PCa, with a higher expression level and enzymatic activity of D-bifunctional protein (DBP) [251]. α-Methylacyl-CoA

racemase (AMACR), an enzyme involved in both mitochondria and peroxisome FAO, has also been reported to be increased in PCa [251,252]. Peroxisomes are a single-membrane bound organelle, with ABCD proteins importing the CoA esters of FAs [253]. On the other hand, mitochondrial FA import utilizes the carnitine shuttle, which is composed of carnitine palmitoyltransferases (CPT1, CPT2) and the carnitine–acylcarnitine translocase (SLC25A20). Subsequently, acetyl-CoA derived from FAO enters the TCA cycle, and NADH drives ATP synthesis through OXPHOS. The outer mitochondrial membrane (OMM) enzyme CPT1 is the rate limiting enzyme in FAO and is repressed by the FASN substrate malonyl-CoA. It controls the balance between FA synthesis and oxidation depending on metabolic demands [216].

4. Metabolites and Gene Regulation

As early as 1961, the link between metabolism and transcription has already been recognized in *Escherichia coli* as the "lac operon theory". At the molecular level, the presence of lactose and the absence of glucose turns on the expression of genes involved in lactose metabolism [254,255]. Now, a growing body of evidence suggests that, in mammalian cells, specific metabolites mediate the crosstalk between cellular metabolism and gene regulation in multiple layers [256]. Cholesterol deprivation promotes the dissociation of precursor SREBP in complex with SREBP cleavage-activating protein (SCAP) from insulin-induced gene (INSIG1) at ER membranes, allowing it to move to the Golgi apparatus. There, it undergoes proteolytic cleavage to release the mature form of SREBPs, which act as transcription factors in nucleus [257]. MondoA and its binding partner Mlx are localized at the OMM [258,259]. Binding of the glycolysis intermediate G6P to MondoA initiates the translocation of the MondoA/Mlx complex to the nucleus, where it drives TXNIP and its paralog ARRDC4, which in turn downregulates the expression of glycolytic enzymes in a feedback manner. In this setting, elevated mitochondrial ATP levels regulate MondoA functions through the production of G6P by mitochondria-bound hexokinases [258,259]. Arginine is a conditionally essential amino acid, particularly in cells with low or null expression of argininosuccinate synthethase 1 (ASS1), which catalyzes arginine synthesis from citrulline and aspartate in concert with argininosuccinate lyase [260]. Arginine starvation activates the p38 MAPK pathway to promote nuclear export of TEA domain transcription factor 4 (TEAD4), which otherwise epigenetically modulates nuclear encoded OXPHOS genes to maintain mitochondrial activities [260].

4.1. Post-Translational Modifications

Metabolites can also be integrated into gene regulation as substrates for DNA methylation and as post-translational modulators of transcription factors and chromatin modifiers [261–263]. Modification status and resulting outputs are orchestrated via coordinated actions on modification marks by writers, erasers, and readers. In many cases, the Michaelis–Menten constants (Km) for these enzymes are higher than metabolic substrates, making them susceptible to changes in metabolite levels [264]. In addition to phosphorylation, acetylation, and other acyl modifications, methylation and O-linked N-acetylglucosamine modification (O-GlcNAcylation) are important post-translational modifications (PTMs) requiring metabolites as substrates [265].

Uridine diphosphate N-acetyl glucosamine (UDP-GlcNAc), which is the end product of the hexosamine biosynthetic pathway (HBP), serves as the substrate for O-linked β-N-acetylglucosamine transferase (O-GlcNAc transferase, OGT). It transfers N-acetylglucosamine to the serine and threonine residues of numerous proteins, including transcription factors and chromatin modifier [266]. High OGT activity is essential for the proliferation of MYC-driven PCa cells, while CRPC reportedly have reduced HBP metabolites, suggesting an intricate metabolic re-wiring process during PCa progression [267,268].

Protein lysine acetylation represents a highly dynamic and reversibly regulated PTM of transcription factors, histones, and chromatin modifiers [269]. Lysine acetyltransferases use acetyl-CoA as a substrate to transfer acetyl groups to the lysine residues of target

proteins. Cytoplasmic acetyl-CoA enters the nucleus to serve as the substrate for lysine acetyltransferase. Alternatively, pyruvate, acetate, and citrate diffuse into the nucleus to be converted to acetyl-CoA by the nuclear counterparts of corresponding enzymes [270] (Figure 4A). Nuclear PDH complex (PDC) coordinates lipogenic programs by epigenetically controlling the expression of SREBP target genes through localized acetyl-CoA supply and histone acetylation [156]. On the other hand, protein deacetylases are grouped into zinc-dependent class I, II and IV enzymes, and class III enzymes which require NAD^+ as a cofactor [271]. The availability of nuclear pools of acetyl-CoA and NAD^+ partly determines the activities of the corresponding enzymes, thereby linking the general energetic status of the cell to epigenetic and non-epigenetic controls of gene regulation [263]. The Class III enzyme sirtuin (SIRT1) couples epigenetics with cellular redox by utilizing NAD^+ as a rate-limiting substrate. The nuclear pool of NAD^+ is regenerated either via the NAD^+ salvage pathway with the precursor nicotinamide (NAM) in the nucleus, or through nuclear entry of cytoplasmic NAD^+ [272]. Interestingly, DNA damage leads to PARP1 activation to drastically consume nuclear NAD^+ for polyADP-ribosylation, presumably outcompeting SIRTs [273]. Aging is associated with declining NAD^+ levels, reducing SIRT activity [272]. Nevertheless, SIRT1 is overexpressed in multiple cancers, and ADT promotes its nuclear accumulation in PCa models [274]. Nuclear SIRT1 levels correlate with adverse outcomes in PCa. Pharmacologic inhibition of SIRT1 by EX-527 is effective in suppressing the growth of multiple PCa models, suggesting a potential therapeutic strategy in combining SIRT1 inhibition with anti-AR therapy [274].

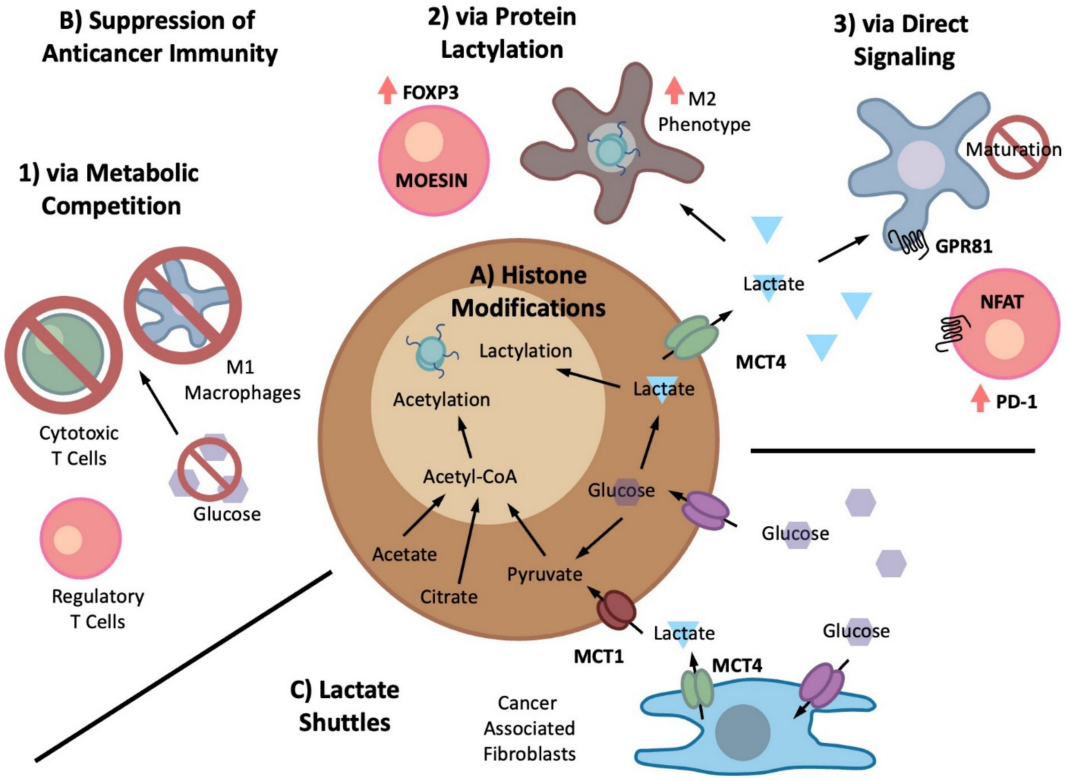

Figure 4. Altered glucose metabolism in aggressive PCa and the effects of increased lactic acid production on (**A**) gene regulation via histone modifications, and (**B**,**C**) the TME, especially its impacts on suppressing the anticancer immune response.

4.1.1. Lactylation

Recent advancements in analytical tools have led to discovery of various types of lysine acylation by metabolites, including succinylation, malonylation, glutarylation, lactylation, and serotoninylation [275]. Lysine succinylation, malonylation, and glutarylation are physiologically linked and known to be deacylated by Sirt5 [164,276]. However, specific

enzymes for many of these modifications are not precisely known, and some reactions may proceed in non-enzymatic manners [275]. Nevertheless, the biological significance of protein lactylation has just begun to be unraveled [277] (Figure 4B). Histone lactylation and acetylation compete for the same modification sites, thus reflecting the cellular metabolic status of whether pyruvate is committed to lactate or acetyl-CoA generation [278]. Glycolytic inhibition and activation decrease and increase lysine lactylation, respectively, while genetic inhibition of LDH abolishes lysine lactylation [279]. This PTM was first discovered in the context of macrophages as part of mechanistic studies investigating how an acidic microenvironment contributes to immunosuppression. It was shown that histone lactylation stimulated gene transcription from the chromatin and induced a homeostatic gene expression program that reverted M1-polarized macrophages back towards a more suppressive, wound-healing, M2-like phenotype characterized by arginase 1 (Arg1) expression [279]. Since then, the immunosuppressive effects of protein lactylation has been demonstrated in additional anticancer immune cell types [280]. For example, lactylation of MOESIN in regulatory T cells (Tregs) enhanced its interaction with TGF-beta receptors TGFBR1 and helped increase FOXP3 expression to mediate its immunosuppressive effects [281]. Furthermore, histone lactylation in tumor-infiltrating myeloid cells also enhanced their immunosuppressive effects via a METTL3-mediated RNA modification [282].

Beyond mediating immunosuppression, the mechanisms and functional effects of histone/protein lactylation are becoming progressively unveiled [283]. For example, it is now known that the acetyltransferase p300 mediates histone lactylation, while HDAC1-3 serves as delactylases [284]. Furthermore, it has been shown that lactylation on the glycolytic enzyme ALDOA serves to allosterically inhibit its enzymatic activity, potentially mediating a negative feedback loop for the glycolysis pathway in the presence of excess lactic acid [283]. Finally, the functional relevance of lactylation has also been reported in RNA splicing, neurodevelopment, osteoblast differentiation, and cancer progression [285–288]. While there are no published studies of lactylation in PCa at this time, it is likely that this novel PTM will be validated as functionally relevant in promoting PCa progression, especially with respect to having regulatory effects on metabolic pathways and immunosuppressive effects on various components of anticancer immunity.

4.1.2. Methylation

SAM is linked to one-carbon metabolism and is a universal methyl donor for protein, DNA, and RNA modifications [289]. Histone and non-histone proteins undergo protein methylation at arginine and lysine residues. Except for disruptor of telomeric silencing 1 like (DOT1L), lysine methyltransferases (KMT) contain a highly conserved Su(var)3-9, E(z) and Trithorax (SET) domain, examples being the EZH2 and mixed-lineage leukemia (MLL) methyltransferases. Arginine methylation involves the protein arginine methyltransferase (PRMT) family [290]. Demethylases are divided into two subgroups: the flavin adenine dinucleotide (FAD)-dependent lysine-specific demethylases (LSD1 and LSD2) and the Jumonji C domain-containing (JMJD) protein family, which acts on both methylated arginine and lysine residues [291]. Nearly all have been found to be overexpressed in PCa [292,293]. JMJD2 family proteins interact with ETV1 and AR to promote PCa growth [294]. JMJD1a/KDM3A activates AR signaling by upregulating c-MYC expression through H3K9 demethylation and promoting alternative splicing to generate AR-V7 [295,296].

DNA methylation occurs as 5-methylcytosine (m5C) and is controlled by the opposite actions of DNA methyltransferases (DNMTs) and ten-eleven translocation (TET) proteins, which primarily play a demethylation role [297,298]. DNA methylation status is not static during PCa progression [299]. The early and recurrent acquisition of hypermethylation in the glutathione *S*-transferase P1 (GSTP1) promoter has been observed in prostate tumorigenesis [300]. In later stages of the disease, overexpression of the oncogenic drivers AR, MYC, FOXA1, HOXB13, and ERG is associated with hypermethylation at the intergenic regions of these genes and colocalization of H3K27 acetylation [301].

The m6A modification is a reversible PTM of RNA that impacts RNA metabolism, including transcription, pre-mRNA splicing, mRNA export, mRNA stability, and translation [302]. This methylation status is dynamically and reversibly regulated by methyltransferase as writers (METTL3/14, WTAP, RBM15/15B and KIAA1429), demethylases as erasers (FTO/ALKBH5 and ALKBH5), and the binding proteins (YTHDF1/2/3, IGF2BP1 and HNRNPA2B1) as readers. Several reports suggest that METTL3 expression is elevated in PCa, possibly leading to increased m6A RNA methylation. The reader YTHDF2 has also been found to be upregulated in PCa, its expression predicting worse overall survival [303–305].

Finally, three key oncometabolites (2-hydroxyglutarate, succinate, and fumarate) drive malignant transformation primarily through methylation regulation and pseudohypoxic signaling. They serve as structural mimetics to α-KG and thus competitively inhibit protein, DNA, and RNA demethylases and proline hydroxylases belonging to the superfamily of α-KG-dependent dioxygenases [44,45]. Indeed, genome-wide methylation landscape studies identified a new epigenetic CpG methylator phenotype (CMP) subtype of mCRPC, which is enriched for mutually exclusive mutations in TET2 and IDH1 [301]. 2-HG producing-mutations in IDH1 are associated with CpG island hyper-methylations in the Cancer Genome Atlas (TCGA) primary PCa database [306]. It remains to be answered how germline SDH and FH mutations exhibit a high degree of tissue specificity in the patients without drastic adverse effects in most other tissues [44,45,307].

5. Tumor Microenvironment (TME)

Oxygen and nutrients are supplied from the tumor vasculature, which distributes unevenly in the TME. Both competitive and cooperative metabolic interactions further shape and orchestrate the TME to support metastatic heterogeneity and therapeutic resistance [308–311]. The TME forms pro-tumorigenic niches, consisting of different cell types such as cancer-associated fibroblasts (CAF), immune cells, and endothelial cells [308,311–314]. The differential metabolic demands among TME cells result in metabolic competition and symbiosis to support tumor-specific metabolic reprogramming. This causes the release of immunosuppressive metabolites, facilitates tumor progression, and mediates mechanisms of therapeutic resistance [312,314–318]. Exosomes from prostate CAFs are capable of shifting metabolism in recipient tumor cells by suppressing OXPHOS, thereby increasing glycolysis and enhancing glutamine metabolism as a source of intermediate metabolites [319]. Therefore, pharmacological manipulation of TME metabolism has been recognized and ought to be integrated into overall therapeutic strategies [320,321].

5.1. Metabolite-Driven Immunosuppression

PCa is occasionally considered to represent the types of cancer that mainly display immune-desert or immune-excluded phenotypes, although still not conclusive [322]. This may be due to a general lack of PD-L1 expression and the presence of immunosuppressive cytokines and metabolites (adenosine, lactate, kynurenine, etc.) within the TME [323–325]. Immunometabolism generally dictates the fate of immune cells and their immunological functions [316,326]. Once activated, natural killer (NK) cells and T cells shift their metabolisms from oxidative metabolism to aerobic glycolysis to proliferate and develop effector functions. On the other hand, Treg cells, which repress antitumor immune responses, are primarily dependent on OXPHOS rather than glycolysis for cell persistence and function. Moreover, pro-inflammatory M1 macrophages are characterized by glycolytic metabolism while tumor-associated macrophages (generally defined as anti-inflammatory M2 macrophages) rely on mitochondrial OXPHOS [327]. Highly glycolytic tumors with expression of HK2 and LDHA thus competitively deprive glucose from the TME to impair antitumor immunity and support tumor progression and metastasis in preclinical models of cancers such as sarcoma [328]. Increased tryptophan catabolism by PCa cells produce kynurenine by the concerted actions of indoleamine-2,3-dioxygenase 1 and 2 (IDO1/2) and tryptophan-2,3-dioxygenase (TDO2) [329]. TDO2 expression is elevated

in drug resistant PCa tumor tissues [330]. Kynurenine exhibits tumor promoting activities in cell autonomous and non-autonomous manners. In PCa cells, kynurenine is a ligand for the transcription factor aryl hydrocarbon receptor (AhR), promoting its nuclear translocation and cooperation with NF-κB to transactivate C-MYC expression [330,331]. C-MYC upregulates ATP-binding cassette (ABC) transporters and tryptophan transporters, establishing a tryptophan/TDO2/Kyn/AhR/c-Myc loop to sustain drug resistance [330]. Kynurenine also inhibits the activity of NK cells, dendritic cells (DCs), and proliferating T cells, thus providing an immunosuppressive TME [325,329]. Likewise, tryptophan depletion inhibits proliferation and activation of effector T-cells [329]. Conversely, increased IDO expression promotes M2 polarization in tumor associated macrophages [332], and IDO inhibition is a therapeutic strategy that aims to suppress cancer cell proliferation and reactivate antitumor immunity [333]. A phase 2 clinical trial with the IDO inhibitor indoximod (NLG-8189, 1-Methyl-D-tryptophan) (NCT01560923) provided significant evidence of the efficacy of indoximod as an immunometabolic adjuvant in combination with the DC vaccine sipuleucel-T (Provenge®) in advanced PCa [334].

Two conditionally essential amino acids, asparagine and glutamine, work in concert to drive tumor growth and metastasis [335–337]. When extracellular glutamine levels decline in preclinical models of breast cancer, asparagine becomes essential for supporting de novo glutamine biosynthesis via upregulation of glutamine synthetase (GLUL) [338]. On the other hand, in PCa models, glutamine deprivation in the TME enhances asparagine biosynthesis in CAFs. This occurs via ATF4 activation due to downregulation of the autophagy adaptor protein p62 [339]. CAFs release asparagine to support tumor growth in the glutamine-limited environment.

Cancer-Generated Lactic Acid

The extracellular abundance of lactate in the TME is a result of increased intracellular production and MCT4-mediated efflux of lactate. An acidic TME caused by increased lactic acid production can have multi-fold effects on tumorigenesis and progression. These cancer-promoting consequences include enhancing local tissue invasion and distant metastasis, resisting hypoxia and anticancer therapeutics, and stimulating angiogenesis [168,340,341]. Given the multi-faceted role of lactic acid, one aspect that deserves greater attention is its ability to suppress the anticancer immune response [169] (Figure 4B). The recent reappreciation of lactic acid's functional role in the TME has coincided with the clinical successes of various anticancer immunotherapeutics. As such, there has been an explosion of interest in trying to understand how lactic acid suppresses the anticancer immune response. By this point, almost every conceivable subtype of immune cell is known to be impacted by cancer-generated lactic acid, whether positively or negatively [342,343]. The existing literature on this topic is extensive [169,315,342,344,345], and we will limit the scope of our discussion here to only the major immune contributors. While some of the immunosuppressive mechanisms have already been highlighted in the previous sections (e.g., lactylation and epigenetic changes), other functional impacts are worth considering. In PCa, lactate flux is indeed critical and MCT4 is a potential therapeutic target. Thus, it is reasonable to extrapolate experimental data in non-PCa models to PCa therapeutics.

Discussions of anticancer immunity begin with the cytotoxic effector subtypes, and more particularly, the balance between the effector $CD8^+$ cytotoxic T cells and Tregs. Multiple studies have demonstrated how an acidic TME hampers typical cytotoxic T cell function while allowing Tregs to remain relatively unaffected, thus tipping the balance in favor of an immunosuppressive response [346]. For example, given the recent successes of checkpoint inhibitors in anticancer immunotherapy, it is important to note that lactic acid increases PD-1 expression in tumor-associated Tregs through nuclear factor of activated T-cells (NFAT) signaling. The blockade of PD-1 in Tregs further enhances their immunosuppressive functions, leading to tumor escape [347]. Similarly, increased lactate in the TME reduces the efficacy of f vascular endothelial growth factor (VEGF) inhibition by inducing PD-L1 expression in neutrophils, skewing their differentiation towards a tumor

promoting N2 phenotype [348]. Alternatively, as mentioned above, it has been shown that Tregs possess a distinct metabolic profile compared to cytotoxic T cells. Treg activity is suppressed under high-glucose conditions but is enhanced in a high-lactic acid environment, partially through an increased availability of biomolecular intermediates necessary for further Treg proliferation [349,350]. Similarly, metabolic competition with tumor cells for available glucose can also negatively impact effector T cells and their ability to eliminate cancer cells [328,351,352]. An acidic environment can also negatively impact the secretion of pro-inflammatory cytokines such as interferon-γ (IFNγ), further reducing the immune system's ability to mount an effective anticancer response [353,354]. Finally, lactic acid can also alter T cell differentiation away from the cytotoxic phenotypes and induce anergy in the existing cytotoxic T cell population [355,356].

Beyond cytotoxic effector cells, an acidic TME can also negatively affect the anticancer activities of DCs and macrophages in a broad-ranging manner, impacting maturation, antigen presentation, migration, and the secretion of cytokines [357]. For example, lactate itself can be a negative signaling molecule for antigen presenting cells, mediating an overall immune suppression through both GPR81 and GPR132 [358–362]. Lactate can also inhibit DC maturation and antigen presentation, thus preventing an adequate anticancer immune response [363,364]. Increased lactic acid also skews macrophage polarization towards the M2 phenotype partly through epigenetic modulation involving histone lactylation, causing their loss of immunostimulatory functions [362,365–368]. This is especially mediated through the reduced production of various pro-inflammatory cytokines necessary to elicit an anticancer immune response [369–371]. Thus, tumor-specific glycolytic inhibition not only impairs tumor growth and proliferation but also augments antitumor immunity in the TME [328].

5.2. Lactate Shuttle

From a purely metabolic perspective, the combination of MCT1 and MCT4 function can facilitate a "symbiotic" interaction that enhances cancer cell survival. Known as the "lactate shuttle", it has been suggested that adjacent cancer (and stromal) cells can coordinate their nutrient uptake and processing in order to achieve greater metabolic efficiency [372] (Figure 4C). In a nutrient/oxygen-starved environment, especially towards the interior of the tumor, glucose is metabolized via glycolysis to produce lactic acid. This lactic acid is excreted primarily through the lactate exporter MCT4 and is taken up via MCT1 by more oxidative cancer cells, especially those in a nutrient/oxygen-rich environment. Lactate is converted back into pyruvate in these oxidative cells through a "reversed Warburg effect", and energy metabolism proceeds via the typical TCA cycle and OXPHOS [373]. There is some indication that this metabolic coupling, specifically between MCT1-expressing cancer cells and MCT4-expressing stromal cells, can help fuel PCa growth [374–376]. This tumor metabolic symbiosis requires the specific settings where CAF is glycolytic and tumor cells continuously use lactate as a fuel under complete aerobic conditions [377].

5.3. Fatty Acid Signaling

Adipocytes are known to play a role in carcinogenesis, and epidemiological studies have shown a correlation between obesity and cancer incidence, as well as worse prognosis in patients with excess weight [378]. Particularly for PCa, adipocytes from the periprostatic adipose tissue (PPAT) surrounding the prostate gland can support prostate epithelial cancer cell migration through chemokine modulation [379]. PCa cells stimulate these adipocytes to undergo metabolic rewiring, promoting lipolysis and the release metabolic products such as free FAs (FFAs) that serve as the source of FAO in tumor cells. Lipid transfer proteins FABP4 and/or CD36 have been reported to mediate the transfer of FAs from adipocytes into cancer cells including PCa [380]. Pharmacological inhibition of adipocyte lipolysis or lipid transfer may provide effective antitumor activities.

Excess dietary carbohydrates can be converted into lipid through DNL and accumulate into lipid droplets. Dietary lipids can be stored in lipid droplets as well. Regardless of

the origin, nearly all cell types can store fat in lipid droplets; adipocytes, however, are specialized cells known for the controlled mechanism of FA accumulation and utilization through lipolysis [381]. Increased FASN expression has been reported in adipose tissue and inversely correlates with insulin sensitivity [382]. As a reservoir of FA, adipocytes are an important energetic support for highly proliferative tumor cells. AR antagonism induces reprograming of lipid metabolism through lowered FASN expression, thereby decreasing intracellular saturated FA levels and promoting uptake of nutrient derived polyunsaturated FAs (PUFAs) in PCa [245,383,384]. The rise in PUFA enhances membrane fluidity and lipid peroxidation, causing hypersensitivity to glutathione peroxidase 4 (GPX4) inhibition and ferroptosis in PCa [384]. Dietary FA also shapes immunity in TME. Uptake of FAs support Treg and memory T cells to drive FAO and OXPHOS for their survival and function [314,385]. Moreover, metabolic fitness and plasticity allow $CD8^+$ T cells to upregulate FA catabolism to support their effector functions when glucose is not available [314].

Another key role of lipids in the TME is the pro-inflammatory and pro-tumorigenic function of oxidized FAs such as eicosanoid species in various cancer models, including PCa. There are several types of eicosanoids, including prostaglandins, thromboxanes, leukotrienes, lipoxins, resolvins, and eoxins, and they are all derived from PUFA. Prostaglandins can be produced from arachidonic acid metabolism through the enzymatic activity of cyclooxygenase (COX). Prostaglandins have been implicated in carcinogenesis, and studies show that COX inhibition by non-steroidal anti-inflammatory drugs (NSAIDs) can help delay or prevent PCa [386,387]. Interestingly, prostaglandins have also been shown to impair NK cells viability and activity, modulating the antitumor immune response [388]. Leukotrienes can be obtained by the action of lipoxygenases (LOX) on arachidonic acid. These molecules have also been correlated with carcinogenesis, and overexpression of LOX5 was observed to be upregulated in prostate adenocarcinoma in comparison to benign tissue [389].

6. Therapeutic Interventions

A number of factors must be considered when developing metabolism-based therapeutic interventions. To start, the therapeutic targeting of metabolic complexes or enzymes in many cases affects not only tumor cells but also normal proliferating cells [35,46,320]. Multiple enzymatic isoforms can also perform overlapping functions, and metabolic flexibility can divert processes away from inhibited pathways. Therefore, redundancy among metabolic genes could shape the landscape of positive and negative impact on targeting tumor metabolism. A better understanding of the different alterations that facilitate a cancer's unique metabolic landscape can help ensure efficacy and avoid generic toxicity. Beside the careful selection of therapeutic targets, the fact that metabolites generally require specialized membrane transporters for influx and efflux presents another unique therapeutic challenge. Furthermore, common nutrients such as glucose, glutamine, or FAs can also be utilized through metabolic symbiosis and competition occurring between the tumor cells and the stroma cells in the TME [311–313,318]. Thus, interference with these intercellular metabolic interactions can elicit antitumor effects and overcome therapeutic resistance. When these factors are considered collectively, in order to minimize potential toxicity and increase specificity, it is necessary to identify selective metabolic vulnerabilities within a particular cancer in a manner that is associated with specific oncogenic activations. Currently, there are only a limited number of such drugs which are immediately applicable to PCa treatment [51,55]. However, we can take advantage of the potentially effective metabolism-targeted therapeutics being developed in the preclinical setting, as well as those with some clinical trial data for various diseases. This can include indications for non-prostate cancers, diabetes, and infectious diseases as shown in Table 1 (Indications for PCa are shaded) [46,320]. As stated above, various types of cancers share alterations in some metabolic pathways such as fatty acid synthesis, glutamine addiction, and mitochondrial metabolism. One can speculate that corresponding therapeutic agents in clinical

trials (Table 1B) will be readily applicable for PCa. Indeed, drug repurposing is becoming one of the most promising strategies for PCa therapeutics due to the high safety profile of established drugs such as metformin and statins [390,391].

There are two classes of drug development platforms which begin with either target-based or phenotypic-based screening of compound libraries [392–394]. Typical molecular target-based drug screening programs involve identification of specific targets for a disease of interest, and is followed by in silico or experimental screening of compounds and subsequent chemical optimization of lead candidates for further preclinical testing. Transporters are a notoriously difficult class of therapeutic targets due to the presence of multiple transmembrane domains needed to form the central channel. Such channels are often difficult to undergo crystallization for X-ray structural determination, thus limiting the amount of information available for drug design. However, recent advances in drug development approaches and structural biology have offered unique opportunities to overcome such hurdles. For example, the increasing maturity of cryo-electron microscopy (cryo-EM) techniques have allowed the structures of various important membrane transporters to be determined, including LAT1, LAT2, MCT1, MCT2, and GLUT4 [395–399]. These structures provide critical information for accurately designing and studying potential inhibitors. Alternatively, in our experience with designing selective MCT4 inhibitors, using a computer-assisted drug discovery platform can also be an effective approach [400,401]. Recent developments in big data, graphics processing unit (GPU)-computing, and deep learning has advanced drug discovery into a new artificial intelligence era capable of accurately calculating drug-like properties and binding [400,402–404]. Multiple state-of-the-art drug design software and molecular docking programs are now available [405–407], and these can be used in combination with advanced structural prediction algorithms such as AlphaFold to arrive at potential therapeutic compounds, especially for difficult drug targets that lack available structural information [408]. Another example includes the integrated platform of high-throughput virtual screening and graphite dots–assisted laser desorption/ionization mass spectrometry for drug discovery (GLMSD), allowing for rapid screening and identification of five potent HK2 inhibitors from initial 240,000 compounds [409].

In contrast, phenotypic screening is aimed at perturbing the biological process without prior understanding of the molecular mechanism of action. This approach requires subsequent steps involving target deconvolution, which can be a challenging and lengthy endeavor. Indeed, direct interaction with a single target is not necessarily responsible for phenotypes observed in screenings. Rather, observed phenotypes may reflect the superposition of polypharmacological effects. Nevertheless, the benefit of an unbiased approach is underscored by the discovery of new therapeutic targets such as FKBP12, mTOR, and histone deacetylases [394]. There is a growing interest in reinventing phenotypic screens with the advent of new tools such as high content imaging, RNA profiling, and CRISPR/Cas9-based genome engineering as discovery platforms [410]. For example, metabolism-focused CRISPR genetic screens revealed tumor-specific metabolic vulnerabilities, thus identifying potential druggable targets [411]. Recently established yeast with full humanization of the glycolytic pathway can also be used as both a target- and a phenotypic-based drug discovery platform, thus integrating traditional high throughput screening for identifying effective anti-glycolytic agents [412].

Isoform specific contribution to tumor progression is exemplified by HK2. Its deficiency is therapeutic despite continued HK1 expression, thus underscoring its potential as a therapeutic target [413,414]. HK2 is required for survival of PTEN/p53-deficient CRPC tumors [127]. Aerobic glycolysis not only supports glycolytic tumors but also drives effector T cell differentiation and proliferation [326,328]. Whereas increased HK2 expression is associated with the Warburg effect in tumors, HK2 is dispensable for T-cell dependent immunity [126,127,415,416]. Moreover, silencing or deletion of specific isozymes results in a therapeutic liability that can be exploited in preclinical cancer models. With silenced HK1, HK2 positive tumor cells become more sensitive to HK2 inhibition [417,418]. As another example of isoform specificity, TEPP-46 binds to PKM2 but not PKM1 at an al-

losteric site distinct from the 1,6-FBP site, which is required for the formation of a tight tetrameric enzyme [419,420]. PKM2 is abundantly found as a dimer in proliferating cells. The lower enzymatic activity of PKM2 compared to PKM1 allows cancer cells to rewire their metabolism and utilize the intermediates of glycolysis for biosynthetic pathways [133]. Consistently, pharmacological activation of PKM2 by TEPP-46 suppresses tumor progression in PCa models [134]. Finally, passenger deletion of enolase 1 (ENO1) is associated with homozygous deletion of the 1p36 tumor-suppressor locus, which provides selective vulnerability to a potent prodrug of the competitive ENO2 inhibitor, POMHEX [421,422].

Targeting glutamine addiction is attractive in cancer therapeutics [423,424]. Clinically tested CB-839 is a selective allosteric inhibitor for GLS1 without discrimination between KGA and GAC and spares GLS2 [425]. GLS1 inhibition may offer clinical benefits in advanced and therapy-resistant PCa overexpressing the GAC isoform, which is sensitive to GLS1 inhibition by CB-839 [180]. CB-839 has been in clinical trials for various cancer types as a monotherapy and in combination with an immune checkpoint inhibitor (Table 1). Furthermore, pan-inhibition of glutamine metabolism in the TME provides therapeutical benefits in the context of cancer immunotherapy. Pro-drug JHU-083 is activated in the TME to release the glutamine analog 6-diazo-5-oxo-L-norleucine (DON), which elicits covalent inhibition of multiple glutamine-utilizing enzymes [426]. Warburg-type cancer cells direct pyruvate away from mitochondria and rely on glutamine as an anaplerotic substrate to replenish TCA cycle intermediates. Glucose deficiency or excessive lactate in TME can create glutamine dependency in effector T cells and NK cells for their immune functions. Therefore, JHU-083 administration presumably leads to suppression of tumor cells and blunts the immune competent environment. JHU-083 simultaneously inhibits glycolysis and OXPHOS, thereby comprehensively disintegrating bioenergetics in tumor cells. Nevertheless, JHU-083 augments oxidative phenotypes in effector $CD8^+$ T cells, which upregulates ACSS2 to generate high levels of acetyl-CoA to fuel the TCA cycle. Glutamine-based metabolic symbiosis is also observed in PCa. Thus, pan-inhibition of glutamine metabolism may also offer promising therapeutic benefits in PCa.

As a hallmark of cancer, lipid metabolism has been investigated as a therapeutic target to treat several types of tumors. Particularly, FASN inhibitors have been developed and characterized in several preclinical models, including in PCa. First-generation FASN inhibitors, such as C75, orlistat, and cerulenin, successfully reduced cancer cell growth in preclinical models [427–429]. However, an undesirable side-effect profile and a poor pharmacological response have prevented such molecules from clinical usage in cancer therapy. C75 and cerulenin caused reduced food intake and a profound weight and adipose mass loss [430]. C75 was also observed to increase FAO through CPT1 activity stimulation, further impairing energetic metabolism [431]. Despite therapeutic implications for obesity, pharmacologically induced weight loss is threatening for cancer patients that commonly experience cachexia. Newer molecules targeting FASN with promising results in preclinical models have been recently developed, such as GSK2194069 [432], Fasnall [433], IPI-9119 [86] and BI99179 [434]. However, so far, only one FASN inhibitor has entered clinical trials (TVB-2640 from Sagimet Biosciences) as shown in Table 1B. This compound has demonstrated potent FASN inhibition as well as a favorable and manageable safety profile, characterized by very limited, non-serious, reversable adverse events when tested in patients with previously treated advanced metastatic solid tumors, including 4 PCa patients [435]. Particularly in PCa, FASN inhibition leads to reduced cell growth, increased apoptosis, cell cycle arrest and down-regulation of both full-length AR and splice variants in vitro and in vivo, as well as suppression of AR-V7-driven gene-sets and modulation of both AR and AR-V7 nuclear translocation [86]. Because of its effects on AR/AR-V7 as known drivers of ADT resistance, inhibitors of FASN can be used to sensitize cells to AR antagonists to delay or overcome therapy resistance. Thus, targeting lipid synthesis represents a novel therapeutic strategy to target AR-dependent CRPC.

Mutant-specific inhibitors provide effective anticancer therapies through preferential inhibition of oncogenic signaling without compromising normal cell functions. A

mutant specific BRAF inhibitor, vemurafenib, specifically targets oncogenic MAPK signaling associated with BRAF V600mut for effective targeted therapies [436]. Imatinib and gefitinib improve the outcomes of patients with tumors harboring BCR-ABL fusion and EGFR mutation, respectively, [437]. Besides SDH and FH mutations, isocitrate dehydrogenase 1 (IDH1) and 2 (IDH2) mutations are the only known oncogenic mutations of metabolic enzymes [438]. 2-HG is virtually absent in normal tissues, unlike the two other well-characterized oncometabolites succinate and fumarate. 2-HG has been reported to reach millimolar concentrations in tumors with mutant IDH1 and IDH2 [439]. Ivosidenib (AG-120) and enasidenib (AG-221) allosterically inhibit these neomorphic functions of mutant IDH1 and IDH2, respectively, [438]. Targeting mutant IDH is attractive but limited in PCa: IDH1 mutations account for only 0.3–2.7% of PCa incidence, while neomorphic IDH2 mutations are not reported [440].

The recent clinical success of PARP inhibitors in BRCA-less cancers led researchers to explore other synthetic lethal interactions [441,442]. Development of genome-wide RNAi-mediated knockdown and CRISPR knockout screens allowed researchers to discover cancer-specific metabolic vulnerabilities, including synthetic lethal interactions between *PRMT5* inhibition and *MTAP* deletion [443,444]. Furthermore, simultaneous perturbation of functional paralogs led to the identification of the dual deletion of dual-specificity phosphatase DUSP4 and DUSP6 as digenic synthetic lethal targets in BRAF- and NRAS-mutant melanoma with persistent hyperactivation of MAPK signaling [445]. These approaches taken in non-PCa cases can be simply extended to PCa studies. Effective new targets relevant to the most common oncogenic drivers (PTEN, P53, MYC) remain to be uncovered [442].

Increased demand for exogenous supply of amino acids causes auxotrophy for non-essential amino acids [446]. Application of therapeutic enzymes is an emerging field of research and leads to systemic depletion of specific metabolites, especially those that tumors cells are addicted to. Asparaginase was the first Food and Drug Administration (FDA)-approved amino acid degrading enzyme used to treat acute lymphoblastic leukemia (ALL) [447]. Depletion of arginine by administration of recombinant proteins such as the human arginase and the bacterial arginine deiminase is being explored for the treatment of arginine-auxotrophic tumors, including ASS1-deficient PCa [448]. Introduction of cysteinase suppressed tumor cell proliferation in patient-derived xenografts (PDXs) derived from PCa [449]. Dietary restriction of amino acids represents another strategy for selective auxotrophic tumors [450]. Serine starvation is effective in p53-deficient tumors, while glycine deprivation is well fitted to treat rapid cancer cell proliferation [204,451,452].

Table 1. Agents targeting metabolism in preclinical and clinical studies. (**A**) Preclinical studies; (**B**) Clinical studies.

(**A**)

Target	Agent	Modes of Action	Study Design and Results	Reference
Glycolysis				
PKM2	TEPP-46	Small molecule pyruvate kinase activators have been identified that stabilize the PKM2 tetramer to promote an enzyme state similar to PKM1.	Activation of PKM2 led to tumor inhibition in mice with prostate specific deletion of PTEN.	[420]
LDHA	GSK2837808A	A potent, selective and NADH-competitive inhibitor of LDH-A.	Combination therapy with radiation improved antitumoral T-cell response and reduced tumor progression in pancreatic cancer models.	[453,454]
MCT1	AR-C122982/SR13800	Selective MCT1 inhibitor.	Antitumor effects on MYC-overexpressing breast cancer and neuroblastoma in preclinical models.	[455,456]
Mitochondrial metabolism				
MPC	MSDC-0160	Thiazolidinedione that reversibly binds to MPC1 and 2 heterodimer.	Inhibition of tumor growth in preclinical models of both castration-sensitive and resistant AR-driven prostate tumors.	[147,457]
MPC	UK-5099	Inhibits the MPC complex by binding to Cys54 of MPC2 in a covalent manner.	Inhibition of tumor growth in preclinical models of both castration-sensitive and resistant AR-driven prostate tumors.	[458]
Complex V	Gboxin	Inhibits Complex V (F0F1-ATP synthase).	Antitumorigenic effects on in vivo and in vitro glioblastoma model.	[459]
Amino acid metabolism				
ASCT2	V-9302	Competitive small molecule antagonist of ASCT2, leading to decrease in glutamine influx.	Antitumor effects on preclinical models including xenografts from triple negative breast cancer cell line HCC-1806.	[460]
			Improves antitumor T cell activity in triple-negative breast cancer.	[461]
GLS1 (KGA and GAC)	CB-839/Telaglenastat	Orally available potent allosteric inhibitor for GLS1.	Antitumor effects on triple negative breast cancer models and lung tumor models.	[425,462,463]
IDO1	BMS-986205	Inhibits apo-IDO1 binding to heme which is co-factor for IDO1 catalytic action.	Iinrodostat potently and specifically inhibits IDO1 to block an immunosuppressive mechanism that could be responsible for tumor escape from host immune surveillance with favorable PK/PD characteristics that support clinical development.	[464]

Table 1. *Cont.*

Fatty acid metabolism					
SREBP	Fatostatin	Prevent nuclear translocation of SREBPs by inhibiting the SREBP cleavage-activating protein (SCAP) that facilitates the ER-Golgi translocation of SREBPs.		Inhibition of SREBP and AR transcription networks is associated with antitumorigenic effects on in vitro and in vivo PCa models.	[465,466]
FASN	IPI-9119	Inhibits the FASN thioesterase domain by promoting acylation of the catalytic serine.		Tumor inhibition is associated with altered fatty acid metabolism and reduced AR signaling.	[86]
ACC1 and ACC2	ND-654	Allosteric inhibitor of the ACC (Acetyl-CoA carboxylase) enzymes that prevents dimerization of ACC.		Inhibition of de novo lipogenesis in liver and the development of hepatocellular carcinoma.	[467]
ACC1 and ACC2	ND-646	Allosteric inhibitor of the ACC (Acetyl-CoA carboxylase) enzymes that prevents dimerization of ACC.		Suppression of lung tumor growth in the mouse models of non-small cell lung cancer.	[468]
(**B**)					
Target	**Agent**	**Modes of Action**	**Clinical Relevance (NCT Number, Study Phase, etc.)**	**Study Design**	**Reference**
Glycolysis					
MCT1 and MCT2	AZD3965	A potent pyrimidine-derived inhibitor of MCT1 with activity against MCT2 but selectivity over MCT3 and MCT4.	NCT01791595 (Phase 1)	Trial of AZD3965 in patients with advanced cancer.	[469–472]
Mitochondrial metabolism					
PDH/alfa-KGDH	CPI-613/devimistat	Lipoate analog that inhibits two lipoate-dependent enzymes, ketoglutarate dehydrogenase (KGDH) and pyruvate dehydrogenase (PDH).	NCT03504423 (Phase 3)	Study evaluating efficacy and safety of thymidylate synthase inhibitor FFX versus combination of CPI-613 with mFFX (modified FFX) in patients with metastatic adenocarcinoma of the pancreas.	[473–477]
			NCT03435289 (Phase 1)	CPI-613 with nucleoside metabolic inhibitor Gemcitabine and albumin-bound paclitaxel Nab-paclitaxel for patients with advanced or metastatic pancreatic cancer.	
mutant IDH2	Enasidenib/AG-221	Allosteric binding of AG-221 stabilizes inhibitory open conformation of the mutant IDH2.	FDA approval	Treatment of relapsed or refractory acute myeloid leukemia (AML).	[478]

Table 1. *Cont.*

Complex I, PEN2, polypharmaco-logic	Metformin	Inhibits complex I to decrease OXPHOS activity. Metformin binds to PEN2 (presenilin 2) to form a complex with ATP6AP1, a subunit of the v-ATPase8 and inhibit v-ATPase.	NCT02614859 (Phase 2)	Bicalutamide with or without metformin for biochemical recurrence in overweight or obese PCa patients (BIMET-1).	[479–483]
			NCT02339168 (Phase 1)	Enzalutamide and metformin hydrochloride in treating patients with hormone-resistant PCa.	
			NCT03291938 (Phase 1)	Test in advanced cancers.	
			NCT02339168 (Phase 1)	Enzalutamide and metformin hydrochloride in treating patients with hormone-resistant PCa.	
Complex I	IACS-010759	Binds to inhibit complex I (NADH ubiquinone oxidoreductase).	NCT02882321 (Phase 1)	Treating patients with relapsed or refractory acute myeloid leukemia (AML).	[484,485]
Complex I	IM156	Orally available metformin derivative.	NCT03272256 (Phase 1)	Patients with advanced solid tumor and lymphoma.	[486–488]
Amino acid metabolism					
LAT1	JPH203	Selective L-type amino acid transporter 1 inhibitor.	UMIN000016546 (Clinical trial registration in Japan)	Exploratory analyses of biomarker using change of blood free amino-acid concentration related to JPH203 (LAT1 inhibitor).	[489–491]
GLS1 (KGA and GAC)	CB-839/Telaglenastat	Orally available potent allosteric inhibitor for GLS1.	NCT03875313 (Phase 1b/2)	Combination with PARP inhibitor Talazoparib in patients with solid tumors.	[425,462,492]
			NCT04250545 (Phase 1)	To determine the safety and tolerability of CB-839 combination with mTORC1/2 inhibitor MLN0128 (sapanisertib) and determine the recommended phase 2 dose (RP2D) of the combination.	
GLS1 (KGA and GAC)	IPN60090	Orally available potent allosteric inhibitor for GLS1.	NCT03894540 (Phase 1)	Dose escalation and dose expansion study of IPN60090 in patients with advanced solid tumors.	[493]

Table 1. *Cont.*

Glutamine metabolism	Sirpiglenastat/DRP-104	Pro-drug form of a broad acting glutamine antagonist that irreversibly inhibits multiple enzymes involved in glutamine metabolism. Different from JHU083.	NCT04471415 (Phase1/2)	As single agent and in combination with checkpoint inhibitor atezolizumab in patients with advanced solid tumors.	[494]
IDO1	Epacadostat/INCB024360	Orally available reversible competitive potent IDO1 inhibitor.	NCT03516708 (Phase 1)	Epacadostat (INCB024360) added to preoperative chemoradiation in patients with locally advanced rectal cancer.	[495]
			NCT03589651 (Phase 1)	Checkpoint inhibitor INCMGA00012 in combination with other therapies in patients with advanced solid tumors.	[494]
IDO1	Indoximod	Orally available reversible competitive potent IDO1 inhibitor.	NCT02073123 (Phase 1/2)	IDO inhibitor in combination with checkpoint inhibitors for adult patients with metastatic melanoma.	[334,464]
			NCT04049669 (Phase 2)	Indoximod with chemotherapy and radiation for relapsed brain tumors or newly diagnosed diffuse intrinsic pontine gliomas (DIPG).	
			NCT01560923 (Phase 2)	Combined therapy with Sipuleucel-T and Indoximod for patients with refractory metastatic PCa.	[334]
MAT2A	AG-270	Allosterically inhibits MAT2A (methionine adenosyltransferase 2A) activity by preventing product release, leading to decrease in intracellular SAM levels.	NCT03435250 (Phase 1)	Participants with advanced solid tumors or lymphoma With MTAP loss.	[496,497]
Fatty acid metabolism					
HMG-CoA reductase	statin, Atorvastatin	Competitive inhibitor for HMG-CoA reductase to decrease cholesterol level.	NCT04026230 (Phase 3)	Atorvastatin on PCa progression during ADT (ESTO2).	[390,391,498]
			NCT02003924 (Phase 3), PROSPER	Safety and efficacy study of enzalutamide in patients with nonmetastatic CRPC.	

Table 1. *Cont.*

			NCT01212991 (Phase 3), PREVAIL	Safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic PCa.	
			NCT00974311 (Phase 3), AFFIRM	Safety and efficacy study of MDV3100 in patients with CRPC who have been previously treated with docetaxel-based chemotherapy.	
				Retrospective analyses of all three trials pooled and AFFIRM + PREVAIL pooled revealed that statin but not metformin use was significantly associated with a reduced risk of death in enzalutamide-treated patients.	
FASN	TVB-2640	Inhibits the β-ketoacyl-ACP reductase activity of FASN.	NCT03179904 (Phase 2)	TVB-2640 and Trastuzumab (herceptin) in combination with paclitaxel or endocrine therapy for the treatment of HER2 positive metastatic breast cancer.	[499,500]
			NCT03808558 (Phase 2)	TVB-2640 in KRAS non-small cell lung carcinomas.	
ACC1 and ACC2	GS-0976/ND-630/NDI 010976/Firsocostat	Allosteric inhibitor of the ACC (Acetyl-CoA carboxylase) enzymes that prevents dimerization of ACC.	NCT03449446 (Phase 1)	Study to evaluate the safety and efficacy of Selonsertib, Firsocostat, Cilofexor, and combinations in participants with bridging fibrosis or compensated cirrhosis due to nonalcoholic steatohepatitis (NASH).	[501,502]
Another metabolism					
mutant IDH1	Ivosidenib/AG-120	Allosteric binding of Ivosidenib stabilizes inhibitory open conformation of the mutant IDH1 active site.	FDA approval	Newly diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation.	[503]
Sirt1	EX-527/Selisistat/ SEN0014196	Stabilize the closed enzyme conformation preventing product release.	NCT04184323 (Phase 2) terminated due to lack to funding	SIRT-1 antagonism for endometrial receptivity.	[504]
				This compound has reached Phase 2 clinical trials for Huntington's disease (HD) found to be safe and well tolerated in early HD patients at plasma levels within the therapeutic concentration range in preclinical HD models.	[505]

Table 1. *Cont.*

DHODH	Leflunomide	Competitive inhibitor for mitochondrial enzyme DHODH.	NCT03709446 (Phase1/2)	Treating patients with previously treated metastatic triple negative breast cancer.	[506,507]
			NCT04997993 (Phase 1)	Patients with PTEN-null advanced solid malignancies.	
ODC1	2-difluoromethyl ornithine (DFMO)/eflornithine	Competitive and irreversible inhibitor of ODC1.	NCT04301843 (Phase 2)	Eflornithine (DFMO) and etoposide for relapsed/refractory neuroblastoma.	[508,509]
			NCT01349881 (Phase 3)	Adenoma and second primary prevention trial.	

7. Concluding Remarks

There is a growing number of promising biomarkers, such as AR, SPOP, PTEN, AKT, RB1, BRCA1/2, PSMA, and CDK12, to inform treatment decisions for PCa. Despite considerable efforts with significant success, precision oncology in advanced PCa had to face challenges, including drug resistance and limited population who benefit from the related therapeutics [48].

Tumor metabolism has emerged as a highly attractive therapeutic target for a single therapy or in combination with chemotherapy and immunotherapy [35,39,41,46]. The recent FDA approval of inhibitors for IDH neomorphic mutants represents a milestone achievement in precision oncology in the context of cancer metabolism [438]. Understanding the multi-faceted metabolic interactions will help discover and develop reliable diagnostic and predictive markers for precision oncology applications [51,52,54,55]. Currently, however, there are a limited number of reliable metabolic biomarkers, including PET-based tumor imaging, that characterizes related metabolic pathways and bioenergetics, alterations in metabolic genes, and circulating oncometabolites.

Advancement in analytical technologies allow us to characterize tumor metabolism in different aspects. Matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI MSI) allows for spatial differentiation of metabolism in PCa tissue [510]. Though still challenging, single-cell metabolomics can be potentially used to optimize metabolome-based treatment decisions [511]. Tumor cells may rewire metabolic pathways to develop resistance to specific metabolic interference. In this regard, simultaneous blockade of multiple pathways may offer advantageous therapy as exemplified by JHU-083 [426]. CRISPR based genome-wide knockout screens have incredible opportunities to accelerate identification of synthetic lethal pairings for combined therapies targeting metabolism [442].

We have described the metabolic phenotypes, networks, and interactions in relation to the disease stages and the TME during PCa progression. In addition to AR, oncogenic drivers display distinct dominant metabolic dependencies. To develop effective metabolism-targeting precision therapies, it is crucial to further identify the unique metabolic signatures that define and support the malignant phenotypes of PCa, particularly that of CRPC.

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References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer statistics, 2022. *CA Cancer J. Clin.* **2022**, *72*, 7–33. [CrossRef] [PubMed]
2. Mostaghel, E.A.; Plymate, S.R.; Montgomery, B. Molecular pathways: Targeting resistance in the androgen receptor for therapeutic benefit. *Clin. Cancer Res.* **2014**, *20*, 791–798. [CrossRef] [PubMed]
3. Uo, T.; Plymate, S.R.; Sprenger, C.C. Allosteric alterations in the androgen receptor and activity in prostate cancer. *Endocr. Relat. Cancer* **2017**, *24*, R335–R348. [CrossRef] [PubMed]

4. Chen, C.D.; Welsbie, D.S.; Tran, C.; Baek, S.H.; Chen, R.; Vessella, R.; Rosenfeld, M.G.; Sawyers, C.L. Molecular determinants of resistance to antiandrogen therapy. *Nat. Med.* **2004**, *10*, 33–39. [CrossRef] [PubMed]
5. Watson, P.A.; Arora, V.K.; Sawyers, C.L. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat. Rev. Cancer* **2015**, *15*, 701–711. [CrossRef]
6. Uo, T.; Plymate, S.R.; Sprenger, C.C. The potential of AR-V7 as a therapeutic target. *Expert Opin. Ther. Targets* **2018**, *22*, 201–216. [CrossRef]
7. Ferraldeschi, R.; Welti, J.; Luo, J.; Attard, G.; de Bono, J.S. Targeting the androgen receptor pathway in castration-resistant prostate cancer: Progresses and prospects. *Oncogene* **2015**, *34*, 1745–1757. [CrossRef]
8. Westaby, D.; Fenor de La Maza, M.L.D.; Paschalis, A.; Jimenez-Vacas, J.M.; Welti, J.; de Bono, J.; Sharp, A. A New Old Target: Androgen Receptor Signaling and Advanced Prostate Cancer. *Annu. Rev. Pharmacol. Toxicol.* **2022**, *62*, 131–153. [CrossRef]
9. Beltran, H.; Hruszkewycz, A.; Scher, H.I.; Hildesheim, J.; Isaacs, J.; Yu, E.Y.; Kelly, K.; Lin, D.; Dicker, A.; Arnold, J.; et al. The Role of Lineage Plasticity in Prostate Cancer Therapy Resistance. *Clin. Cancer Res.* **2019**, *25*, 6916–6924. [CrossRef]
10. Beltran, H.; Tomlins, S.; Aparicio, A.; Arora, V.; Rickman, D.; Ayala, G.; Huang, J.; True, L.; Gleave, M.E.; Soule, H.; et al. Aggressive variants of castration-resistant prostate cancer. *Clin. Cancer Res.* **2014**, *20*, 2846–2850. [CrossRef]
11. Bluemn, E.G.; Coleman, I.M.; Lucas, J.M.; Coleman, R.T.; Hernandez-Lopez, S.; Tharakan, R.; Bianchi-Frias, D.; Dumpit, R.F.; Kaipainen, A.; Corella, A.N.; et al. Androgen Receptor Pathway-Independent Prostate Cancer Is Sustained through FGF Signaling. *Cancer Cell* **2017**, *32*, 474–489.e476. [CrossRef]
12. Myung, J.K.; Banuelos, C.A.; Fernandez, J.G.; Mawji, N.R.; Wang, J.; Tien, A.H. An androgen receptor N-terminal domain antagonist for treating prostate cancer. *J. Clin. Investig.* **2013**, *123*, 2948–2960. [CrossRef]
13. Monaghan, A.E.; McEwan, I.J. A sting in the tail: The N-terminal domain of the androgen receptor as a drug target. *Asian J.* **2016**, *18*, 687–694. [CrossRef]
14. Asangani, I.A.; Dommeti, V.L.; Wang, X.; Malik, R.; Cieslik, M.; Yang, R.; Escara-Wilke, J.; Wilder-Romans, K.; Dhanireddy, S.; Engelke, C.; et al. Therapeutic targeting of BET bromodomain proteins in castration-resistant prostate cancer. *Nature* **2014**, *510*, 278–282. [CrossRef]
15. Yang, Y.C.; Banuelos, C.A.; Mawji, N.R.; Wang, J.; Kato, M.; Haile, S.; McEwan, I.J.; Plymate, S.; Sadar, M.D. Targeting Androgen Receptor Activation Function-1 with EPI to Overcome Resistance Mechanisms in Castration-Resistant Prostate Cancer. *Clin. Cancer Res.* **2016**, *22*, 4466–4477. [CrossRef]
16. Antonarakis, E.S.; Chandhasin, C.; Osbourne, E.; Luo, J.; Sadar, M.D.; Perabo, F. Targeting the N-Terminal Domain of the Androgen Receptor: A New Approach for the Treatment of Advanced Prostate Cancer. *Oncologist* **2016**, *21*, 1427–1435. [CrossRef]
17. Hong, N.H.; Le Moigne, R.; Pearson, P.; Lauriault, V.; Banuelos, C.A.; Mawji, N.R.; Tam, T.; Wang, J.; Virsik, P.; Andersen, R.J.; et al. 181 Poster—The preclinical characterization of the N-terminal domain androgen receptor inhibitor, EPI-7386, for the treatment of prostate cancer. *Eur. J. Cancer* **2020**, *138*, S51. [CrossRef]
18. Moigne, R.L.; Banuelos, C.A.; Mawji, N.R.; Tam, T.; Wang, J.; Jian, K.; Andersen, R.J.; Cesano, A.; Sadar, M.D.; Zhou, H.J.; et al. 503P—EPI-7386 is a novel N-terminal domain androgen receptor inhibitor for the treatment of prostate cancer. *Ann. Oncol.* **2019**, *30*, v189–v190. [CrossRef]
19. Ma, B.; Fan, Y.; Zhang, D.; Wei, Y.; Jian, Y.; Liu, D.; Wang, Z.; Gao, Y.; Ma, J.; Chen, Y.; et al. De Novo Design of an Androgen Receptor DNA Binding Domain-Targeted peptide PROTAC for Prostate Cancer Therapy. *Adv. Sci.* **2022**, *9*, 2201859. [CrossRef]
20. Hong, N.H.; Biannic, B.; Virsik, P.; Zhou, H.-J.; Moigne, R.L. Abstract 429: Androgen receptor (AR) N-terminal domain degraders can degrade AR full length and AR splice variants in CRPC preclinical models. *Cancer Res.* **2022**, *82*, 429. [CrossRef]
21. Hofman, M.S.; Emmett, L.; Sandhu, S.; Iravani, A.; Joshua, A.M.; Goh, J.C.; Pattison, D.A.; Tan, T.H.; Kirkwood, I.D.; Francis, R.J.; et al. TheraP: 177Lu-PSMA-617 (LuPSMA) versus cabazitaxel in metastatic castration-resistant prostate cancer (mCRPC) progressing after docetaxel—Overall survival after median follow-up of 3 years (ANZUP 1603). *J. Clin. Oncol.* **2022**, *40*, 5000. [CrossRef]
22. Hofman, M.S.; Emmett, L.; Sandhu, S.; Iravani, A.; Joshua, A.M.; Goh, J.C.; Pattison, D.A.; Tan, T.H.; Kirkwood, I.D.; Ng, S.; et al. [(177)Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): A randomised, open-label, phase 2 trial. *Lancet* **2021**, *397*, 797–804. [CrossRef]
23. Sartor, O.; de Bono, J.; Chi, K.N.; Fizazi, K.; Herrmann, K.; Rahbar, K.; Tagawa, S.T.; Nordquist, L.T.; Vaishampayan, N.; El-Haddad, G.; et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N. Engl. J. Med.* **2021**, *385*, 1091–1103. [CrossRef] [PubMed]
24. Sun, M.; Niaz, M.O.; Nelson, A.; Skafida, M.; Niaz, M.J. Review of 177Lu-PSMA-617 in Patients With Metastatic Castration-Resistant Prostate Cancer. *Cureus* **2020**, *12*, e8921. [CrossRef]
25. Mateo, J.; Carreira, S.; Sandhu, S.; Miranda, S.; Mossop, H.; Perez-Lopez, R.; Nava Rodrigues, D.; Robinson, D.; Omlin, A.; Tunariu, N.; et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. *N. Engl. J. Med.* **2015**, *373*, 1697–1708. [CrossRef] [PubMed]
26. Schiewer, M.J.; Knudsen, K.E. DNA Damage Response in Prostate Cancer. *Cold Spring Harb. Perspect. Med.* **2019**, *9*, a030486. [CrossRef]
27. Mollica, V.; Rizzo, A.; Rosellini, M.; Marchetti, A.; Ricci, A.D.; Cimadamore, A.; Scarpelli, M.; Bonucci, C.; Andrini, E.; Errani, C.; et al. Bone Targeting Agents in Patients with Metastatic Prostate Cancer: State of the Art. *Cancers* **2021**, *13*, 546. [CrossRef]

28. Furesi, G.; Rauner, M.; Hofbauer, L.C. Emerging Players in Prostate Cancer-Bone Niche Communication. *Trends Cancer* **2021**, *7*, 112–121. [CrossRef]
29. He, Y.; Xu, W.; Xiao, Y.T.; Huang, H.; Gu, D.; Ren, S. Targeting signaling pathways in prostate cancer: Mechanisms and clinical trials. *Signal Transduct. Target. Ther.* **2022**, *7*, 198. [CrossRef]
30. Sandhu, S.; Moore, C.M.; Chiong, E.; Beltran, H.; Bristow, R.G.; Williams, S.G. Prostate cancer. *Lancet* **2021**, *398*, 1075–1090. [CrossRef]
31. Hsu, P.P.; Sabatini, D.M. Cancer cell metabolism: Warburg and beyond. *Cell* **2008**, *134*, 703–707. [CrossRef]
32. Vander Heiden, M.G.; Cantley, L.C.; Thompson, C.B. Understanding the Warburg effect: The metabolic requirements of cell proliferation. *Science* **2009**, *324*, 1029–1033. [CrossRef]
33. Koppenol, W.H.; Bounds, P.L.; Dang, C.V. Otto Warburg's contributions to current concepts of cancer metabolism. *Nat. Rev. Cancer* **2011**, *11*, 325–337. [CrossRef]
34. Landau, B.R.; Laszlo, J.; Stengle, J.; Burk, D. Certain Metabolic and Pharmacologic Effects in Cancer Patients Given Infusions of 2-Deoxy-D-Glucose. *JNCI J. Natl. Cancer Inst.* **1958**, *21*, 485–494. [CrossRef]
35. Stine, Z.E.; Schug, Z.T.; Salvino, J.M.; Dang, C.V. Targeting cancer metabolism in the era of precision oncology. *Nat. Rev. Drug Discov.* **2022**, *21*, 141–162. [CrossRef]
36. Farber, S.; Diamond, L.K.; Mercer, R.D.; Sylvester, R.F.; Wolff, J.A. Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist, 4-Aminopteroyl-Glutamic Acid (Aminopterin). *N. Engl. J. Med.* **1948**, *238*, 787–793. [CrossRef]
37. Miller, D.R. A tribute to Sidney Farber—The father of modern chemotherapy. *Br. J. Haematol.* **2006**, *134*, 20–26. [CrossRef]
38. Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell* **2000**, *100*, 57–70. [CrossRef]
39. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. *Cell* **2011**, *144*, 646–674. [CrossRef]
40. Dang, C.V. MYC, metabolism, cell growth, and tumorigenesis. *Cold Spring Harb. Perspect. Med.* **2013**, *3*, a014217. [CrossRef]
41. Hanahan, D. Hallmarks of Cancer: New Dimensions. *Cancer Discov.* **2022**, *12*, 31–46. [CrossRef] [PubMed]
42. DeBerardinis, R.J.; Chandel, N.S. Fundamentals of cancer metabolism. *Sci. Adv.* **2016**, *2*, e1600200. [CrossRef] [PubMed]
43. DeBerardinis, R.J.; Keshari, K.R. Metabolic analysis as a driver for discovery, diagnosis, and therapy. *Cell* **2022**, *185*, 2678–2689. [CrossRef] [PubMed]
44. Di Gregorio, E.; Miolo, G.; Saorin, A.; Steffan, A.; Corona, G. From Metabolism to Genetics and Vice Versa: The Rising Role of Oncometabolites in Cancer Development and Therapy. *Int. J. Mol. Sci* **2021**, *22*, 5574. [CrossRef]
45. Yang, M.; Soga, T.; Pollard, P.J. Oncometabolites: Linking altered metabolism with cancer. *J. Clin. Investig.* **2013**, *123*, 3652–3658. [CrossRef]
46. Luengo, A.; Gui, D.Y.; Vander Heiden, M.G. Targeting Metabolism for Cancer Therapy. *Cell Chem. Biol.* **2017**, *24*, 1161–1180. [CrossRef]
47. Ku, S.Y.; Gleave, M.E.; Beltran, H. Towards precision oncology in advanced prostate cancer. *Nat. Rev. Urol.* **2019**, *16*, 645–654. [CrossRef]
48. Mateo, J.; McKay, R.; Abida, W.; Aggarwal, R.; Alumkal, J.; Alva, A.; Feng, F.; Gao, X.; Graff, J.; Hussain, M.; et al. Accelerating precision medicine in metastatic prostate cancer. *Nat. Cancer* **2020**, *1*, 1041–1053. [CrossRef]
49. Awad, D.; Pulliam, T.L.; Lin, C.; Wilkenfeld, S.R.; Frigo, D.E. Delineation of the androgen-regulated signaling pathways in prostate cancer facilitates the development of novel therapeutic approaches. *Curr. Opin. Pharmacol.* **2018**, *41*, 1–11. [CrossRef]
50. Uo, T.; Sprenger, C.C.; Plymate, S.R. Androgen Receptor Signaling and Metabolic and Cellular Plasticity During Progression to Castration Resistant Prostate Cancer. *Front. Oncol.* **2020**, *10*, 580617. [CrossRef]
51. Bader, D.A.; McGuire, S.E. Tumour metabolism and its unique properties in prostate adenocarcinoma. *Nat. Rev. Urol.* **2020**, *17*, 214–231. [CrossRef]
52. Giunchi, F.; Fiorentino, M.; Loda, M. The Metabolic Landscape of Prostate Cancer. *Eur. Urol. Oncol.* **2019**, *2*, 28–36. [CrossRef] [PubMed]
53. Zadra, G.; Loda, M. Metabolic Vulnerabilities of Prostate Cancer: Diagnostic and Therapeutic Opportunities. *Cold Spring Harb. Perspect. Med.* **2018**, *8*, a030569. [CrossRef] [PubMed]
54. Peitzsch, C.; Gorodetska, I.; Klusa, D.; Shi, Q.; Alves, T.C.; Pantel, K.; Dubrovska, A. Metabolic regulation of prostate cancer heterogeneity and plasticity. *Semin. Cancer Biol.* **2022**, *82*, 94–119. [CrossRef] [PubMed]
55. Fidelito, G.; Watt, M.J.; Taylor, R.A. Personalized Medicine for Prostate Cancer: Is Targeting Metabolism a Reality? *Front. Oncol.* **2021**, *11*, 778761. [CrossRef] [PubMed]
56. Kolenko, V.; Teper, E.; Kutikov, A.; Uzzo, R. Zinc and zinc transporters in prostate carcinogenesis. *Nat. Rev. Urol.* **2013**, *10*, 219–226. [CrossRef]
57. Costello, L.C.; Franklin, R.B. A comprehensive review of the role of zinc in normal prostate function and metabolism; and its implications in prostate cancer. *Arch. Biochem. Biophys.* **2016**, *611*, 100–112. [CrossRef]
58. Franklin, R.B.; Zou, J.; Yu, Z.; Costello, L.C. EAAC1 is expressed in rat and human prostate epithelial cells; functions as a high-affinity L-aspartate transporter; and is regulated by prolactin and testosterone. *BMC Biochem.* **2006**, *7*, 10. [CrossRef]
59. Franklin, R.B.; Kukoyi, B.I.; Akuffo, V.; Costello, L.C. Testosterone stimulation of mitochondrial aspartate aminotransferase levels and biosynthesis in rat ventral prostate. *J. Steroid Biochem.* **1987**, *28*, 247–256. [CrossRef]
60. Costello, L.C.; Liu, Y.; Zou, J.; Franklin, R.B. The pyruvate dehydrogenase E1 alpha gene is testosterone and prolactin regulated in prostate epithelial cells. *Endocr. Res.* **2000**, *26*, 23–39. [CrossRef]

61. Franklin, R.B.; Feng, P.; Milon, B.; Desouki, M.M.; Singh, K.K.; Kajdacsy-Balla, A.; Bagasra, O.; Costello, L.C. hZIP1 zinc uptake transporter down regulation and zinc depletion in prostate cancer. *Mol. Cancer* **2005**, *4*, 32. [CrossRef]
62. Costello, L.C.; Franklin, R.B. The clinical relevance of the metabolism of prostate cancer; zinc and tumor suppression: Connecting the dots. *Mol. Cancer* **2006**, *5*, 17. [CrossRef]
63. Jadvar, H. Is There Use for FDG-PET in Prostate Cancer? *Semin. Nucl. Med.* **2016**, *46*, 502–506. [CrossRef]
64. Sahin, E.; Elboga, U.; Kalender, E.; Basibuyuk, M.; Demir, H.D.; Celen, Y.Z. Clinical significance of incidental FDG uptake in the prostate gland detected by PET/CT. *Int. J. Clin. Exp. Med.* **2015**, *8*, 10577–10585.
65. Taplin, M.E.; Bubley, G.J.; Shuster, T.D.; Frantz, M.E.; Spooner, A.E.; Ogata, G.K.; Keer, H.N.; Balk, S.P. Mutation of the androgen-receptor gene in metastatic androgen-independent prostate cancer. *N. Engl. J. Med.* **1995**, *332*, 1393–1398. [CrossRef] [PubMed]
66. Taylor, B.S.; Schultz, N.; Hieronymus, H.; Gopalan, A.; Xiao, Y.; Carver, B.S.; Arora, V.K.; Kaushik, P.; Cerami, E.; Reva, B.; et al. Integrative genomic profiling of human prostate cancer. *Cancer Cell* **2010**, *18*, 11–22. [CrossRef] [PubMed]
67. Koivisto, P.; Kononen, J.; Palmberg, C.; Tammela, T.; Hyytinen, E.; Isola, J.; Trapman, J.; Cleutjens, K.; Noordzij, A.; Visakorpi, T.; et al. Androgen receptor gene amplification: A possible molecular mechanism for androgen deprivation therapy failure in prostate cancer. *Cancer Res.* **1997**, *57*, 314–319. [PubMed]
68. Buchanan, G.; Greenberg, N.M.; Scher, H.I.; Harris, J.M.; Marshall, V.R.; Tilley, W.D. Collocation of androgen receptor gene mutations in prostate cancer. *Clin. Cancer Res.* **2001**, *7*, 1273–1281. [PubMed]
69. Grasso, C.S.; Wu, Y.M.; Robinson, D.R.; Cao, X.; Dhanasekaran, S.M.; Khan, A.P.; Quist, M.J.; Jing, X.; Lonigro, R.J.; Brenner, J.C.; et al. The mutational landscape of lethal castration-resistant prostate cancer. *Nature* **2012**, *487*, 239–243. [CrossRef]
70. Dehm, S.M.; Schmidt, L.J.; Heemers, H.V.; Vessella, R.L.; Tindall, D.J. Splicing of a novel androgen receptor exon generates a constitutively active androgen receptor that mediates prostate cancer therapy resistance. *Cancer Res.* **2008**, *68*, 5469–5477. [CrossRef]
71. Lu, C.; Luo, J. Decoding the androgen receptor splice variants. *Transl. Androl. Urol.* **2013**, *2*, 178–186. [CrossRef]
72. Tran, C.; Ouk, S.; Clegg, N.J.; Chen, Y.; Watson, P.A.; Arora, V.; Wongvipat, J.; Smith-Jones, P.M.; Yoo, D.; Kwon, A.; et al. Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science* **2009**, *324*, 787–790. [CrossRef]
73. Clegg, N.J.; Wongvipat, J.; Joseph, J.D.; Tran, C.; Ouk, S.; Dilhas, A.; Chen, Y.; Grillot, K.; Bischoff, E.D.; Cai, L.; et al. ARN-509: A novel antiandrogen for prostate cancer treatment. *Cancer Res.* **2012**, *72*, 1494–1503. [CrossRef]
74. Scher, H.I.; Fizazi, K.; Saad, F.; Taplin, M.E.; Sternberg, C.N.; Miller, K.; de Wit, R.; Mulders, P.; Chi, K.N.; Shore, N.D.; et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* **2012**, *367*, 1187–1197. [CrossRef]
75. Smith, M.R.; Saad, F.; Chowdhury, S.; Oudard, S.; Hadaschik, B.A.; Graff, J.N.; Olmos, D.; Mainwaring, P.N.; Lee, J.Y.; Uemura, H.; et al. Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N. Engl. J. Med.* **2018**, *378*, 1408–1418. [CrossRef]
76. Berchuck, J.E.; Viscuse, P.V.; Beltran, H.; Aparicio, A. Clinical considerations for the management of androgen indifferent prostate cancer. *Prostate Cancer Prostatic Dis.* **2021**, *24*, 623–637. [CrossRef]
77. Beltran, H.; Tagawa, S.T.; Park, K.; MacDonald, T.; Milowsky, M.I.; Mosquera, J.M.; Rubin, M.A.; Nanus, D.M. Challenges in recognizing treatment-related neuroendocrine prostate cancer. *J. Clin. Oncol.* **2012**, *30*, e386-9. [CrossRef]
78. Beltran, H.; Rickman, D.S.; Park, K.; Chae, S.S.; Sboner, A.; MacDonald, T.Y.; Wang, Y.; Sheikh, K.L.; Terry, S.; Tagawa, S.T.; et al. Molecular characterization of neuroendocrine prostate cancer and identification of new drug targets. *Cancer Discov.* **2011**, *1*, 487–495. [CrossRef]
79. Culine, S.; El Demery, M.; Lamy, P.J.; Iborra, F.; Avances, C.; Pinguet, F. Docetaxel and cisplatin in patients with metastatic androgen independent prostate cancer and circulating neuroendocrine markers. *J. Urol.* **2007**, *178*, 844–848, discussion 848. [CrossRef]
80. Flechon, A.; Pouessel, D.; Ferlay, C.; Perol, D.; Beuzeboc, P.; Gravis, G.; Joly, F.; Oudard, S.; Deplanque, G.; Zanetta, S.; et al. Phase II study of carboplatin and etoposide in patients with anaplastic progressive metastatic castration-resistant prostate cancer (mCRPC) with or without neuroendocrine differentiation: Results of the French Genito-Urinary Tumor Group (GETUG) P01 trial. *Ann. Oncol.* **2011**, *22*, 2476–2481. [CrossRef]
81. Saunders, L.R.; Bankovich, A.J.; Anderson, W.C.; Aujay, M.A.; Bheddah, S.; Black, K.; Desai, R.; Escarpe, P.A.; Hampl, J.; Laysang, A.; et al. A DLL3-targeted antibody-drug conjugate eradicates high-grade pulmonary neuroendocrine tumor-initiating cells in vivo. *Sci. Transl. Med.* **2015**, *7*, 302ra136. [CrossRef] [PubMed]
82. Zhang, W.; Liu, B.; Wu, W.; Li, L.; Broom, B.M.; Basourakos, S.P.; Korentzelos, D.; Luan, Y.; Wang, J.; Yang, G.; et al. Targeting the MYCN-PARP-DNA Damage Response Pathway in Neuroendocrine Prostate Cancer. *Clin. Cancer Res.* **2018**, *24*, 696–707. [CrossRef] [PubMed]
83. Shafi, A.A.; Putluri, V.; Arnold, J.M.; Tsouko, E.; Maity, S.; Roberts, J.M.; Coarfa, C.; Frigo, D.E.; Putluri, N.; Sreekumar, A.; et al. Differential regulation of metabolic pathways by androgen receptor (AR) and its constitutively active splice variant, AR-V7, in prostate cancer cells. *Oncotarget* **2015**, *6*, 31997–32012. [CrossRef] [PubMed]
84. Swinnen, J.V.; Heemers, H.; van de Sande, T.; de Schrijver, E.; Brusselmans, K.; Heyns, W.; Verhoeven, G. Androgens, lipogenesis and prostate cancer. *J. Steroid Biochem. Mol. Biol.* **2004**, *92*, 273–279. [CrossRef] [PubMed]

85. Ettinger, S.L.; Sobel, R.; Whitmore, T.G.; Akbari, M.; Bradley, D.R.; Gleave, M.E.; Nelson, C.C. Dysregulation of sterol response element-binding proteins and downstream effectors in prostate cancer during progression to androgen independence. *Cancer Res.* **2004**, *64*, 2212–2221. [CrossRef]
86. Zadra, G.; Ribeiro, C.F.; Chetta, P.; Ho, Y.; Cacciatore, S.; Gao, X.; Syamala, S.; Bango, C.; Photopoulos, C.; Huang, Y.; et al. Inhibition of de novo lipogenesis targets androgen receptor signaling in castration-resistant prostate cancer. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 631–640. [CrossRef]
87. Rossi, S.; Graner, E.; Febbo, P.; Weinstein, L.; Bhattacharya, N.; Onody, T.; Bubley, G.; Balk, S.; Loda, M. Fatty acid synthase expression defines distinct molecular signatures in prostate cancer. *Mol. Cancer Res.* **2003**, *1*, 707–715.
88. Jadvar, H. Prostate cancer: PET with 18F-FDG, 18F- or 11C-acetate, and 18F- or 11C-choline. *J. Nucl. Med.* **2011**, *52*, 81–89. [CrossRef]
89. Emonds, K.M.; Swinnen, J.V.; Lerut, E.; Koole, M.; Mortelmans, L.; Mottaghy, F.M. Evaluation of androgen-induced effects on the uptake of [18F]FDG, [11C]choline and [11C]acetate in an androgen-sensitive and androgen-independent prostate cancer xenograft model. *EJNMMI Res.* **2013**, *3*, 31. [CrossRef]
90. Bakht, M.K.; Lovnicki, J.M.; Tubman, J.; Stringer, K.F.; Chiaramonte, J.; Reynolds, M.R.; Derecichei, I.; Ferraiuolo, R.M.; Fifield, B.A.; Lubanska, D.; et al. Differential Expression of Glucose Transporters and Hexokinases in Prostate Cancer with a Neuroendocrine Gene Signature: A Mechanistic Perspective for ^{18}F-FDG Imaging of PSMA-Suppressed Tumors. *J. Nucl. Med.* **2020**, *61*, 904–910. [CrossRef]
91. Lewis, D.Y.; Boren, J.; Shaw, G.L.; Bielik, R.; Ramos-Montoya, A.; Larkin, T.J.; Martins, C.P.; Neal, D.E.; Soloviev, D.; Brindle, K.M. Late Imaging with [1-^{11}C]Acetate Improves Detection of Tumor Fatty Acid Synthesis with PET. *J. Nucl. Med.* **2014**, *55*, 1144–1149. [CrossRef]
92. Yu, E.Y.; Muzi, M.; Hackenbracht, J.A.; Rezvani, B.B.; Link, J.M.; Montgomery, R.B.; Higano, C.S.; Eary, J.F.; Mankoff, D.A. C11-acetate and F-18 FDG PET for men with prostate cancer bone metastases: Relative findings and response to therapy. *Clin. Nucl. Med.* **2011**, *36*, 192–198. [CrossRef]
93. Fox, J.J.; Gavane, S.C.; Blanc-Autran, E.; Nehmeh, S.; Gonen, M.; Beattie, B.; Vargas, H.A.; Schoder, H.; Humm, J.L.; Fine, S.W.; et al. Positron Emission Tomography/Computed Tomography-Based Assessments of Androgen Receptor Expression and Glycolytic Activity as a Prognostic Biomarker for Metastatic Castration-Resistant Prostate Cancer. *JAMA Oncol.* **2018**, *4*, 217–224. [CrossRef]
94. Liu, Y. FDG PET-CT demonstration of metastatic neuroendocrine tumor of prostate. *World J. Surg. Oncol.* **2008**, *6*, 64. [CrossRef]
95. Spratt, D.E.; Gavane, S.; Tarlinton, L.; Fareedy, S.B.; Doran, M.G.; Zelefsky, M.J.; Osborne, J.R. Utility of FDG-PET in clinical neuroendocrine prostate cancer. *Prostate* **2014**, *74*, 1153–1159. [CrossRef]
96. Sung, J.; Espiritu, J.I.; Segall, G.M.; Terris, M.K. Fluorodeoxyglucose positron emission tomography studies in the diagnosis and staging of clinically advanced prostate cancer. *BJU Int.* **2003**, *92*, 24–27. [CrossRef]
97. Momcilovic, M.; Jones, A.; Bailey, S.T.; Waldmann, C.M.; Li, R.; Lee, J.T.; Abdelhady, G.; Gomez, A.; Holloway, T.; Schmid, E.; et al. In vivo imaging of mitochondrial membrane potential in non-small-cell lung cancer. *Nature* **2019**, *575*, 380–384. [CrossRef]
98. Vander Heiden, M.G.; DeBerardinis, R.J. Understanding the Intersections between Metabolism and Cancer Biology. *Cell* **2017**, *168*, 657–669. [CrossRef]
99. Warburg, O. The Chemical Constitution of Respiration Ferment. *Science* **1928**, *68*, 437–443. [CrossRef]
100. Warburg, O.; Wind, F.; Negelein, E. The Metabolism of Tumors in the Body. *J. Gen. Physiol.* **1927**, *8*, 519–530. [CrossRef]
101. Warburg, O. On respiratory impairment in cancer cells. *Science* **1956**, *124*, 269–270. [CrossRef] [PubMed]
102. Scroggins, B.T.; Matsuo, M.; White, A.O.; Saito, K.; Munasinghe, J.P.; Sourbier, C.; Yamamoto, K.; Diaz, V.; Takakusagi, Y.; Ichikawa, K.; et al. Hyperpolarized [1-^{13}C]-Pyruvate Magnetic Resonance Spectroscopic Imaging of Prostate Cancer In Vivo Predicts Efficacy of Targeting the Warburg Effect. *Clin. Cancer Res.* **2018**, *24*, 3137–3148. [CrossRef]
103. Javaeed, A.; Ghauri, S.K. MCT4 has a potential to be used as a prognostic biomarker—A systematic review and meta-analysis. *Oncol. Rev.* **2019**, *13*, 403. [CrossRef] [PubMed]
104. Bovenzi, C.D.; Hamilton, J.; Tassone, P.; Johnson, J.; Cognetti, D.M.; Luginbuhl, A.; Keane, W.M.; Zhan, T.; Tuluc, M.; Bar-Ad, V.; et al. Prognostic Indications of Elevated MCT4 and CD147 across Cancer Types: A Meta-Analysis. *BioMed Res. Int.* **2015**, *2015*, 242437. [CrossRef] [PubMed]
105. Choi, S.Y.; Xue, H.; Wu, R.; Fazli, L.; Lin, D.; Collins, C.C.; Gleave, M.E.; Gout, P.W.; Wang, Y. The MCT4 Gene: A Novel, Potential Target for Therapy of Advanced Prostate Cancer. *Clin. Cancer Res.* **2016**, *22*, 2721–2733. [CrossRef]
106. Yu, M.; Yongzhi, H.; Chen, S.; Luo, X.; Lin, Y.; Zhou, Y.; Jin, H.; Hou, B.; Deng, Y.; Tu, L.; et al. The prognostic value of GLUT1 in cancers: A systematic review and meta-analysis. *Oncotarget* **2017**, *8*, 43356–43367. [CrossRef]
107. Lv, J.; Zhou, Z.; Wang, J.; Yu, H.; Lu, H.; Yuan, B.; Han, J.; Zhou, R.; Zhang, X.; Yang, X.; et al. Prognostic Value of Lactate Dehydrogenase Expression in Different Cancers: A Meta-Analysis. *Am. J. Med. Sci.* **2019**, *358*, 412–421. [CrossRef]
108. Fregeau-Proulx, L.; Lacouture, A.; Berthiaume, L.; Weidmann, C.; Harvey, M.; Gonthier, K.; Pelletier, J.F.; Neveu, B.; Jobin, C.; Bastien, D.; et al. Multiple metabolic pathways fuel the truncated tricarboxylic acid cycle of the prostate to sustain constant citrate production and secretion. *Mol. Metab.* **2022**, *62*, 101516. [CrossRef]
109. Pliszka, M.; Szablewski, L. Glucose Transporters as a Target for Anticancer Therapy. *Cancers* **2021**, *13*, 4184. [CrossRef]
110. Meng, Y.; Xu, X.; Luan, H.; Li, L.; Dai, W.; Li, Z.; Bian, J. The progress and development of GLUT1 inhibitors targeting cancer energy metabolism. *Future Med. Chem.* **2019**, *11*, 2333–2352. [CrossRef]

111. Liu, Y.; Cao, Y.; Zhang, W.; Bergmeier, S.; Qian, Y.; Akbar, H.; Colvin, R.; Ding, J.; Tong, L.; Wu, S.; et al. A small-molecule inhibitor of glucose transporter 1 downregulates glycolysis, induces cell-cycle arrest, and inhibits cancer cell growth in vitro and in vivo. *Mol. Cancer* **2012**, *11*, 1672–1682. [CrossRef]
112. Meziou, S.; Ringuette Goulet, C.; Hovington, H.; Lefebvre, V.; Lavallee, E.; Bergeron, M.; Brisson, H.; Champagne, A.; Neveu, B.; Lacombe, D.; et al. GLUT1 expression in high-risk prostate cancer: Correlation with (18)F-FDG-PET/CT and clinical outcome. *Prostate Cancer Prostatic Dis.* **2020**, *23*, 441–448. [CrossRef]
113. Wang, J.; Xu, W.; Wang, B.; Lin, G.; Wei, Y.; Abudurexiti, M.; Zhu, W.; Liu, C.; Qin, X.; Dai, B.; et al. GLUT1 is an AR target contributing to tumor growth and glycolysis in castration-resistant and enzalutamide-resistant prostate cancers. *Cancer Lett.* **2020**, *485*, 45–55. [CrossRef]
114. Gonzalez-Menendez, P.; Hevia, D.; Mayo, J.C.; Sainz, R.M. The dark side of glucose transporters in prostate cancer: Are they a new feature to characterize carcinomas? *Int. J. Cancer* **2018**, *142*, 2414–2424. [CrossRef]
115. Massie, C.E.; Lynch, A.; Ramos-Montoya, A.; Boren, J.; Stark, R.; Fazli, L.; Warren, A.; Scott, H.; Madhu, B.; Sharma, N.; et al. The androgen receptor fuels prostate cancer by regulating central metabolism and biosynthesis. *EMBO J.* **2011**, *30*, 2719–2733. [CrossRef]
116. Tahir, S.A.; Yang, G.; Goltsov, A.; Song, K.D.; Ren, C.; Wang, J.; Chang, W.; Thompson, T.C. Caveolin-1-LRP6 signaling module stimulates aerobic glycolysis in prostate cancer. *Cancer Res.* **2013**, *73*, 1900–1911. [CrossRef]
117. Ryniawec, J.M.; Coope, M.R.; Loertscher, E.; Bageerathan, V.; de Oliveira Pessoa, D.; Warfel, N.A.; Cress, A.E.; Padi, M.; Rogers, G.C. GLUT3/SLC2A3 Is an Endogenous Marker of Hypoxia in Prostate Cancer Cell Lines and Patient-Derived Xenograft Tumors. *Diagnostics* **2022**, *12*, 676. [CrossRef]
118. Hoshi, S.; Meguro, S.; Imai, H.; Matsuoka, Y.; Yoshida, Y.; Onagi, A.; Tanji, R.; Honda-Takinami, R.; Matsuoka, K.; Koguchi, T.; et al. Upregulation of glucocorticoid receptor-mediated glucose transporter 4 in enzalutamide-resistant prostate cancer. *Cancer Sci.* **2021**, *112*, 1899–1910. [CrossRef]
119. Zhang, L.; Wang, B.; Wang, Z.S.; Guo, Y.L.; Shen, H. Construction of Glycolytic Regulator Gene Signature to Predict the Prognosis and Tumor Immune Cell Infiltration Levels for Prostate Cancer. *Comput. Math. Methods Med.* **2022**, *2022*, 9273559. [CrossRef]
120. Wang, J.; Li, J.; Li, X.; Peng, S.; Li, J.; Yan, W.; Cui, Y.; Xiao, H.; Wen, X. Increased expression of glycolytic enzymes in prostate cancer tissues and association with Gleason scores. *Int. J. Clin. Exp. Pathol.* **2017**, *10*, 11080–11089.
121. Choi, S.Y.C.; Ettinger, S.L.; Lin, D.; Xue, H.; Ci, X.; Nabavi, N.; Bell, R.H.; Mo, F.; Gout, P.W.; Fleshner, N.E.; et al. Targeting MCT4 to reduce lactic acid secretion and glycolysis for treatment of neuroendocrine prostate cancer. *Cancer Med.* **2018**, *7*, 3385–3392. [CrossRef] [PubMed]
122. Fontana, F.; Anselmi, M.; Limonta, P. Exploiting the Metabolic Consequences of PTEN Loss and Akt/Hexokinase 2 Hyperactivation in Prostate Cancer: A New Role for delta-Tocotrienol. *Int. J. Mol. Sci.* **2022**, *23*, 5269. [CrossRef] [PubMed]
123. Shangguan, X.; He, J.; Ma, Z.; Zhang, W.; Ji, Y.; Shen, K.; Yue, Z.; Li, W.; Xin, Z.; Zheng, Q.; et al. SUMOylation controls the binding of hexokinase 2 to mitochondria and protects against prostate cancer tumorigenesis. *Nat. Commun.* **2021**, *12*, 1812. [CrossRef]
124. Lee, H.J.; Li, C.F.; Ruan, D.; He, J.; Montal, E.D.; Lorenz, S.; Girnun, G.D.; Chan, C.H. Non-proteolytic ubiquitination of Hexokinase 2 by HectH9 controls tumor metabolism and cancer stem cell expansion. *Nat. Commun.* **2019**, *10*, 2625. [CrossRef] [PubMed]
125. Martin, P.L.; Yin, J.J.; Seng, V.; Casey, O.; Corey, E.; Morrissey, C.; Simpson, R.M.; Kelly, K. Androgen deprivation leads to increased carbohydrate metabolism and hexokinase 2-mediated survival in Pten/Tp53-deficient prostate cancer. *Oncogene* **2017**, *36*, 525–533. [CrossRef]
126. Wang, L.; Wang, J.; Xiong, H.; Wu, F.; Lan, T.; Zhang, Y.; Guo, X.; Wang, H.; Saleem, M.; Jiang, C.; et al. Co-targeting hexokinase 2-mediated Warburg effect and ULK1-dependent autophagy suppresses tumor growth of PTEN- and TP53-deficiency-driven castration-resistant prostate cancer. *eBioMedicine* **2016**, *7*, 50–61. [CrossRef]
127. Wang, L.; Xiong, H.; Wu, F.; Zhang, Y.; Wang, J.; Zhao, L.; Guo, X.; Chang, L.J.; Zhang, Y.; You, M.J.; et al. Hexokinase 2-mediated Warburg effect is required for PTEN- and p53-deficiency-driven prostate cancer growth. *Cell Rep.* **2014**, *8*, 1461–1474. [CrossRef]
128. Ros, S.; Schulze, A. Balancing glycolytic flux: The role of 6-phosphofructo-2-kinase/fructose 2,6-bisphosphatases in cancer metabolism. *Cancer Metab.* **2013**, *1*, 8. [CrossRef]
129. Mor, I.; Cheung, E.C.; Vousden, K.H. Control of glycolysis through regulation of PFK1: Old friends and recent additions. *Cold Spring Harb. Symp. Quant. Biol.* **2011**, *76*, 211–216. [CrossRef]
130. Vaz, C.V.; Marques, R.; Alves, M.G.; Oliveira, P.F.; Cavaco, J.E.; Maia, C.J.; Socorro, S. Androgens enhance the glycolytic metabolism and lactate export in prostate cancer cells by modulating the expression of GLUT1, GLUT3, PFK, LDH and MCT4 genes. *J. Cancer Res. Clin. Oncol.* **2016**, *142*, 5–16. [CrossRef]
131. Moon, J.S.; Jin, W.J.; Kwak, J.H.; Kim, H.J.; Yun, M.J.; Kim, J.W.; Park, S.W.; Kim, K.S. Androgen stimulates glycolysis for de novo lipid synthesis by increasing the activities of hexokinase 2 and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 in prostate cancer cells. *Biochem. J.* **2011**, *433*, 225–233. [CrossRef]
132. Kuang, Q.; Liang, Y.; Zhuo, Y.; Cai, Z.; Jiang, F.; Xie, J.; Zheng, Y.; Zhong, W. The ALDOA Metabolism Pathway as a Potential Target for Regulation of Prostate Cancer Proliferation. *OncoTargets Ther.* **2021**, *14*, 3353–3366. [CrossRef]
133. Dayton, T.L.; Jacks, T.; Vander Heiden, M.G. PKM2, cancer metabolism, and the road ahead. *EMBO Rep.* **2016**, *17*, 1721–1730. [CrossRef]

134. Davidson, S.M.; Schmidt, D.R.; Heyman, J.E.; O'Brien, J.P.; Liu, A.C.; Israelsen, W.J.; Dayton, T.L.; Sehgal, R.; Bronson, R.T.; Freinkman, E.; et al. Pyruvate Kinase M1 Suppresses Development and Progression of Prostate Adenocarcinoma. *Cancer Res.* **2022**, *82*, 2403–2416. [CrossRef]
135. Yoon, Y.J.; Kim, Y.H.; Jin, Y.; Chi, S.W.; Moon, J.H.; Han, D.C.; Kwon, B.M. 2′-hydroxycinnamaldehyde inhibits cancer cell proliferation and tumor growth by targeting the pyruvate kinase M2. *Cancer Lett.* **2018**, *434*, 42–55. [CrossRef]
136. Zhu, S.; Guo, Y.; Zhang, X.; Liu, H.; Yin, M.; Chen, X.; Peng, C. Pyruvate kinase M2 (PKM2) in cancer and cancer therapeutics. *Cancer Lett.* **2021**, *503*, 240–248. [CrossRef]
137. Lee, Y.B.; Min, J.K.; Kim, J.G.; Cap, K.C.; Islam, R.; Hossain, A.J.; Dogsom, O.; Hamza, A.; Mahmud, S.; Choi, D.R.; et al. Multiple functions of pyruvate kinase M2 in various cell types. *J. Cell. Physiol.* **2022**, *237*, 128–148. [CrossRef]
138. Dylgjeri, E.; Kothari, V.; Shafi, A.A.; Semenova, G.; Gallagher, P.T.; Guan, Y.F.; Pang, A.; Goodwin, J.F.; Irani, S.; McCann, J.J.; et al. A Novel Role for DNA-PK in Metabolism by Regulating Glycolysis in Castration-Resistant Prostate Cancer. *Clin. Cancer Res.* **2022**, *28*, 1446–1459. [CrossRef]
139. Guo, W.; Zhang, Z.; Li, G.; Lai, X.; Gu, R.; Xu, W.; Chen, H.; Xing, Z.; Chen, L.; Qian, J.; et al. Pyruvate Kinase M2 Promotes Prostate Cancer Metastasis Through Regulating ERK1/2-COX-2 Signaling. *Front. Oncol.* **2020**, *10*, 544288. [CrossRef]
140. Giannoni, E.; Taddei, M.L.; Morandi, A.; Comito, G.; Calvani, M.; Bianchini, F.; Richichi, B.; Raugei, G.; Wong, N.; Tang, D.; et al. Targeting stromal-induced pyruvate kinase M2 nuclear translocation impairs oxphos and prostate cancer metastatic spread. *Oncotarget* **2015**, *6*, 24061–24074. [CrossRef]
141. Dai, J.; Escara-Wilke, J.; Keller, J.M.; Jung, Y.; Taichman, R.S.; Pienta, K.J.; Keller, E.T. Primary prostate cancer educates bone stroma through exosomal pyruvate kinase M2 to promote bone metastasis. *J. Exp. Med.* **2019**, *216*, 2883–2899. [CrossRef] [PubMed]
142. Hasan, D.; Gamen, E.; Abu Tarboush, N.; Ismail, Y.; Pak, O.; Azab, B. PKM2 and HIF-1alpha regulation in prostate cancer cell lines. *PLoS ONE* **2018**, *13*, e0203745. [CrossRef] [PubMed]
143. Yasumizu, Y.; Hongo, H.; Kosaka, T.; Mikami, S.; Nishimoto, K.; Kikuchi, E.; Oya, M. PKM2 under hypoxic environment causes resistance to mTOR inhibitor in human castration resistant prostate cancer. *Oncotarget* **2018**, *9*, 27698–27707. [CrossRef] [PubMed]
144. McCommis, K.S.; Finck, B.N. Mitochondrial pyruvate transport: A historical perspective and future research directions. *Biochem. J.* **2015**, *466*, 443–454. [CrossRef]
145. Bensard, C.L.; Wisidagama, D.R.; Olson, K.A.; Berg, J.A.; Krah, N.M.; Schell, J.C.; Nowinski, S.M.; Fogarty, S.; Bott, A.J.; Wei, P.; et al. Regulation of Tumor Initiation by the Mitochondrial Pyruvate Carrier. *Cell Metab.* **2020**, *31*, 284–300.e7. [CrossRef]
146. Schell, J.C.; Olson, K.A.; Jiang, L.; Hawkins, A.J.; Van Vranken, J.G.; Xie, J.; Egnatchik, R.A.; Earl, E.G.; DeBerardinis, R.J.; Rutter, J. A role for the mitochondrial pyruvate carrier as a repressor of the Warburg effect and colon cancer cell growth. *Mol. Cell* **2014**, *56*, 400–413. [CrossRef]
147. Bader, D.A.; Hartig, S.M.; Putluri, V.; Foley, C.; Hamilton, M.P.; Smith, E.A.; Saha, P.K.; Panigrahi, A.; Walker, C.; Zong, L.; et al. Mitochondrial pyruvate import is a metabolic vulnerability in androgen receptor-driven prostate cancer. *Nat. Metab.* **2019**, *1*, 70–85. [CrossRef]
148. Yang, C.; Ko, B.; Hensley, C.T.; Jiang, L.; Wasti, A.T.; Kim, J.; Sudderth, J.; Calvaruso, M.A.; Lumata, L.; Mitsche, M.; et al. Glutamine oxidation maintains the TCA cycle and cell survival during impaired mitochondrial pyruvate transport. *Mol. Cell* **2014**, *56*, 414–424. [CrossRef]
149. Vacanti, N.M.; Divakaruni, A.S.; Green, C.R.; Parker, S.J.; Henry, R.R.; Ciaraldi, T.P.; Murphy, A.N.; Metallo, C.M. Regulation of substrate utilization by the mitochondrial pyruvate carrier. *Mol. Cell* **2014**, *56*, 425–435. [CrossRef]
150. Xu, H.; Liu, Z.; Gao, D.; Li, P.; Shen, Y.; Sun, Y.; Xu, L.; Song, N.; Wang, Y.; Zhan, M.; et al. Reprogramming hormone-sensitive prostate cancer to a lethal neuroendocrine cancer lineage by mitochondrial pyruvate carrier (MPC). *Mol. Metab.* **2022**, *59*, 101466. [CrossRef]
151. Roche, T.E.; Baker, J.C.; Yan, X.; Hiromasa, Y.; Gong, X.; Peng, T.; Dong, J.; Turkan, A.; Kasten, S.A. Distinct regulatory properties of pyruvate dehydrogenase kinase and phosphatase isoforms. *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, *70*, 33–75. [CrossRef]
152. Nunes-Xavier, C.E.; Mingo, J.; Emaldi, M.; Flem-Karlsen, K.; Maelandsmo, G.M.; Fodstad, O.; Llarena, R.; Lopez, J.I.; Pulido, R. Heterogeneous Expression and Subcellular Localization of Pyruvate Dehydrogenase Complex in Prostate Cancer. *Front. Oncol.* **2022**, *12*, 873516. [CrossRef]
153. Atas, E.; Oberhuber, M.; Kenner, L. The Implications of PDK1-4 on Tumor Energy Metabolism, Aggressiveness and Therapy Resistance. *Front. Oncol.* **2020**, *10*, 583217. [CrossRef]
154. Kikani, C.K.; Verona, E.V.; Ryu, J.; Shen, Y.; Ye, Q.; Zheng, L.; Qian, Z.; Sakaue, H.; Nakamura, K.; Du, J.; et al. Proliferative and antiapoptotic signaling stimulated by nuclear-localized PDK1 results in oncogenesis. *Sci. Signal.* **2012**, *5*, ra80. [CrossRef]
155. Wang, L.Y.; Hung, C.L.; Chen, Y.R.; Yang, J.C.; Wang, J.; Campbell, M.; Izumiya, Y.; Chen, H.W.; Wang, W.C.; Ann, D.K.; et al. KDM4A Coactivates E2F1 to Regulate the PDK-Dependent Metabolic Switch between Mitochondrial Oxidation and Glycolysis. *Cell Rep.* **2016**, *16*, 3016–3027. [CrossRef]
156. Chen, J.; Guccini, I.; Di Mitri, D.; Brina, D.; Revandkar, A.; Sarti, M.; Pasquini, E.; Alajati, A.; Pinton, S.; Losa, M.; et al. Compartmentalized activities of the pyruvate dehydrogenase complex sustain lipogenesis in prostate cancer. *Nat. Genet.* **2018**, *50*, 219–228. [CrossRef]
157. Li, Y.; Li, X.; Li, X.; Zhong, Y.; Ji, Y.; Yu, D.; Zhang, M.; Wen, J.G.; Zhang, H.; Goscinski, M.A.; et al. PDHA1 gene knockout in prostate cancer cells results in metabolic reprogramming towards greater glutamine dependence. *Oncotarget* **2016**, *7*, 53837–53852. [CrossRef]

158. Li, W.; Qian, L.; Lin, J.; Huang, G.; Hao, N.; Wei, X.; Wang, W.; Liang, J. CD44 regulates prostate cancer proliferation, invasion and migration via PDK1 and PFKFB4. *Oncotarget* **2017**, *8*, 65143–65151. [CrossRef]
159. Sheng, W.; Xu, W.; Ding, J.; Li, L.; You, X.; Wu, Y.; He, Q. Curcumol inhibits the malignant progression of prostate cancer and regulates the PDK1/AKT/mTOR pathway by targeting miR9. *Oncol. Rep.* **2021**, *46*, 246. [CrossRef]
160. Oberhuber, M.; Pecoraro, M.; Rusz, M.; Oberhuber, G.; Wieselberg, M.; Haslinger, P.; Gurnhofer, E.; Schlederer, M.; Limberger, T.; Lagger, S.; et al. STAT3-dependent analysis reveals PDK4 as independent predictor of recurrence in prostate cancer. *Mol. Syst. Biol.* **2020**, *16*, e9247. [CrossRef]
161. Jiang, X.; Guo, S.; Wang, S.; Zhang, Y.; Chen, H.; Wang, Y.; Liu, R.; Niu, Y.; Xu, Y. EIF4A3-Induced circARHGAP29 Promotes Aerobic Glycolysis in Docetaxel-Resistant Prostate Cancer through IGF2BP2/c-Myc/LDHA Signaling. *Cancer Res.* **2022**, *82*, 831–845. [CrossRef] [PubMed]
162. Muramatsu, H.; Sumitomo, M.; Morinaga, S.; Kajikawa, K.; Kobayashi, I.; Nishikawa, G.; Kato, Y.; Watanabe, M.; Zennami, K.; Kanao, K.; et al. Targeting lactate dehydrogenaseA promotes docetaxelinduced cytotoxicity predominantly in castrationresistant prostate cancer cells. *Oncol. Rep.* **2019**, *42*, 224–230. [CrossRef] [PubMed]
163. Lin, C.Y.; Wang, B.J.; Fu, Y.K.; Huo, C.; Wang, Y.P.; Chen, B.C.; Liu, W.Y.; Tseng, J.C.; Jiang, S.S.; Sie, Z.L.; et al. Inhibition of KDM4C/c-Myc/LDHA signalling axis suppresses prostate cancer metastasis via interference of glycolytic metabolism. *Clin. Transl. Med.* **2022**, *12*, e764. [CrossRef]
164. Kwon, O.K.; Bang, I.H.; Choi, S.Y.; Jeon, J.M.; Na, A.Y.; Gao, Y.; Cho, S.S.; Ki, S.H.; Choe, Y.; Lee, J.N.; et al. SIRT5 Is the desuccinylase of LDHA as novel cancer metastatic stimulator in aggressive prostate cancer. *Genom. Proteom. Bioinform.* 2022; *in press*. [CrossRef] [PubMed]
165. Liu, J.; Chen, G.; Liu, Z.; Liu, S.; Cai, Z.; You, P.; Ke, Y.; Lai, L.; Huang, Y.; Gao, H.; et al. Aberrant FGFR Tyrosine Kinase Signaling Enhances the Warburg Effect by Reprogramming LDH Isoform Expression and Activity in Prostate Cancer. *Cancer Res.* **2018**, *78*, 4459–4470. [CrossRef]
166. Andersen, S.; Solstad, O.; Moi, L.; Donnem, T.; Eilertsen, M.; Nordby, Y.; Ness, N.; Richardsen, E.; Busund, L.T.; Bremnes, R.M. Organized metabolic crime in prostate cancer: The coexpression of MCT1 in tumor and MCT4 in stroma is an independent prognosticator for biochemical failure. *Urol. Oncol.* **2015**, *33*, 338.e9–338.e17. [CrossRef]
167. Sushentsev, N.; McLean, M.A.; Warren, A.Y.; Benjamin, A.J.V.; Brodie, C.; Frary, A.; Gill, A.B.; Jones, J.; Kaggie, J.D.; Lamb, B.W.; et al. Hyperpolarised (13)C-MRI identifies the emergence of a glycolytic cell population within intermediate-risk human prostate cancer. *Nat. Commun.* **2022**, *13*, 466. [CrossRef]
168. Choi, S.Y.; Collins, C.C.; Gout, P.W.; Wang, Y. Cancer-generated lactic acid: A regulatory, immunosuppressive metabolite? *J. Pathol.* **2013**, *230*, 350–355. [CrossRef]
169. Wang, J.X.; Choi, S.Y.C.; Niu, X.; Kang, N.; Xue, H.; Killam, J.; Wang, Y. Lactic Acid and an Acidic Tumor Microenvironment suppress Anticancer Immunity. *Int. J. Mol. Sci* **2020**, *21*, 8363. [CrossRef]
170. Carreno, D.; Corro, N.; Torres-Estay, V.; Veliz, L.P.; Jaimovich, R.; Cisternas, P.; San Francisco, I.F.; Sotomayor, P.C.; Tanasova, M.; Inestrosa, N.C.; et al. Fructose and prostate cancer: Toward an integrated view of cancer cell metabolism. *Prostate Cancer Prostatic Dis.* **2019**, *22*, 49–58. [CrossRef]
171. Frenette, G.; Thabet, M.; Sullivan, R. Polyol pathway in human epididymis and semen. *J. Androl.* **2006**, *27*, 233–239. [CrossRef]
172. Szabo, Z.; Hamalainen, J.; Loikkanen, I.; Moilanen, A.M.; Hirvikoski, P.; Vaisanen, T.; Paavonen, T.K.; Vaarala, M.H. Sorbitol dehydrogenase expression is regulated by androgens in the human prostate. *Oncol. Rep.* **2010**, *23*, 1233–1239. [CrossRef]
173. Carreno, D.V.; Corro, N.B.; Cerda-Infante, J.F.; Echeverria, C.E.; Asencio-Barria, C.A.; Torres-Estay, V.A.; Mayorga-Weber, G.A.; Rojas, P.A.; Veliz, L.P.; Cisternas, P.A.; et al. Dietary Fructose Promotes Prostate Cancer Growth. *Cancer Res.* **2021**, *81*, 2824–2832. [CrossRef]
174. Echeverria, C.; Nualart, F.; Ferrada, L.; Smith, G.J.; Godoy, A.S. Hexose Transporters in Cancer: From Multifunctionality to Diagnosis and Therapy. *Trends Endocrinol. Metab.* **2021**, *32*, 198–211. [CrossRef]
175. Xu, L.; Zhao, B.; Butler, W.; Xu, H.; Song, N.; Chen, X.; Spencer Hauck, J.; Gao, X.; Zhang, H.; Groth, J.; et al. Targeting glutamine metabolism network for the treatment of therapy-resistant prostate cancer. *Oncogene* **2022**, *41*, 1140–1154. [CrossRef]
176. Strmiska, V.; Michalek, P.; Eckschlager, T.; Stiborova, M.; Adam, V.; Krizkova, S.; Heger, Z. Prostate cancer-specific hallmarks of amino acids metabolism: Towards a paradigm of precision medicine. *Biochim. Biophys. Acta Rev. Cancer* **2019**, *1871*, 248–258. [CrossRef]
177. Fu, Y.M.; Lin, H.; Liu, X.; Fang, W.; Meadows, G.G. Cell death of prostate cancer cells by specific amino acid restriction depends on alterations of glucose metabolism. *J. Cell. Physiol.* **2010**, *224*, 491–500. [CrossRef]
178. Yang, L.; Venneti, S.; Nagrath, D. Glutaminolysis: A Hallmark of Cancer Metabolism. *Annu. Rev. Biomed. Eng.* **2017**, *19*, 163–194. [CrossRef]
179. Cardoso, H.J.; Figueira, M.I.; Vaz, C.V.; Carvalho, T.M.A.; Bras, L.A.; Madureira, P.A.; Oliveira, P.J.; Sardao, V.A.; Socorro, S. Glutaminolysis is a metabolic route essential for survival and growth of prostate cancer cells and a target of 5alpha-dihydrotestosterone regulation. *Cell. Oncol.* **2021**, *44*, 385–403. [CrossRef]
180. Xu, L.; Yin, Y.; Li, Y.; Chen, X.; Chang, Y.; Zhang, H.; Liu, J.; Beasley, J.; McCaw, P.; Zhang, H.; et al. A glutaminase isoform switch drives therapeutic resistance and disease progression of prostate cancer. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2012748118. [CrossRef]

181. Malviya, G.; Patel, R.; Salji, M.; Martinez, R.S.; Repiscak, P.; Mui, E.; Champion, S.; Mrowinska, A.; Johnson, E.; AlRasheedi, M.; et al. 18F-Fluciclovine PET metabolic imaging reveals prostate cancer tumour heterogeneity associated with disease resistance to androgen deprivation therapy. *EJNMMI Res.* **2020**, *10*, 143. [CrossRef] [PubMed]
182. Martinez, R.S.; Salji, M.J.; Rushworth, L.; Ntala, C.; Rodriguez Blanco, G.; Hedley, A.; Clark, W.; Peixoto, P.; Hervouet, E.; Renaude, E.; et al. SLFN5 Regulates LAT1-Mediated mTOR Activation in Castration-Resistant Prostate Cancer. *Cancer Res.* **2021**, *81*, 3664–3678. [CrossRef] [PubMed]
183. Xu, M.; Sakamoto, S.; Matsushima, J.; Kimura, T.; Ueda, T.; Mizokami, A.; Kanai, Y.; Ichikawa, T. Up-Regulation of LAT1 during Antiandrogen Therapy Contributes to Progression in Prostate Cancer Cells. *J. Urol.* **2016**, *195*, 1588–1597. [CrossRef] [PubMed]
184. Wang, Q.; Hardie, R.A.; Hoy, A.J.; van Geldermalsen, M.; Gao, D.; Fazli, L.; Sadowski, M.C.; Balaban, S.; Schreuder, M.; Nagarajah, R.; et al. Targeting ASCT2-mediated glutamine uptake blocks prostate cancer growth and tumour development. *J. Pathol.* **2015**, *236*, 278–289. [CrossRef] [PubMed]
185. Katt, W.P.; Lukey, M.J.; Cerione, R.A. A tale of two glutaminases: Homologous enzymes with distinct roles in tumorigenesis. *Future Med. Chem.* **2017**, *9*, 223–243. [CrossRef]
186. Dorai, T.; Dorai, B.; Pinto, J.T.; Grasso, M.; Cooper, A.J.L. High Levels of Glutaminase II Pathway Enzymes in Normal and Cancerous Prostate Suggest a Role in 'Glutamine Addiction'. *Biomolecules* **2019**, *10*, 2. [CrossRef]
187. He, Z.; Gao, Y.; Li, T.; Yu, C.; Ou, L.; Luo, C. HepaCAMPIK3CA axis regulates the reprogramming of glutamine metabolism to inhibit prostate cancer cell proliferation. *Int. J. Oncol.* **2022**, *60*, 37. [CrossRef]
188. Shao, Y.; Ye, G.; Ren, S.; Piao, H.L.; Zhao, X.; Lu, X.; Wang, F.; Ma, W.; Li, J.; Yin, P.; et al. Metabolomics and transcriptomics profiles reveal the dysregulation of the tricarboxylic acid cycle and related mechanisms in prostate cancer. *Int. J. Cancer* **2018**, *143*, 396–407. [CrossRef]
189. Liu, W.; Le, A.; Hancock, C.; Lane, A.N.; Dang, C.V.; Fan, T.W.; Phang, J.M. Reprogramming of proline and glutamine metabolism contributes to the proliferative and metabolic responses regulated by oncogenic transcription factor c-MYC. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 8983–8988. [CrossRef]
190. Mukha, A.; Kahya, U.; Linge, A.; Chen, O.; Lock, S.; Lukiyanchuk, V.; Richter, S.; Alves, T.C.; Peitzsch, M.; Telychko, V.; et al. GLS-driven glutamine catabolism contributes to prostate cancer radiosensitivity by regulating the redox state, stemness and ATG5-mediated autophagy. *Theranostics* **2021**, *11*, 7844–7868. [CrossRef]
191. Zhang, J.; Mao, S.; Guo, Y.; Wu, Y.; Yao, X.; Huang, Y. Inhibition of GLS suppresses proliferation and promotes apoptosis in prostate cancer. *Biosci. Rep.* **2019**, *39*, BSR20181826. [CrossRef]
192. Zacharias, N.M.; McCullough, C.; Shanmugavelandy, S.; Lee, J.; Lee, Y.; Dutta, P.; McHenry, J.; Nguyen, L.; Norton, W.; Jones, L.W.; et al. Metabolic Differences in Glutamine Utilization Lead to Metabolic Vulnerabilities in Prostate Cancer. *Sci. Rep.* **2017**, *7*, 16159. [CrossRef]
193. Peng, H.; Wang, Y.; Luo, W. Multifaceted role of branched-chain amino acid metabolism in cancer. *Oncogene* **2020**, *39*, 6747–6756. [CrossRef]
194. Mullen, A.R.; Wheaton, W.W.; Jin, E.S.; Chen, P.H.; Sullivan, L.B.; Cheng, T.; Yang, Y.; Linehan, W.M.; Chandel, N.S.; DeBerardinis, R.J. Reductive carboxylation supports growth in tumour cells with defective mitochondria. *Nature* **2011**, *481*, 385–388. [CrossRef]
195. Sachdeva, A.; Hart, C.A.; Carey, C.D.; Vincent, A.E.; Greaves, L.C.; Heer, R.; Oliveira, P.; Brown, M.D.; Clarke, N.W.; Turnbull, D.M. Automated quantitative high-throughput multiplex immunofluorescence pipeline to evaluate OXPHOS defects in formalin-fixed human prostate tissue. *Sci. Rep.* **2022**, *12*, 6660. [CrossRef]
196. Burke, L.; Guterman, I.; Palacios Gallego, R.; Britton, R.G.; Burschowsky, D.; Tufarelli, C.; Rufini, A. The Janus-like role of proline metabolism in cancer. *Cell Death Discov.* **2020**, *6*, 104. [CrossRef]
197. Tanner, J.J.; Fendt, S.M.; Becker, D.F. The Proline Cycle As a Potential Cancer Therapy Target. *Biochemistry* **2018**, *57*, 3433–3444. [CrossRef]
198. Liu, W.; Hancock, C.N.; Fischer, J.W.; Harman, M.; Phang, J.M. Proline biosynthesis augments tumor cell growth and aerobic glycolysis: Involvement of pyridine nucleotides. *Sci. Rep.* **2015**, *5*, 17206. [CrossRef]
199. Lin, D.; Ettinger, S.L.; Qu, S.; Xue, H.; Nabavi, N.; Choi, S.Y.C.; Bell, R.H.; Mo, F.; Haegert, A.M.; Gout, P.W.; et al. Metabolic heterogeneity signature of primary treatment-naive prostate cancer. *Oncotarget* **2017**, *8*, 25928–25941. [CrossRef]
200. Locasale, J.W. Serine, glycine and one-carbon units: Cancer metabolism in full circle. *Nat. Rev. Cancer* **2013**, *13*, 572–583. [CrossRef]
201. Spinelli, J.B.; Haigis, M.C. The multifaceted contributions of mitochondria to cellular metabolism. *Nat. Cell Biol.* **2018**, *20*, 745–754. [CrossRef] [PubMed]
202. Amelio, I.; Cutruzzola, F.; Antonov, A.; Agostini, M.; Melino, G. Serine and glycine metabolism in cancer. *Trends Biochem. Sci.* **2014**, *39*, 191–198. [CrossRef] [PubMed]
203. Ganini, C.; Amelio, I.; Bertolo, R.; Candi, E.; Cappello, A.; Cipriani, C.; Mauriello, A.; Marani, C.; Melino, G.; Montanaro, M.; et al. Serine and one-carbon metabolisms bring new therapeutic venues in prostate cancer. *Discov. Oncol.* **2021**, *12*, 45. [CrossRef] [PubMed]
204. Labuschagne, C.F.; van den Broek, N.J.; Mackay, G.M.; Vousden, K.H.; Maddocks, O.D. Serine, but not glycine, supports one-carbon metabolism and proliferation of cancer cells. *Cell Rep.* **2014**, *7*, 1248–1258. [CrossRef] [PubMed]
205. Corbin, J.M.; Ruiz-Echevarria, M.J. One-Carbon Metabolism in Prostate Cancer: The Role of Androgen Signaling. *Int. J. Mol. Sci.* **2016**, *17*, 1208. [CrossRef]

206. Vazquez, A.; Tedeschi, P.M.; Bertino, J.R. Overexpression of the mitochondrial folate and glycine-serine pathway: A new determinant of methotrexate selectivity in tumors. *Cancer Res.* **2013**, *73*, 478–482. [CrossRef]
207. Pallmann, N.; Deng, K.; Livgard, M.; Tesikova, M.; Jin, Y.; Frengen, N.S.; Kahraman, N.; Mokhlis, H.M.; Ozpolat, B.; Kildal, W.; et al. Stress-Mediated Reprogramming of Prostate Cancer One-Carbon Cycle Drives Disease Progression. *Cancer Res.* **2021**, *81*, 4066–4078. [CrossRef]
208. Reina-Campos, M.; Linares, J.F.; Duran, A.; Cordes, T.; L'Hermitte, A.; Badur, M.G.; Bhangoo, M.S.; Thorson, P.K.; Richards, A.; Rooslid, T.; et al. Increased Serine and One-Carbon Pathway Metabolism by PKClambda/iota Deficiency Promotes Neuroendocrine Prostate Cancer. *Cancer Cell* **2019**, *35*, 385–400.E9. [CrossRef]
209. Sreekumar, A.; Poisson, L.M.; Rajendiran, T.M.; Khan, A.P.; Cao, Q.; Yu, J.; Laxman, B.; Mehra, R.; Lonigro, R.J.; Li, Y.; et al. Metabolomic profiles delineate potential role for sarcosine in prostate cancer progression. *Nature* **2009**, *457*, 910–914. [CrossRef]
210. Reina-Campos, M.; Diaz-Meco, M.T.; Moscat, J. The complexity of the serine glycine one-carbon pathway in cancer. *J. Cell Biol.* **2020**, *219*, e201907022. [CrossRef]
211. Casero, R.A., Jr.; Murray Stewart, T.; Pegg, A.E. Polyamine metabolism and cancer: Treatments, challenges and opportunities. *Nat. Rev. Cancer* **2018**, *18*, 681–695. [CrossRef]
212. Bai, G.; Kasper, S.; Matusik, R.J.; Rennie, P.S.; Moshier, J.A.; Krongrad, A. Androgen regulation of the human ornithine decarboxylase promoter in prostate cancer cells. *J. Androl.* **1998**, *19*, 127–135.
213. Zabala-Letona, A.; Arruabarrena-Aristorena, A.; Martin-Martin, N.; Fernandez-Ruiz, S.; Sutherland, J.D.; Clasquin, M.; Tomas-Cortazar, J.; Jimenez, J.; Torres, I.; Quang, P.; et al. mTORC1-dependent AMD1 regulation sustains polyamine metabolism in prostate cancer. *Nature* **2017**, *547*, 109–113. [CrossRef]
214. Affronti, H.C.; Rowsam, A.M.; Pellerite, A.J.; Rosario, S.R.; Long, M.D.; Jacobi, J.J.; Bianchi-Smiraglia, A.; Boerlin, C.S.; Gillard, B.M.; Karasik, E.; et al. Pharmacological polyamine catabolism upregulation with methionine salvage pathway inhibition as an effective prostate cancer therapy. *Nat. Commun.* **2020**, *11*, 52. [CrossRef] [PubMed]
215. Koundouros, N.; Poulogiannis, G. Reprogramming of fatty acid metabolism in cancer. *Br. J. Cancer* **2020**, *122*, 4–22. [CrossRef]
216. Nagarajan, S.R.; Butler, L.M.; Hoy, A.J. The diversity and breadth of cancer cell fatty acid metabolism. *Cancer Metab.* **2021**, *9*, 2. [CrossRef]
217. Smith, S.; Witkowski, A.; Joshi, A.K. Structural and functional organization of the animal fatty acid synthase. *Prog. Lipid Res.* **2003**, *42*, 289–317. [CrossRef]
218. Schug, Z.T.; Peck, B.; Jones, D.T.; Zhang, Q.; Grosskurth, S.; Alam, I.S.; Goodwin, L.M.; Smethurst, E.; Mason, S.; Blyth, K.; et al. Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. *Cancer Cell* **2015**, *27*, 57–71. [CrossRef]
219. Schug, Z.T.; Vande Voorde, J.; Gottlieb, E. The metabolic fate of acetate in cancer. *Nat. Rev. Cancer* **2016**, *16*, 708–717. [CrossRef]
220. Vavere, A.L.; Kridel, S.J.; Wheeler, F.B.; Lewis, J.S. 1-11C-acetate as a PET radiopharmaceutical for imaging fatty acid synthase expression in prostate cancer. *J. Nucl. Med.* **2008**, *49*, 327–334. [CrossRef] [PubMed]
221. Semenkovich, C.F.; Coleman, T.; Fiedorek, F.T., Jr. Human fatty acid synthase mRNA: Tissue distribution, genetic mapping, and kinetics of decay after glucose deprivation. *J. Lipid Res.* **1995**, *36*, 1507–1521. [CrossRef]
222. Weiss, L.; Hoffmann, G.E.; Schreiber, R.; Andres, H.; Fuchs, E.; Korber, E.; Kolb, H.J. Fatty-acid biosynthesis in man, a pathway of minor importance. Purification, optimal assay conditions, and organ distribution of fatty-acid synthase. *Biol. Chem. Hoppe Seyler* **1986**, *367*, 905–912. [CrossRef] [PubMed]
223. Zadra, G.; Photopoulos, C.; Loda, M. The fat side of prostate cancer. *Biochim. Biophys. Acta* **2013**, *1831*, 1518–1532. [CrossRef]
224. Rashid, A.; Pizer, E.S.; Moga, M.; Milgraum, L.Z.; Zahurak, M.; Pasternack, G.R.; Kuhajda, F.P.; Hamilton, S.R. Elevated expression of fatty acid synthase and fatty acid synthetic activity in colorectal neoplasia. *Am. J. Pathol.* **1997**, *150*, 201–208. [PubMed]
225. Pizer, E.S.; Lax, S.F.; Kuhajda, F.P.; Pasternack, G.R.; Kurman, R.J. Fatty acid synthase expression in endometrial carcinoma: Correlation with cell proliferation and hormone receptors. *Cancer* **1998**, *83*, 528–537. [CrossRef]
226. Gelebart, P.; Zak, Z.; Anand, M.; Belch, A.; Lai, R. Blockade of fatty acid synthase triggers significant apoptosis in mantle cell lymphoma. *PLoS ONE* **2012**, *7*, e33738. [CrossRef]
227. Bhatt, A.P.; Jacobs, S.R.; Freemerman, A.J.; Makowski, L.; Rathmell, J.C.; Dittmer, D.P.; Damania, B. Dysregulation of fatty acid synthesis and glycolysis in non-Hodgkin lymphoma. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 11818–11823. [CrossRef]
228. Wang, W.Q.; Zhao, X.Y.; Wang, H.Y.; Liang, Y. Increased fatty acid synthase as a potential therapeutic target in multiple myeloma. *J. Zhejiang Univ. Sci. B* **2008**, *9*, 441–447. [CrossRef]
229. Cai, Y.; Wang, J.; Zhang, L.; Wu, D.; Yu, D.; Tian, X.; Liu, J.; Jiang, X.; Shen, Y.; Zhang, L.; et al. Expressions of fatty acid synthase and HER2 are correlated with poor prognosis of ovarian cancer. *Med. Oncol.* **2015**, *32*, 391. [CrossRef]
230. Alo, P.L.; Visca, P.; Marci, A.; Mangoni, A.; Botti, C.; Di Tondo, U. Expression of fatty acid synthase (FAS) as a predictor of recurrence in stage I breast carcinoma patients. *Cancer* **1996**, *77*, 474–482. [CrossRef]
231. Swinnen, J.V.; Roskams, T.; Joniau, S.; Van Poppel, H.; Oyen, R.; Baert, L.; Heyns, W.; Verhoeven, G. Overexpression of fatty acid synthase is an early and common event in the development of prostate cancer. *Int. J. Cancer* **2002**, *98*, 19–22. [CrossRef] [PubMed]
232. Shurbaji, M.S.; Kalbfleisch, J.H.; Thurmond, T.S. Immunohistochemical detection of a fatty acid synthase (OA-519) as a predictor of progression of prostate cancer. *Hum. Pathol.* **1996**, *27*, 917–921. [CrossRef]

233. Abumrad, N.A.; el-Maghrabi, M.R.; Amri, E.Z.; Lopez, E.; Grimaldi, P.A. Cloning of a rat adipocyte membrane protein implicated in binding or transport of long-chain fatty acids that is induced during preadipocyte differentiation. Homology with human CD36. *J. Biol. Chem.* **1993**, *268*, 17665–17668. [CrossRef]
234. Chen, Y.; Yang, M.; Huang, W.; Chen, W.; Zhao, Y.; Schulte, M.L.; Volberding, P.; Gerbec, Z.; Zimmermann, M.T.; Zeighami, A.; et al. Mitochondrial Metabolic Reprogramming by CD36 Signaling Drives Macrophage Inflammatory Responses. *Circ. Res.* **2019**, *125*, 1087–1102. [CrossRef] [PubMed]
235. Rahaman, S.O.; Lennon, D.J.; Febbraio, M.; Podrez, E.A.; Hazen, S.L.; Silverstein, R.L. A CD36-dependent signaling cascade is necessary for macrophage foam cell formation. *Cell Metab.* **2006**, *4*, 211–221. [CrossRef] [PubMed]
236. Jiang, M.; Wu, N.; Xu, B.; Chu, Y.; Li, X.; Su, S.; Chen, D.; Li, W.; Shi, Y.; Gao, X.; et al. Fatty acid-induced CD36 expression via O-GlcNAcylation drives gastric cancer metastasis. *Theranostics* **2019**, *9*, 5359–5373. [CrossRef]
237. Lim, H.J.; Lee, S.; Lee, K.S.; Park, J.H.; Jang, Y.; Lee, E.J.; Park, H.Y. PPARgamma activation induces CD36 expression and stimulates foam cell like changes in rVSMCs. *Prostaglandins Other Lipid Mediat.* **2006**, *80*, 165–174. [CrossRef]
238. Tao, N.; Wagner, S.J.; Lublin, D.M. CD36 is palmitoylated on both N- and C-terminal cytoplasmic tails. *J. Biol. Chem.* **1996**, *271*, 22315–22320. [CrossRef]
239. Zhang, Y.; Dong, D.; Xu, X.; He, H.; Zhu, Y.; Lei, T.; Ou, H. Oxidized high-density lipoprotein promotes CD36 palmitoylation and increases lipid uptake in macrophages. *J. Biol. Chem.* **2022**, *298*, 102000. [CrossRef]
240. Ye, H.; Adane, B.; Khan, N.; Sullivan, T.; Minhajuddin, M.; Gasparetto, M.; Stevens, B.; Pei, S.; Balys, M.; Ashton, J.M.; et al. Leukemic Stem Cells Evade Chemotherapy by Metabolic Adaptation to an Adipose Tissue Niche. *Cell Stem Cell* **2016**, *19*, 23–37. [CrossRef]
241. Feng, W.W.; Wilkins, O.; Bang, S.; Ung, M.; Li, J.; An, J.; Del Genio, C.; Canfield, K.; DiRenzo, J.; Wells, W.; et al. CD36-Mediated Metabolic Rewiring of Breast Cancer Cells Promotes Resistance to HER2-Targeted Therapies. *Cell Rep.* **2019**, *29*, 3405–3420.E5. [CrossRef]
242. Martini, C.; DeNichilo, M.; King, D.P.; Cockshell, M.P.; Ebert, B.; Dale, B.; Ebert, L.M.; Woods, A.; Bonder, C.S. CD36 promotes vasculogenic mimicry in melanoma by mediating adhesion to the extracellular matrix. *BMC Cancer* **2021**, *21*, 765. [CrossRef]
243. Watt, M.J.; Clark, A.K.; Selth, L.A.; Haynes, V.R.; Lister, N.; Rebello, R.; Porter, L.H.; Niranjan, B.; Whitby, S.T.; Lo, J.; et al. Suppressing fatty acid uptake has therapeutic effects in preclinical models of prostate cancer. *Sci. Transl. Med.* **2019**, *11*, eaau5758. [CrossRef]
244. Zhao, Y.; Peng, X.; Baldwin, H.; Zhang, C.; Liu, Z.; Lu, X. Anti-androgen therapy induces transcriptomic reprogramming in metastatic castration-resistant prostate cancer in a murine model. *Biochim. Biophys. Acta Mol. Basis Dis.* **2021**, *1867*, 166151. [CrossRef]
245. Rysman, E.; Brusselmans, K.; Scheys, K.; Timmermans, L.; Derua, R.; Munck, S.; Van Veldhoven, P.P.; Waltregny, D.; Daniels, V.W.; Machiels, J.; et al. De novo lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. *Cancer Res.* **2010**, *70*, 8117–8126. [CrossRef]
246. Rae, C.; Fragkoulis, G.I.; Chalmers, A.J. Cytotoxicity and Radiosensitizing Activity of the Fatty Acid Synthase Inhibitor C75 Is Enhanced by Blocking Fatty Acid Uptake in Prostate Cancer Cells. *Adv. Radiat. Oncol.* **2020**, *5*, 994–1005. [CrossRef]
247. Olzmann, J.A.; Carvalho, P. Dynamics and functions of lipid droplets. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 137–155. [CrossRef]
248. Getiye, Y.; Rice, T.A.; Phillips, B.D.; Carrillo, D.F.; He, G. Dysregulated lipolysis and lipophagy in lipid droplets of macrophages from high fat diet-fed obese mice. *J. Cell. Mol. Med.* **2022**, *26*, 4825–4836. [CrossRef]
249. Nomura, D.K.; Long, J.Z.; Niessen, S.; Hoover, H.S.; Ng, S.W.; Cravatt, B.F. Monoacylglycerol lipase regulates a fatty acid network that promotes cancer pathogenesis. *Cell* **2010**, *140*, 49–61. [CrossRef]
250. Talley, J.T.; Mohiuddin, S.S. *Biochemistry, Fatty Acid Oxidation*; StatPearls: Treasure Island, FL, USA, 2022.
251. Zha, S.; Ferdinandusse, S.; Hicks, J.L.; Denis, S.; Dunn, T.A.; Wanders, R.J.; Luo, J.; De Marzo, A.M.; Isaacs, W.B. Peroxisomal branched chain fatty acid beta-oxidation pathway is upregulated in prostate cancer. *Prostate* **2005**, *63*, 316–323. [CrossRef]
252. Jiang, Z.; Woda, B.A.; Rock, K.L.; Xu, Y.; Savas, L.; Khan, A.; Pihan, G.; Cai, F.; Babcook, J.S.; Rathanaswami, P.; et al. P504S: A new molecular marker for the detection of prostate carcinoma. *Am. J. Surg. Pathol.* **2001**, *25*, 1397–1404. [CrossRef] [PubMed]
253. Houten, S.M.; Wanders, R.J.A.; Ranea-Robles, P. Metabolic interactions between peroxisomes and mitochondria with a special focus on acylcarnitine metabolism. *Biochim. Biophys. Acta Mol. Basis Dis.* **2020**, *1866*, 165720. [CrossRef] [PubMed]
254. Jacob, F.; Monod, J. Genetic regulatory mechanisms in the synthesis of proteins. *J. Mol. Biol.* **1961**, *3*, 318–356. [CrossRef]
255. Marte, B. A visionary pair. *Nat. Rev. Mol. Cell Biol.* **2005**, *6*, S6. [CrossRef]
256. Van der Knaap, J.A.; Verrijzer, C.P. Undercover: Gene control by metabolites and metabolic enzymes. *Genes Dev.* **2016**, *30*, 2345–2369. [CrossRef]
257. Shimano, H.; Sato, R. SREBP-regulated lipid metabolism: Convergent physiology—Divergent pathophysiology. *Nat. Rev. Endocrinol.* **2017**, *13*, 710–730. [CrossRef]
258. Sans, C.L.; Satterwhite, D.J.; Stoltzman, C.A.; Breen, K.T.; Ayer, D.E. MondoA-Mlx heterodimers are candidate sensors of cellular energy status: Mitochondrial localization and direct regulation of glycolysis. *Mol. Cell. Biol.* **2006**, *26*, 4863–4871. [CrossRef]
259. Wilde, B.R.; Ye, Z.; Lim, T.Y.; Ayer, D.E. Cellular acidosis triggers human MondoA transcriptional activity by driving mitochondrial ATP production. *eLife* **2019**, *8*, e40199. [CrossRef]
260. Chen, C.L.; Hsu, S.C.; Chung, T.Y.; Chu, C.Y.; Wang, H.J.; Hsiao, P.W.; Yeh, S.D.; Ann, D.K.; Yen, Y.; Kung, H.J. Arginine is an epigenetic regulator targeting TEAD4 to modulate OXPHOS in prostate cancer cells. *Nat. Commun.* **2021**, *12*, 2398. [CrossRef]

261. Dai, Z.; Ramesh, V.; Locasale, J.W. The evolving metabolic landscape of chromatin biology and epigenetics. *Nat. Rev. Genet.* **2020**, *21*, 737–753. [CrossRef]
262. Campbell, S.L.; Wellen, K.E. Metabolic Signaling to the Nucleus in Cancer. *Mol. Cell* **2018**, *71*, 398–408. [CrossRef]
263. Boon, R. Metabolic Fuel for Epigenetic: Nuclear Production Meets Local Consumption. *Front. Genet.* **2021**, *12*, 768996. [CrossRef]
264. Meier, J.L. Metabolic mechanisms of epigenetic regulation. *ACS Chem. Biol.* **2013**, *8*, 2607–2621. [CrossRef]
265. Ramazi, S.; Zahiri, J. Post-translational modifications in proteins: Resources, tools and prediction methods. *Database* **2021**, *2021*, baab012. [CrossRef]
266. Akella, N.M.; Ciraku, L.; Reginato, M.J. Fueling the fire: Emerging role of the hexosamine biosynthetic pathway in cancer. *BMC Biol.* **2019**, *17*, 52. [CrossRef]
267. Kaushik, A.K.; Shojaie, A.; Panzitt, K.; Sonavane, R.; Venghatakrishnan, H.; Manikkam, M.; Zaslavsky, A.; Putluri, V.; Vasu, V.T.; Zhang, Y.; et al. Inhibition of the hexosamine biosynthetic pathway promotes castration-resistant prostate cancer. *Nat. Commun.* **2016**, *7*, 11612. [CrossRef]
268. Itkonen, H.M.; Urbanucci, A.; Martin, S.E.; Khan, A.; Mathelier, A.; Thiede, B.; Walker, S.; Mills, I.G. High OGT activity is essential for MYC-driven proliferation of prostate cancer cells. *Theranostics* **2019**, *9*, 2183–2197. [CrossRef]
269. Choudhary, C.; Weinert, B.T.; Nishida, Y.; Verdin, E.; Mann, M. The growing landscape of lysine acetylation links metabolism and cell signalling. *Nat. Rev. Mol. Cell Biol.* **2014**, *15*, 536–550. [CrossRef]
270. Sivanand, S.; Viney, I.; Wellen, K.E. Spatiotemporal Control of Acetyl-CoA Metabolism in Chromatin Regulation. *Trends Biochem. Sci.* **2018**, *43*, 61–74. [CrossRef] [PubMed]
271. Bolden, J.E.; Peart, M.J.; Johnstone, R.W. Anticancer activities of histone deacetylase inhibitors. *Nat. Rev. Drug Discov.* **2006**, *5*, 769–784. [CrossRef]
272. Amjad, S.; Nisar, S.; Bhat, A.A.; Shah, A.R.; Frenneaux, M.P.; Fakhro, K.; Haris, M.; Reddy, R.; Patay, Z.; Baur, J.; et al. Role of NAD^+ in regulating cellular and metabolic signaling pathways. *Mol. Metab.* **2021**, *49*, 101195. [CrossRef] [PubMed]
273. Hurtado-Bages, S.; Knobloch, G.; Ladurner, A.G.; Buschbeck, M. The taming of PARP1 and its impact on NAD^+ metabolism. *Mol. Metab.* **2020**, *38*, 100950. [CrossRef]
274. Huang, S.B.; Thapa, D.; Munoz, A.R.; Hussain, S.S.; Yang, X.; Bedolla, R.G.; Osmulski, P.; Gaczynska, M.E.; Lai, Z.; Chiu, Y.C.; et al. Androgen deprivation-induced elevated nuclear SIRT1 promotes prostate tumor cell survival by reactivation of AR signaling. *Cancer Lett.* **2021**, *505*, 24–36. [CrossRef] [PubMed]
275. Wang, Z.A.; Cole, P.A. The Chemical Biology of Reversible Lysine Post-translational Modifications. *Cell Chem. Biol.* **2020**, *27*, 953–969. [CrossRef] [PubMed]
276. Hirschey, M.D.; Zhao, Y. Metabolic Regulation by Lysine Malonylation, Succinylation, and Glutarylation. *Mol. Cell. Proteom.* **2015**, *14*, 2308–2315. [CrossRef]
277. Wu, X.; Tao, W.A. Uncovering ubiquitous protein lactylation. *Nat. Methods* **2022**, *19*, 793–794. [CrossRef]
278. Izzo, L.T.; Wellen, K.E. Histone lactylation links metabolism and gene regulation. *Nature* **2019**, *574*, 492–493. [CrossRef]
279. Zhang, D.; Tang, Z.; Huang, H.; Zhou, G.; Cui, C.; Weng, Y.; Liu, W.; Kim, S.; Lee, S.; Perez-Neut, M.; et al. Metabolic regulation of gene expression by histone lactylation. *Nature* **2019**, *574*, 575–580. [CrossRef]
280. Chen, A.N.; Luo, Y.; Yang, Y.H.; Fu, J.T.; Geng, X.M.; Shi, J.P.; Yang, J. Lactylation, a Novel Metabolic Reprogramming Code: Current Status and Prospects. *Front. Immunol.* **2021**, *12*, 688910. [CrossRef]
281. Gu, J.; Zhou, J.; Chen, Q.; Xu, X.; Gao, J.; Li, X.; Shao, Q.; Zhou, B.; Zhou, H.; Wei, S.; et al. Tumor metabolite lactate promotes tumorigenesis by modulating MOESIN lactylation and enhancing TGF-beta signaling in regulatory T cells. *Cell Rep.* **2022**, *39*, 110986. [CrossRef]
282. Xiong, J.; He, J.; Zhu, J.; Pan, J.; Liao, W.; Ye, H.; Wang, H.; Song, Y.; Du, Y.; Cui, B.; et al. Lactylation-driven METTL3-mediated RNA m(6)A modification promotes immunosuppression of tumor-infiltrating myeloid cells. *Mol. Cell* **2022**, *82*, 1660–1677.E10. [CrossRef]
283. Wan, N.; Wang, N.; Yu, S.; Zhang, H.; Tang, S.; Wang, D.; Lu, W.; Li, H.; Delafield, D.G.; Kong, Y.; et al. Cyclic immonium ion of lactyllysine reveals widespread lactylation in the human proteome. *Nat. Methods* **2022**, *19*, 854–864. [CrossRef]
284. Moreno-Yruela, C.; Zhang, D.; Wei, W.; Baek, M.; Liu, W.; Gao, J.; Dankova, D.; Nielsen, A.L.; Bolding, J.E.; Yang, L.; et al. Class I histone deacetylases (HDAC1-3) are histone lysine delactylases. *Sci. Adv.* **2022**, *8*, eabi6696. [CrossRef]
285. Yang, D.; Yin, J.; Shan, L.; Yi, X.; Zhang, W.; Ding, Y. Identification of lysine-lactylated substrates in gastric cancer cells. *iScience* **2022**, *25*, 104630. [CrossRef]
286. Dai, S.K.; Liu, P.P.; Li, X.; Jiao, L.F.; Teng, Z.Q.; Liu, C.M. Dynamic profiling and functional interpretation of histone lysine crotonylation and lactylation during neural development. *Development* **2022**, *149*, dev200049. [CrossRef]
287. Nian, F.; Qian, Y.; Xu, F.; Yang, M.; Wang, H.; Zhang, Z. LDHA promotes osteoblast differentiation through histone lactylation. *Biochem. Biophys. Res. Commun.* **2022**, *615*, 31–35. [CrossRef]
288. Yang, J.; Luo, L.; Zhao, C.; Li, X.; Wang, Z.; Zeng, Z.; Yang, X.; Zheng, X.; Jie, H.; Kang, L.; et al. A Positive Feedback Loop between Inactive VHL-Triggered Histone Lactylation and PDGFRbeta Signaling Drives Clear Cell Renal Cell Carcinoma Progression. *Int. J. Biol. Sci.* **2022**, *18*, 3470–3483. [CrossRef] [PubMed]
289. Mentch, S.J.; Locasale, J.W. One-carbon metabolism and epigenetics: Understanding the specificity. *Ann. N. Y. Acad. Sci.* **2016**, *1363*, 91–98. [CrossRef]

290. Hwang, J.W.; Cho, Y.; Bae, G.U.; Kim, S.N.; Kim, Y.K. Protein arginine methyltransferases: Promising targets for cancer therapy. *Exp. Mol. Med.* **2021**, *53*, 788–808. [CrossRef]
291. Kooistra, S.M.; Helin, K. Molecular mechanisms and potential functions of histone demethylases. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 297–311. [CrossRef]
292. Wang, L.-Y.; Guo, W.; Kim, K.; Pochampalli, M.; Hung, C.-L.; Izumiya, Y.; Kung, H.-J. Histone Demethylases in Prostate Cancer. In *Nuclear Signaling Pathways and Targeting Transcription in Cancer*; Kumar, R., Ed.; Springer: New York, NY, USA, 2014; pp. 373–397. [CrossRef]
293. Wang, H.J.; Pochampalli, M.; Wang, L.Y.; Zou, J.X.; Li, P.S.; Hsu, S.C.; Wang, B.J.; Huang, S.H.; Yang, P.; Yang, J.C.; et al. KDM8/JMJD5 as a dual coactivator of AR and PKM2 integrates AR/EZH2 network and tumor metabolism in CRPC. *Oncogene* **2019**, *38*, 17–32. [CrossRef] [PubMed]
294. Kim, T.D.; Jin, F.; Shin, S.; Oh, S.; Lightfoot, S.A.; Grande, J.P.; Johnson, A.J.; van Deursen, J.M.; Wren, J.D.; Janknecht, R. Histone demethylase JMJD2A drives prostate tumorigenesis through transcription factor ETV1. *J. Clin. Investig.* **2016**, *126*, 706–720. [CrossRef] [PubMed]
295. Fan, L.; Peng, G.; Sahgal, N.; Fazli, L.; Gleave, M.; Zhang, Y.; Hussain, A.; Qi, J. Regulation of c-Myc expression by the histone demethylase JMJD1A is essential for prostate cancer cell growth and survival. *Oncogene* **2016**, *35*, 2441–2452. [CrossRef] [PubMed]
296. Fan, L.; Zhang, F.; Xu, S.; Cui, X.; Hussain, A.; Fazli, L.; Gleave, M.; Dong, X.; Qi, J. Histone demethylase JMJD1A promotes alternative splicing of AR variant 7 (AR-V7) in prostate cancer cells. *Proc. Natl. Acad Sci. USA* **2018**, *115*, E4584–E4593. [CrossRef]
297. Nishiyama, A.; Nakanishi, M. Navigating the DNA methylation landscape of cancer. *Trends Genet.* **2021**, *37*, 1012–1027. [CrossRef]
298. Greenberg, M.V.C.; Bourc'his, D. The diverse roles of DNA methylation in mammalian development and disease. *Nat. Rev. Mol. Cell Biol.* **2019**, *20*, 590–607. [CrossRef]
299. Massie, C.E.; Mills, I.G.; Lynch, A.G. The importance of DNA methylation in prostate cancer development. *J. Steroid Biochem. Mol. Biol.* **2017**, *166*, 1–15. [CrossRef]
300. Millar, D.S.; Ow, K.K.; Paul, C.L.; Russell, P.J.; Molloy, P.L.; Clark, S.J. Detailed methylation analysis of the glutathione S-transferase pi (GSTP1) gene in prostate cancer. *Oncogene* **1999**, *18*, 1313–1324. [CrossRef]
301. Zhao, S.G.; Chen, W.S.; Li, H.; Foye, A.; Zhang, M.; Sjostrom, M.; Aggarwal, R.; Playdle, D.; Liao, A.; Alumkal, J.J.; et al. The DNA methylation landscape of advanced prostate cancer. *Nat. Genet.* **2020**, *52*, 778–789. [CrossRef]
302. Chen, X.Y.; Zhang, J.; Zhu, J.S. The role of m(6)A RNA methylation in human cancer. *Mol. Cancer* **2019**, *18*, 103. [CrossRef]
303. Wang, Y.; Chen, J.; Gao, W.Q.; Yang, R. METTL14 promotes prostate tumorigenesis by inhibiting THBS1 via an m6A-YTHDF2-dependent mechanism. *Cell Death. Discov.* **2022**, *8*, 143. [CrossRef]
304. Cotter, K.A.; Gallon, J.; Uebersax, N.; Rubin, P.; Meyer, K.D.; Piscuoglio, S.; Jaffrey, S.R.; Rubin, M.A. Mapping of m(6)A and Its Regulatory Targets in Prostate Cancer Reveals a METTL3-Low Induction of Therapy Resistance. *Mol. Cancer Res.* **2021**, *19*, 1398–1411. [CrossRef]
305. Lopez, J.; Anazco-Guenkova, A.M.; Monteagudo-Garcia, O.; Blanco, S. Epigenetic and Epitranscriptomic Control in Prostate Cancer. *Genes* **2022**, *13*, 378. [CrossRef]
306. Network, C.G.A.R. The Molecular Taxonomy of Primary Prostate Cancer. *Cell* **2015**, *163*, 1011–1025. [CrossRef]
307. Yong, C.; Stewart, G.D.; Frezza, C. Oncometabolites in renal cancer. *Nat. Rev. Nephrol.* **2020**, *16*, 156–172. [CrossRef]
308. Vander Linden, C.; Corbet, C. Reconciling environment-mediated metabolic heterogeneity with the oncogene-driven cancer paradigm in precision oncology. *Semin. Cell Dev. Biol.* **2020**, *98*, 202–210. [CrossRef]
309. Reina-Campos, M.; Moscat, J.; Diaz-Meco, M. Metabolism shapes the tumor microenvironment. *Curr. Opin. Cell Biol.* **2017**, *48*, 47–53. [CrossRef]
310. Kim, J.; DeBerardinis, R.J. Mechanisms and Implications of Metabolic Heterogeneity in Cancer. *Cell Metab.* **2019**, *30*, 434–446. [CrossRef]
311. Lyssiotis, C.A.; Kimmelman, A.C. Metabolic Interactions in the Tumor Microenvironment. *Trends Cell Biol.* **2017**, *27*, 863–875. [CrossRef]
312. Dey, P.; Kimmelman, A.C.; DePinho, R.A. Metabolic Codependencies in the Tumor Microenvironment. *Cancer Discov.* **2021**, *11*, 1067–1081. [CrossRef]
313. Li, F.; Simon, M.C. Cancer Cells Don't Live Alone: Metabolic Communication within Tumor Microenvironments. *Dev. Cell* **2020**, *54*, 183–195. [CrossRef]
314. Elia, I.; Haigis, M.C. Metabolites and the tumour microenvironment: From cellular mechanisms to systemic metabolism. *Nat. Metab.* **2021**, *3*, 21–32. [CrossRef]
315. Cassim, S.; Pouyssegur, J. Tumor Microenvironment: A Metabolic Player that Shapes the Immune Response. *Int. J. Mol. Sci.* **2019**, *21*, 157. [CrossRef] [PubMed]
316. Ho, P.C.; Liu, P.S. Metabolic communication in tumors: A new layer of immunoregulation for immune evasion. *J. Immunother. Cancer* **2016**, *4*, 4. [CrossRef] [PubMed]
317. Ge, R.; Wang, Z.; Cheng, L. Tumor microenvironment heterogeneity an important mediator of prostate cancer progression and therapeutic resistance. *npj Precis. Oncol.* **2022**, *6*, 31. [CrossRef] [PubMed]
318. Lau, A.N.; Heiden, M.G.V. Metabolism in the Tumor Microenvironment. *Annu. Rev. Cancer Biol.* **2020**, *4*, 17–40. [CrossRef]
319. Zhao, H.; Yang, L.; Baddour, J.; Achreja, A.; Bernard, V.; Moss, T.; Marini, J.C.; Tudawe, T.; Seviour, E.G.; San Lucas, F.A.; et al. Tumor microenvironment derived exosomes pleiotropically modulate cancer cell metabolism. *eLife* **2016**, *5*, e10250. [CrossRef]

320. Lemberg, K.M.; Gori, S.S.; Tsukamoto, T.; Rais, R.; Slusher, B.S. Clinical development of metabolic inhibitors for oncology. *J. Clin. Investig.* **2022**, *132*, e148550. [CrossRef]
321. Bader, J.E.; Voss, K.; Rathmell, J.C. Targeting Metabolism to Improve the Tumor Microenvironment for Cancer Immunotherapy. *Mol. Cell* **2020**, *78*, 1019–1033. [CrossRef]
322. Stultz, J.; Fong, L. How to turn up the heat on the cold immune microenvironment of metastatic prostate cancer. *Prostate Cancer Prostatic Dis.* **2021**, *24*, 697–717. [CrossRef]
323. Martin, A.M.; Nirschl, T.R.; Nirschl, C.J.; Francica, B.J.; Kochel, C.M.; van Bokhoven, A.; Meeker, A.K.; Lucia, M.S.; Anders, R.A.; DeMarzo, A.M.; et al. Paucity of PD-L1 expression in prostate cancer: Innate and adaptive immune resistance. *Prostate Cancer Prostatic Dis.* **2015**, *18*, 325–332. [CrossRef] [PubMed]
324. Melo, C.M.; Vidotto, T.; Chaves, L.P.; Lautert-Dutra, W.; Reis, R.B.D.; Squire, J.A. The Role of Somatic Mutations on the Immune Response of the Tumor Microenvironment in Prostate Cancer. *Int. J. Mol. Sci.* **2021**, *22*, 9550. [CrossRef] [PubMed]
325. Guerra, L.; Bonetti, L.; Brenner, D. Metabolic Modulation of Immunity: A New Concept in Cancer Immunotherapy. *Cell Rep.* **2020**, *32*, 107848. [CrossRef] [PubMed]
326. Roy, D.G.; Kaymak, I.; Williams, K.S.; Ma, E.H.; Jones, R.G. Immunometabolism in the Tumor Microenvironment. *Annu. Rev. Cancer Biol.* **2021**, *5*, 137–159. [CrossRef]
327. Viola, A.; Munari, F.; Sanchez-Rodriguez, R.; Scolaro, T.; Castegna, A. The Metabolic Signature of Macrophage Responses. *Front. Immunol.* **2019**, *10*, 1462. [CrossRef]
328. Chang, C.H.; Qiu, J.; O'Sullivan, D.; Buck, M.D.; Noguchi, T.; Curtis, J.D.; Chen, Q.; Gindin, M.; Gubin, M.M.; van der Windt, G.J.; et al. Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell* **2015**, *162*, 1229–1241. [CrossRef]
329. Opitz, C.A.; Somarribas Patterson, L.F.; Mohapatra, S.R.; Dewi, D.L.; Sadik, A.; Platten, M.; Trump, S. The therapeutic potential of targeting tryptophan catabolism in cancer. *Br. J. Cancer* **2020**, *122*, 30–44. [CrossRef]
330. Li, F.; Zhao, Z.; Zhang, Z.; Zhang, Y.; Guan, W. Tryptophan metabolism induced by TDO2 promotes prostatic cancer chemotherapy resistance in a AhR/c-Myc dependent manner. *BMC Cancer* **2021**, *21*, 1112. [CrossRef]
331. Cheong, J.E.; Sun, L. Targeting the IDO1/TDO2-KYN-AhR Pathway for Cancer Immunotherapy—Challenges and Opportunities. *Trends Pharm. Sci.* **2018**, *39*, 307–325. [CrossRef]
332. Wang, X.F.; Wang, H.S.; Wang, H.; Zhang, F.; Wang, K.F.; Guo, Q.; Zhang, G.; Cai, S.H.; Du, J. The role of indoleamine 2,3-dioxygenase (IDO) in immune tolerance: Focus on macrophage polarization of THP-1 cells. *Cell. Immunol.* **2014**, *289*, 42–48. [CrossRef]
333. Prendergast, G.C.; Malachowski, W.P.; DuHadaway, J.B.; Muller, A.J. Discovery of IDO1 Inhibitors: From Bench to Bedside. *Cancer Res.* **2017**, *77*, 6795–6811. [CrossRef]
334. Jha, G.G.; Gupta, S.; Tagawa, S.T.; Koopmeiners, J.S.; Vivek, S.; Dudek, A.Z.; Cooley, S.A.; Blazar, B.R.; Miller, J.S. A phase II randomized, double-blind study of sipuleucel-T followed by IDO pathway inhibitor, indoximod, or placebo in the treatment of patients with metastatic castration resistant prostate cancer (mCRPC). *J. Clin. Oncol.* **2017**, *35*, 3066. [CrossRef]
335. Luo, M.; Brooks, M.; Wicha, M.S. Asparagine and Glutamine: Co-conspirators Fueling Metastasis. *Cell Metab.* **2018**, *27*, 947–949. [CrossRef]
336. Vettore, L.; Westbrook, R.L.; Tennant, D.A. New aspects of amino acid metabolism in cancer. *Br. J. Cancer* **2020**, *122*, 150–156. [CrossRef]
337. Wei, Z.; Liu, X.; Cheng, C.; Yu, W.; Yi, P. Metabolism of Amino Acids in Cancer. *Front. Cell Dev. Biol.* **2020**, *8*, 603837. [CrossRef]
338. Pavlova, N.N.; Hui, S.; Ghergurovich, J.M.; Fan, J.; Intlekofer, A.M.; White, R.M.; Rabinowitz, J.D.; Thompson, C.B.; Zhang, J. As Extracellular Glutamine Levels Decline, Asparagine Becomes an Essential Amino Acid. *Cell Metab.* **2018**, *27*, 428–438.E5. [CrossRef]
339. Linares, J.F.; Cordes, T.; Duran, A.; Reina-Campos, M.; Valencia, T.; Ahn, C.S.; Castilla, E.A.; Moscat, J.; Metallo, C.M.; Diaz-Meco, M.T. ATF4-Induced Metabolic Reprograming Is a Synthetic Vulnerability of the p62-Deficient Tumor Stroma. *Cell Metab.* **2017**, *26*, 817–829.E6. [CrossRef]
340. Vaupel, P.; Schmidberger, H.; Mayer, A. The Warburg effect: Essential part of metabolic reprogramming and central contributor to cancer progression. *Int. J. Radiat. Biol.* **2019**, *95*, 912–919. [CrossRef]
341. Rawat, D.; Chhonker, S.K.; Naik, R.A.; Mehrotra, A.; Trigun, S.K.; Koiri, R.K. Lactate as a signaling molecule: Journey from dead end product of glycolysis to tumor survival. *Front. Biosci.* **2019**, *24*, 366–381. [CrossRef]
342. Wang, Z.H.; Peng, W.B.; Zhang, P.; Yang, X.P.; Zhou, Q. Lactate in the tumour microenvironment: From immune modulation to therapy. *eBioMedicine* **2021**, *73*, 103627. [CrossRef]
343. Hayes, C.; Donohoe, C.L.; Davern, M.; Donlon, N.E. The oncogenic and clinical implications of lactate induced immunosuppression in the tumour microenvironment. *Cancer Lett.* **2021**, *500*, 75–86. [CrossRef] [PubMed]
344. Bottcher, M.; Baur, R.; Stoll, A.; Mackensen, A.; Mougiakakos, D. Linking Immunoevasion and Metabolic Reprogramming in B-Cell-Derived Lymphomas. *Front. Oncol.* **2020**, *10*, 594782. [CrossRef] [PubMed]
345. Lotscher, J.; Balmer, M.L. Sensing between reactions—How the metabolic microenvironment shapes immunity. *Clin. Exp. Immunol.* **2019**, *197*, 161–169. [CrossRef] [PubMed]
346. Magalhaes, I.; Yogev, O.; Mattsson, J.; Schurich, A. The Metabolic Profile of Tumor and Virally Infected Cells Shapes Their Microenvironment Counteracting T Cell Immunity. *Front. Immunol.* **2019**, *10*, 2309. [CrossRef] [PubMed]

347. Kumagai, S.; Koyama, S.; Itahashi, K.; Tanegashima, T.; Lin, Y.T.; Togashi, Y.; Kamada, T.; Irie, T.; Okumura, G.; Kono, H.; et al. Lactic acid promotes PD-1 expression in regulatory T cells in highly glycolytic tumor microenvironments. *Cancer Cell* **2022**, *40*, 201–218.E9. [CrossRef]
348. Deng, H.; Kan, A.; Lyu, N.; He, M.; Huang, X.; Qiao, S.; Li, S.; Lu, W.; Xie, Q.; Chen, H.; et al. Tumor-derived lactate inhibit the efficacy of lenvatinib through regulating PD-L1 expression on neutrophil in hepatocellular carcinoma. *J. Immunother. Cancer* **2021**, *9*, e002305. [CrossRef]
349. Watson, M.J.; Vignali, P.D.A.; Mullett, S.J.; Overacre-Delgoffe, A.E.; Peralta, R.M.; Grebinoski, S.; Menk, A.V.; Rittenhouse, N.L.; DePeaux, K.; Whetstone, R.D.; et al. Metabolic support of tumour-infiltrating regulatory T cells by lactic acid. *Nature* **2021**, *591*, 645–651. [CrossRef]
350. Angelin, A.; Gil-de-Gomez, L.; Dahiya, S.; Jiao, J.; Guo, L.; Levine, M.H.; Wang, Z.; Quinn, W.J., 3rd; Kopinski, P.K.; Wang, L.; et al. Foxp3 Reprograms T Cell Metabolism to Function in Low-Glucose, High-Lactate Environments. *Cell Metab.* **2017**, *25*, 1282–1293.E7. [CrossRef]
351. Ho, P.C.; Bihuniak, J.D.; Macintyre, A.N.; Staron, M.; Liu, X.; Amezquita, R.; Tsui, Y.C.; Cui, G.; Micevic, G.; Perales, J.C.; et al. Phosphoenolpyruvate Is a Metabolic Checkpoint of Anti-tumor T Cell Responses. *Cell* **2015**, *162*, 1217–1228. [CrossRef]
352. Kedia-Mehta, N.; Finlay, D.K. Competition for nutrients and its role in controlling immune responses. *Nat. Commun.* **2019**, *10*, 2123. [CrossRef]
353. Brand, A.; Singer, K.; Koehl, G.E.; Kolitzus, M.; Schoenhammer, G.; Thiel, A.; Matos, C.; Bruss, C.; Klobuch, S.; Peter, K.; et al. LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells. *Cell Metab.* **2016**, *24*, 657–671. [CrossRef]
354. Fischer, K.; Hoffmann, P.; Voelkl, S.; Meidenbauer, N.; Ammer, J.; Edinger, M.; Gottfried, E.; Schwarz, S.; Rothe, G.; Hoves, S.; et al. Inhibitory effect of tumor cell-derived lactic acid on human T cells. *Blood* **2007**, *109*, 3812–3819. [CrossRef] [PubMed]
355. Comito, G.; Iscaro, A.; Bacci, M.; Morandi, A.; Ippolito, L.; Parri, M.; Montagnani, I.; Raspollini, M.R.; Serni, S.; Simeoni, L.; et al. Lactate modulates CD4(+) T-cell polarization and induces an immunosuppressive environment, which sustains prostate carcinoma progression via TLR8/miR21 axis. *Oncogene* **2019**, *38*, 3681–3695. [CrossRef] [PubMed]
356. Calcinotto, A.; Filipazzi, P.; Grioni, M.; Iero, M.; De Milito, A.; Ricupito, A.; Cova, A.; Canese, R.; Jachetti, E.; Rossetti, M.; et al. Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. *Cancer Res.* **2012**, *72*, 2746–2756. [CrossRef] [PubMed]
357. Manoharan, I.; Prasad, P.D.; Thangaraju, M.; Manicassamy, S. Lactate-Dependent Regulation of Immune Responses by Dendritic Cells and Macrophages. *Front. Immunol.* **2021**, *12*, 691134. [CrossRef]
358. Brown, T.P.; Bhattacharjee, P.; Ramachandran, S.; Sivaprakasam, S.; Ristic, B.; Sikder, M.O.F.; Ganapathy, V. The lactate receptor GPR81 promotes breast cancer growth via a paracrine mechanism involving antigen-presenting cells in the tumor microenvironme.ent. *Oncogene* **2020**, *39*, 3292–3304. [CrossRef]
359. Hoque, R.; Farooq, A.; Ghani, A.; Gorelick, F.; Mehal, W.Z. Lactate reduces liver and pancreatic injury in Toll-like receptor- and inflammasome-mediated inflammation via GPR81-mediated suppression of innate immunity. *Gastroenterology* **2014**, *146*, 1763–1774. [CrossRef]
360. Errea, A.; Cayet, D.; Marchetti, P.; Tang, C.; Kluza, J.; Offermanns, S.; Sirard, J.C.; Rumbo, M. Lactate Inhibits the Pro-Inflammatory Response and Metabolic Reprogramming in Murine Macrophages in a GPR81-Independent Manner. *PLoS ONE* **2016**, *11*, e0163694. [CrossRef]
361. Raychaudhuri, D.; Bhattacharya, R.; Sinha, B.P.; Liu, C.S.C.; Ghosh, A.R.; Rahaman, O.; Bandopadhyay, P.; Sarif, J.; D'Rozario, R.; Paul, S.; et al. Lactate Induces Pro-tumor Reprogramming in Intratumoral Plasmacytoid Dendritic Cells. *Front. Immunol.* **2019**, *10*, 1878. [CrossRef]
362. Chen, P.; Zuo, H.; Xiong, H.; Kolar, M.J.; Chu, Q.; Saghatelian, A.; Siegwart, D.J.; Wan, Y. Gpr132 sensing of lactate mediates tumor-macrophage interplay to promote breast cancer metastasis. *Proc. Natl. Acad Sci. USA* **2017**, *114*, 580–585. [CrossRef]
363. Gottfried, E.; Kunz-Schughart, L.A.; Ebner, S.; Mueller-Klieser, W.; Hoves, S.; Andreesen, R.; Mackensen, A.; Kreutz, M. Tumor-derived lactic acid modulates dendritic cell activation and antigen expression. *Blood* **2006**, *107*, 2013–2021. [CrossRef]
364. Dietl, K.; Renner, K.; Dettmer, K.; Timischl, B.; Eberhart, K.; Dorn, C.; Hellerbrand, C.; Kastenberger, M.; Kunz-Schughart, L.A.; Oefner, P.J.; et al. Lactic acid and acidification inhibit TNF secretion and glycolysis of human monocytes. *J. Immunol.* **2010**, *184*, 1200–1209. [CrossRef]
365. Zhang, L.; Li, S. Lactic acid promotes macrophage polarization through MCT-HIF1alpha signaling in gastric cancer. *Exp. Cell Res.* **2020**, *388*, 111846. [CrossRef]
366. El-Kenawi, A.; Gatenbee, C.; Robertson-Tessi, M.; Bravo, R.; Dhillon, J.; Balagurunathan, Y.; Berglund, A.; Vishvakarma, N.; Ibrahim-Hashim, A.; Choi, J.; et al. Acidity promotes tumour progression by altering macrophage phenotype in prostate cancer. *Br. J. Cancer* **2019**, *121*, 556–566. [CrossRef]
367. Sangsuwan, R.; Thuamsang, B.; Pacifici, N.; Allen, R.; Han, H.; Miakicheva, S.; Lewis, J.S. Lactate Exposure Promotes Immunosuppressive Phenotypes in Innate Immune Cells. *Cell. Mol. Bioeng.* **2020**, *13*, 541–557. [CrossRef]
368. Caronni, N.; Simoncello, F.; Stafetta, F.; Guarnaccia, C.; Ruiz-Moreno, J.S.; Opitz, B.; Galli, T.; Proux-Gillardeaux, V.; Benvenuti, F. Downregulation of Membrane Trafficking Proteins and Lactate Conditioning Determine Loss of Dendritic Cell Function in Lung Cancer. *Cancer Res.* **2018**, *78*, 1685–1699. [CrossRef]

369. Bae, S.; Park, P.S.U.; Lee, Y.; Mun, S.H.; Giannopoulou, E.; Fujii, T.; Lee, K.P.; Violante, S.N.; Cross, J.R.; Park-Min, K.H. MYC-mediated early glycolysis negatively regulates proinflammatory responses by controlling IRF4 in inflammatory macrophages. *Cell Rep.* **2021**, *35*, 109264. [CrossRef]
370. Tu, C.E.; Hu, Y.; Zhou, P.; Guo, X.; Gu, C.; Zhang, Y.; Li, A.; Liu, S. Lactate and TGF-beta antagonistically regulate inflammasome activation in the tumor microenvironment. *J. Cell. Physiol.* **2021**, *236*, 4528–4537. [CrossRef] [PubMed]
371. Zhang, W.; Wang, G.; Xu, Z.G.; Tu, H.; Hu, F.; Dai, J.; Chang, Y.; Chen, Y.; Lu, Y.; Zeng, H.; et al. Lactate Is a Natural Suppressor of RLR Signaling by Targeting MAVS. *Cell* **2019**, *178*, 176–189.E15. [CrossRef]
372. Wang, X.; Liu, H.; Ni, Y.; Shen, P.; Han, X. Lactate shuttle: From substance exchange to regulatory mechanism. *Hum. Cell* **2022**, *35*, 1–14. [CrossRef]
373. Draoui, N.; Feron, O. Lactate shuttles at a glance: From physiological paradigms to anti-cancer treatments. *Dis. Models Mech.* **2011**, *4*, 727–732. [CrossRef] [PubMed]
374. Pertega-Gomes, N.; Vizcaino, J.R.; Attig, J.; Jurmeister, S.; Lopes, C.; Baltazar, F. A lactate shuttle system between tumour and stromal cells is associated with poor prognosis in prostate cancer. *BMC Cancer* **2014**, *14*, 352. [CrossRef] [PubMed]
375. Sanita, P.; Capulli, M.; Teti, A.; Galatioto, G.P.; Vicentini, C.; Chiarugi, P.; Bologna, M.; Angelucci, A. Tumor-stroma metabolic relationship based on lactate shuttle can sustain prostate cancer progression. *BMC Cancer* **2014**, *14*, 154. [CrossRef] [PubMed]
376. Fiaschi, T.; Marini, A.; Giannoni, E.; Taddei, M.L.; Gandellini, P.; De Donatis, A.; Lanciotti, M.; Serni, S.; Cirri, P.; Chiarugi, P. Reciprocal metabolic reprogramming through lactate shuttle coordinately influences tumor-stroma interplay. *Cancer Res.* **2012**, *72*, 5130–5140. [CrossRef] [PubMed]
377. De la Cruz-Lopez, K.G.; Castro-Munoz, L.J.; Reyes-Hernandez, D.O.; Garcia-Carranca, A.; Manzo-Merino, J. Lactate in the Regulation of Tumor Microenvironment and Therapeutic Approaches. *Front. Oncol.* **2019**, *9*, 1143. [CrossRef] [PubMed]
378. Eheman, C.; Henley, S.J.; Ballard-Barbash, R.; Jacobs, E.J.; Schymura, M.J.; Noone, A.M.; Pan, L.; Anderson, R.N.; Fulton, J.E.; Kohler, B.A.; et al. Annual Report to the Nation on the status of cancer, 1975–2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer* **2012**, *118*, 2338–2366. [CrossRef]
379. Laurent, V.; Guerard, A.; Mazerolles, C.; Le Gonidec, S.; Toulet, A.; Nieto, L.; Zaidi, F.; Majed, B.; Garandeau, D.; Socrier, Y.; et al. Periprostatic adipocytes act as a driving force for prostate cancer progression in obesity. *Nat. Commun.* **2016**, *7*, 10230. [CrossRef]
380. Cao, Y. Adipocyte and lipid metabolism in cancer drug resistance. *J. Clin. Investig.* **2019**, *129*, 3006–3017. [CrossRef]
381. Zimmermann, R.; Lass, A.; Haemmerle, G.; Zechner, R. Fate of fat: The role of adipose triglyceride lipase in lipolysis. *Biochim. Biophys. Acta* **2009**, *1791*, 494–500. [CrossRef]
382. Berndt, J.; Kovacs, P.; Ruschke, K.; Kloting, N.; Fasshauer, M.; Schon, M.R.; Korner, A.; Stumvoll, M.; Bluher, M. Fatty acid synthase gene expression in human adipose tissue: Association with obesity and type 2 diabetes. *Diabetologia* **2007**, *50*, 1472–1480. [CrossRef]
383. Swinnen, J.V.; Esquenet, M.; Goossens, K.; Heyns, W.; Verhoeven, G. Androgens stimulate fatty acid synthase in the human prostate cancer cell line LNCaP. *Cancer Res.* **1997**, *57*, 1086–1090. [PubMed]
384. Tousignant, K.D.; Rockstroh, A.; Poad, B.L.J.; Talebi, A.; Young, R.S.E.; Taherian Fard, A.; Gupta, R.; Zang, T.; Wang, C.; Lehman, M.L.; et al. Therapy-induced lipid uptake and remodeling underpin ferroptosis hypersensitivity in prostate cancer. *Cancer Metab.* **2020**, *8*, 11. [CrossRef] [PubMed]
385. Lochner, M.; Berod, L.; Sparwasser, T. Fatty acid metabolism in the regulation of T cell function. *Trends Immunol.* **2015**, *36*, 81–91. [CrossRef]
386. Harris, R.E. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. *Inflammopharmacology* **2009**, *17*, 55–67. [CrossRef] [PubMed]
387. Pruthi, R.S.; Derksen, J.E.; Moore, D. A pilot study of use of the cyclooxygenase-2 inhibitor celecoxib in recurrent prostate cancer after definitive radiation therapy or radical prostatectomy. *BJU Int.* **2004**, *93*, 275–278. [CrossRef]
388. Bottcher, J.P.; Bonavita, E.; Chakravarty, P.; Blees, H.; Cabeza-Cabrerizo, M.; Sammicheli, S.; Rogers, N.C.; Sahai, E.; Zelenay, S.; Reis e Sousa, C. NK Cells Stimulate Recruitment of cDC1 into the Tumor Microenvironment Promoting Cancer Immune Control. *Cell* **2018**, *172*, 1022–1037.E14. [CrossRef]
389. Gupta, S.; Srivastava, M.; Ahmad, N.; Sakamoto, K.; Bostwick, D.G.; Mukhtar, H. Lipoxygenase-5 is overexpressed in prostate adenocarcinoma. *Cancer* **2001**, *91*, 737–743. [CrossRef]
390. Joshua, A.M.; Armstrong, A.; Crumbaker, M.; Scher, H.I.; de Bono, J.; Tombal, B.; Hussain, M.; Sternberg, C.N.; Gillessen, S.; Carles, J.; et al. Statin and metformin use and outcomes in patients with castration-resistant prostate cancer treated with enzalutamide: A meta-analysis of AFFIRM, PREVAIL and PROSPER. *Eur. J. Cancer* **2022**, *170*, 285–295. [CrossRef]
391. Khan, S.; Chang, S.H.; Hicks, V.; Wang, M.; Grubb, R.L., 3rd; Drake, B.F. Improved survival with post-diagnostic metformin and statin use in a racially diverse cohort of US Veterans with advanced prostate cancer. *Prostate Cancer Prostatic Dis.* 2021; *online ahead of print*. [CrossRef]
392. Swinney, D.C.; Anthony, J. How were new medicines discovered? *Nat. Rev. Drug Discov.* **2011**, *10*, 507–519. [CrossRef]
393. Zheng, W.; Thorne, N.; McKew, J.C. Phenotypic screens as a renewed approach for drug discovery. *Drug Discov. Today* **2013**, *18*, 1067–1073. [CrossRef] [PubMed]
394. Schenone, M.; Dancik, V.; Wagner, B.K.; Clemons, P.A. Target identification and mechanism of action in chemical biology and drug discovery. *Nat. Chem. Biol.* **2013**, *9*, 232–240. [CrossRef] [PubMed]

395. Lee, Y.; Wiriyasermkul, P.; Jin, C.; Quan, L.; Ohgaki, R.; Okuda, S.; Kusakizako, T.; Nishizawa, T.; Oda, K.; Ishitani, R.; et al. Cryo-EM structure of the human L-type amino acid transporter 1 in complex with glycoprotein CD98hc. *Nat. Struct. Mol. Biol.* **2019**, *26*, 510–517. [CrossRef] [PubMed]
396. Jeckelmann, J.M.; Fotiadis, D. Sub-Nanometer Cryo-EM Density Map of the Human Heterodimeric Amino Acid Transporter 4F2hc-LAT2. *Int. J. Mol. Sci.* **2020**, *21*, 7094. [CrossRef] [PubMed]
397. Wang, N.; Jiang, X.; Zhang, S.; Zhu, A.; Yuan, Y.; Xu, H.; Lei, J.; Yan, C. Structural basis of human monocarboxylate transporter 1 inhibition by anti-cancer drug candidates. *Cell* **2021**, *184*, 370–383.E13. [CrossRef]
398. Zhang, B.; Jin, Q.; Xu, L.; Li, N.; Meng, Y.; Chang, S.; Zheng, X.; Wang, J.; Chen, Y.; Neculai, D.; et al. Cooperative transport mechanism of human monocarboxylate transporter 2. *Nat. Commun.* **2020**, *11*, 2429. [CrossRef]
399. Yuan, Y.; Kong, F.; Xu, H.; Zhu, A.; Yan, N.; Yan, C. Cryo-EM structure of human glucose transporter GLUT4. *Nat. Commun.* **2022**, *13*, 2671. [CrossRef]
400. Ban, F.; Dalal, K.; Li, H.; LeBlanc, E.; Rennie, P.S.; Cherkasov, A. Best Practices of Computer-Aided Drug Discovery: Lessons Learned from the Development of a Preclinical Candidate for Prostate Cancer with a New Mechanism of Action. *J. Chem. Inf. Model.* **2017**, *57*, 1018–1028. [CrossRef]
401. Ton, A.T.; Gentile, F.; Hsing, M.; Ban, F.; Cherkasov, A. Rapid Identification of Potential Inhibitors of SARS-CoV-2 Main Protease by Deep Docking of 1.3 Billion Compounds. *Mol. Inf.* **2020**, *39*, e2000028. [CrossRef]
402. Ekins, S. The Next Era: Deep Learning in Pharmaceutical Research. *Pharm. Res.* **2016**, *33*, 2594–2603. [CrossRef]
403. Fernandez, M.; Ban, F.; Woo, G.; Hsing, M.; Yamazaki, T.; LeBlanc, E.; Rennie, P.S.; Welch, W.J.; Cherkasov, A. Toxic Colors: The Use of Deep Learning for Predicting Toxicity of Compounds Merely from Their Graphic Images. *J. Chem. Inf. Model.* **2018**, *58*, 1533–1543. [CrossRef]
404. Gentile, F.; Agrawal, V.; Hsing, M.; Ton, A.T.; Ban, F.; Norinder, U.; Gleave, M.E.; Cherkasov, A. Deep Docking: A Deep Learning Platform for Augmentation of Structure Based Drug Discovery. *ACS Cent. Sci.* **2020**, *6*, 939–949. [CrossRef]
405. Friesner, R.A.; Banks, J.L.; Murphy, R.B.; Halgren, T.A.; Klicic, J.J.; Mainz, D.T.; Repasky, M.P.; Knoll, E.H.; Shelley, M.; Perry, J.K.; et al. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J. Med. Chem.* **2004**, *47*, 1739–1749. [CrossRef]
406. Santos-Martins, D.; Solis-Vasquez, L.; Tillack, A.F.; Sanner, M.F.; Koch, A.; Forli, S. Accelerating AutoDock4 with GPUs and Gradient-Based Local Search. *J. Chem. Theory Comput.* **2021**, *17*, 1060–1073. [CrossRef]
407. Wang, L.; Wu, Y.; Deng, Y.; Kim, B.; Pierce, L.; Krilov, G.; Lupyan, D.; Robinson, S.; Dahlgren, M.K.; Greenwood, J.; et al. Accurate and reliable prediction of relative ligand binding potency in prospective drug discovery by way of a modern free-energy calculation protocol and force field. *J. Am. Chem. Soc.* **2015**, *137*, 2695–2703. [CrossRef]
408. Jumper, J.; Evans, R.; Pritzel, A.; Green, T.; Figurnov, M.; Ronneberger, O.; Tunyasuvunakool, K.; Bates, R.; Zidek, A.; Potapenko, A.; et al. Highly accurate protein structure prediction with AlphaFold. *Nature* **2021**, *596*, 583–589. [CrossRef]
409. Shi, R.; Pan, P.; Lv, R.; Ma, C.; Wu, E.; Guo, R.; Zhao, Z.; Song, H.; Zhou, J.; Liu, Y.; et al. High-throughput glycolytic inhibitor discovery targeting glioblastoma by graphite dots-assisted LDI mass spectrometry. *Sci. Adv.* **2022**, *8*, eabl4923. [CrossRef]
410. Wagner, B.K.; Schreiber, S.L. The Power of Sophisticated Phenotypic Screening and Modern Mechanism-of-Action Methods. *Cell Chem. Biol.* **2016**, *23*, 3–9. [CrossRef]
411. Birsoy, K.; Wang, T.; Chen, W.W.; Freinkman, E.; Abu-Remaileh, M.; Sabatini, D.M. An Essential Role of the Mitochondrial Electron Transport Chain in Cell Proliferation Is to Enable Aspartate Synthesis. *Cell* **2015**, *162*, 540–551. [CrossRef]
412. Boonekamp, F.J.; Knibbe, E.; Vieira-Lara, M.A.; Wijsman, M.; Luttik, M.A.H.; van Eunen, K.; Ridder, M.D.; Bron, R.; Almonacid Suarez, A.M.; van Rijn, P.; et al. Full humanization of the glycolytic pathway in *Saccharomyces cerevisiae*. *Cell Rep.* **2022**, *39*, 111010. [CrossRef]
413. Patra, K.C.; Wang, Q.; Bhaskar, P.T.; Miller, L.; Wang, Z.; Wheaton, W.; Chandel, N.; Laakso, M.; Muller, W.J.; Allen, E.L.; et al. Hexokinase 2 is required for tumor initiation and maintenance and its systemic deletion is therapeutic in mouse models of cancer. *Cancer Cell* **2013**, *24*, 213–228. [CrossRef] [PubMed]
414. Shan, W.; Zhou, Y.; Tam, K.Y. The development of small-molecule inhibitors targeting hexokinase 2. *Drug Discov. Today* **2022**, *27*, 2574–2585. [CrossRef] [PubMed]
415. Wolf, A.; Agnihotri, S.; Micallef, J.; Mukherjee, J.; Sabha, N.; Cairns, R.; Hawkins, C.; Guha, A. Hexokinase 2 is a key mediator of aerobic glycolysis and promotes tumor growth in human glioblastoma multiforme. *J. Exp. Med.* **2011**, *208*, 313–326. [CrossRef]
416. Mehta, M.M.; Weinberg, S.E.; Steinert, E.M.; Chhiba, K.; Martinez, C.A.; Gao, P.; Perlman, H.R.; Bryce, P.; Hay, N.; Chandel, N.S. Hexokinase 2 is dispensable for T cell-dependent immunity. *Cancer Metab.* **2018**, *6*, 10. [CrossRef] [PubMed]
417. Xu, S.; Herschman, H.R. A Tumor Agnostic Therapeutic Strategy for Hexokinase 1-Null/Hexokinase 2-Positive Cancers. *Cancer Res.* **2019**, *79*, 5907–5914. [CrossRef]
418. Xu, S.; Zhou, T.; Doh, H.M.; Trinh, K.R.; Catapang, A.; Lee, J.T.; Braas, D.; Bayley, N.A.; Yamada, R.E.; Vasuthasawat, A.; et al. An HK2 Antisense Oligonucleotide Induces Synthetic Lethality in HK1(-)HK2(+) Multiple Myeloma. *Cancer Res.* **2019**, *79*, 2748–2760. [CrossRef]
419. Jiang, J.; Walsh, M.J.; Brimacombe, K.R.; Anastasiou, D.; Yu, Y.; Israelsen, W.J.; Hong, B.S.; Tempel, W.; Dimov, S.; Veith, H.; et al. ML265: A potent PKM2 activator induces tetramerization and reduces tumor formation and size in a mouse xenograft model. In *Probe Reports from the NIH Molecular Libraries Program*; National Center for Biotechnology Information: Bethesda, MD, USA, 2010.

420. Anastasiou, D.; Yu, Y.; Israelsen, W.J.; Jiang, J.K.; Boxer, M.B.; Hong, B.S.; Tempel, W.; Dimov, S.; Shen, M.; Jha, A.; et al. Pyruvate kinase M2 activators promote tetramer formation and suppress tumorigenesis. *Nat. Chem. Biol.* **2012**, *8*, 839–847. [CrossRef]
421. Lin, Y.H.; Satani, N.; Hammoudi, N.; Yan, V.C.; Barekatain, Y.; Khadka, S.; Ackroyd, J.J.; Georgiou, D.K.; Pham, C.D.; Arthur, K.; et al. An enolase inhibitor for the targeted treatment of ENO1-deleted cancers. *Nat. Metab.* **2020**, *2*, 1413–1426. [CrossRef]
422. Muller, F.L.; Colla, S.; Aquilanti, E.; Manzo, V.E.; Genovese, G.; Lee, J.; Eisenson, D.; Narurkar, R.; Deng, P.; Nezi, L.; et al. Passenger deletions generate therapeutic vulnerabilities in cancer. *Nature* **2012**, *488*, 337–342. [CrossRef]
423. Wise, D.R.; Thompson, C.B. Glutamine addiction: A new therapeutic target in cancer. *Trends Biochem. Sci.* **2010**, *35*, 427–433. [CrossRef]
424. Altman, B.J.; Stine, Z.E.; Dang, C.V. From Krebs to clinic: Glutamine metabolism to cancer therapy. *Nat. Rev. Cancer* **2016**, *16*, 619–634. [CrossRef]
425. Gross, M.I.; Demo, S.D.; Dennison, J.B.; Chen, L.; Chernov-Rogan, T.; Goyal, B.; Janes, J.R.; Laidig, G.J.; Lewis, E.R.; Li, J.; et al. Antitumor activity of the glutaminase inhibitor CB-839 in triple-negative breast cancer. *Mol. Cancer* **2014**, *13*, 890–901. [CrossRef]
426. Leone, R.D.; Zhao, L.; Englert, J.M.; Sun, I.M.; Oh, M.H.; Sun, I.H.; Arwood, M.L.; Bettencourt, I.A.; Patel, C.H.; Wen, J.; et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. *Science* **2019**, *366*, 1013–1021. [CrossRef]
427. Kridel, S.J.; Axelrod, F.; Rozenkrantz, N.; Smith, J.W. Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity. *Cancer Res.* **2004**, *64*, 2070–2075. [CrossRef]
428. Pizer, E.S.; Jackisch, C.; Wood, F.D.; Pasternack, G.R.; Davidson, N.E.; Kuhajda, F.P. Inhibition of fatty acid synthesis induces programmed cell death in human breast cancer cells. *Cancer Res.* **1996**, *56*, 2745–2747.
429. Kuhajda, F.P.; Pizer, E.S.; Li, J.N.; Mani, N.S.; Frehywot, G.L.; Townsend, C.A. Synthesis and antitumor activity of an inhibitor of fatty acid synthase. *Proc. Natl. Acad Sci. USA* **2000**, *97*, 3450–3454. [CrossRef]
430. Loftus, T.M.; Jaworsky, D.E.; Frehywot, G.L.; Townsend, C.A.; Ronnett, G.V.; Lane, M.D.; Kuhajda, F.P. Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors. *Science* **2000**, *288*, 2379–2381. [CrossRef]
431. Thupari, J.N.; Landree, L.E.; Ronnett, G.V.; Kuhajda, F.P. C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity. *Proc. Natl. Acad Sci. USA* **2002**, *99*, 9498–9502. [CrossRef]
432. Hardwicke, M.A.; Rendina, A.R.; Williams, S.P.; Moore, M.L.; Wang, L.; Krueger, J.A.; Plant, R.N.; Totoritis, R.D.; Zhang, G.; Briand, J.; et al. A human fatty acid synthase inhibitor binds beta-ketoacyl reductase in the keto-substrate site. *Nat. Chem. Biol.* **2014**, *10*, 774–779. [CrossRef]
433. Alwarawrah, Y.; Hughes, P.; Loiselle, D.; Carlson, D.A.; Darr, D.B.; Jordan, J.L.; Xiong, J.; Hunter, L.M.; Dubois, L.G.; Thompson, J.W.; et al. Fasnall, a Selective FASN Inhibitor, Shows Potent Anti-tumor Activity in the MMTV-Neu Model of HER2(+) Breast Cancer. *Cell Chem. Biol.* **2016**, *23*, 678–688. [CrossRef]
434. Kley, J.T.; Mack, J.; Hamilton, B.; Scheuerer, S.; Redemann, N. Discovery of BI 99179, a potent and selective inhibitor of type I fatty acid synthase with central exposure. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5924–5927. [CrossRef] [PubMed]
435. Falchook, G.; Infante, J.; Arkenau, H.T.; Patel, M.R.; Dean, E.; Borazanci, E.; Brenner, A.; Cook, N.; Lopez, J.; Pant, S.; et al. First-in-human study of the safety, pharmacokinetics, and pharmacodynamics of first-in-class fatty acid synthase inhibitor TVB-2640 alone and with a taxane in advanced tumors. *eClinicalMedicine* **2021**, *34*, 100797. [CrossRef] [PubMed]
436. Bollag, G.; Tsai, J.; Zhang, J.; Zhang, C.; Ibrahim, P.; Nolop, K.; Hirth, P. Vemurafenib: The first drug approved for BRAF-mutant cancer. *Nat. Rev. Drug Discov.* **2012**, *11*, 873–886. [CrossRef] [PubMed]
437. Cohen, P.; Cross, D.; Janne, P.A. Kinase drug discovery 20 years after imatinib: Progress and future directions. *Nat. Rev. Drug Discov.* **2021**, *20*, 551–569. [CrossRef] [PubMed]
438. Golub, D.; Iyengar, N.; Dogra, S.; Wong, T.; Bready, D.; Tang, K.; Modrek, A.S.; Placantonakis, D.G. Mutant Isocitrate Dehydrogenase Inhibitors as Targeted Cancer Therapeutics. *Front. Oncol.* **2019**, *9*, 417. [CrossRef]
439. Andronesi, O.C. Precision oncology in the era of radiogenomics: The case of D-2HG as an imaging biomarker for mutant IDH gliomas. *Neuro Oncol.* **2018**, *20*, 865–867. [CrossRef]
440. Cadoux-Hudson, T.; Schofield, C.J.; McCullagh, J.S.O. Isocitrate dehydrogenase gene variants in cancer and their clinical significance. *Biochem. Soc. Trans.* **2021**, *49*, 2561–2572. [CrossRef]
441. Lord, C.J.; Ashworth, A. PARP inhibitors: Synthetic lethality in the clinic. *Science* **2017**, *355*, 1152–1158. [CrossRef]
442. Mullard, A. What's next for the synthetic lethality drug discovery engine? *Nat. Rev. Drug Discov.* **2022**, *21*, 477–479. [CrossRef]
443. Kryukov, G.V.; Wilson, F.H.; Ruth, J.R.; Paulk, J.; Tsherniak, A.; Marlow, S.E.; Vazquez, F.; Weir, B.A.; Fitzgerald, M.E.; Tanaka, M.; et al. MTAP deletion confers enhanced dependency on the PRMT5 arginine methyltransferase in cancer cells. *Science* **2016**, *351*, 1214–1218. [CrossRef]
444. Mavrakis, K.J.; McDonald, E.R., 3rd; Schlabach, M.R.; Billy, E.; Hoffman, G.R.; deWeck, A.; Ruddy, D.A.; Venkatesan, K.; Yu, J.; McAllister, G.; et al. Disordered methionine metabolism in MTAP/CDKN2A-deleted cancers leads to dependence on PRMT5. *Science* **2016**, *351*, 1208–1213. [CrossRef]
445. Ito, T.; Young, M.J.; Li, R.; Jain, S.; Wernitznig, A.; Krill-Burger, J.M.; Lemke, C.T.; Monducci, D.; Rodriguez, D.J.; Chang, L.; et al. Paralog knockout profiling identifies DUSP4 and DUSP6 as a digenic dependence in MAPK pathway-driven cancers. *Nat. Genet.* **2021**, *53*, 1664–1672. [CrossRef]
446. Butler, M.; van der Meer, L.T.; van Leeuwen, F.N. Amino Acid Depletion Therapies: Starving Cancer Cells to Death. *Trends Endocrinol. Metab.* **2021**, *32*, 367–381. [CrossRef]

447. Batool, T.; Makky, E.A.; Jalal, M.; Yusoff, M.M. A Comprehensive Review on L-Asparaginase and Its Applications. *Appl. Biochem. Biotechnol.* **2016**, *178*, 900–923. [CrossRef]
448. Matos, A.; Carvalho, M.; Bicho, M.; Ribeiro, R. Arginine and Arginases Modulate Metabolism, Tumor Microenvironment and Prostate Cancer Progression. *Nutrients* **2021**, *13*, 4503. [CrossRef]
449. Cramer, S.L.; Saha, A.; Liu, J.; Tadi, S.; Tiziani, S.; Yan, W.; Triplett, K.; Lamb, C.; Alters, S.E.; Rowlinson, S.; et al. Systemic depletion of L-cyst(e)ine with cyst(e)inase increases reactive oxygen species and suppresses tumor growth. *Nat. Med.* **2017**, *23*, 120–127. [CrossRef]
450. Kanarek, N.; Petrova, B.; Sabatini, D.M. Dietary modifications for enhanced cancer therapy. *Nature* **2020**, *579*, 507–517. [CrossRef]
451. Maddocks, O.D.K.; Athineos, D.; Cheung, E.C.; Lee, P.; Zhang, T.; van den Broek, N.J.F.; Mackay, G.M.; Labuschagne, C.F.; Gay, D.; Kruiswijk, F.; et al. Modulating the therapeutic response of tumours to dietary serine and glycine starvation. *Nature* **2017**, *544*, 372–376. [CrossRef]
452. Yang, M.; Vousden, K.H. Serine and one-carbon metabolism in cancer. *Nat. Rev. Cancer* **2016**, *16*, 650–662. [CrossRef] [PubMed]
453. Billiard, J.; Dennison, J.B.; Briand, J.; Annan, R.S.; Chai, D.; Colon, M.; Dodson, C.S.; Gilbert, S.A.; Greshock, J.; Jing, J.; et al. Quinoline 3-sulfonamides inhibit lactate dehydrogenase A and reverse aerobic glycolysis in cancer cells. *Cancer Metab.* **2013**, *1*, 19. [CrossRef]
454. Yang, X.; Lu, Y.; Hang, J.; Zhang, J.; Zhang, T.; Huo, Y.; Liu, J.; Lai, S.; Luo, D.; Wang, L.; et al. Lactate-Modulated Immunosuppression of Myeloid-Derived Suppressor Cells Contributes to the Radioresistance of Pancreatic Cancer. *Cancer Immunol. Res.* **2020**, *8*, 1440–1451. [CrossRef] [PubMed]
455. Doherty, J.R.; Yang, C.; Scott, K.E.; Cameron, M.D.; Fallahi, M.; Li, W.; Hall, M.A.; Amelio, A.L.; Mishra, J.K.; Li, F.; et al. Blocking lactate export by inhibiting the Myc target MCT1 Disables glycolysis and glutathione synthesis. *Cancer Res.* **2014**, *74*, 908–920. [CrossRef] [PubMed]
456. Khan, A.; Valli, E.; Lam, H.; Scott, D.A.; Murray, J.; Hanssen, K.M.; Eden, G.; Gamble, L.D.; Pandher, R.; Flemming, C.L.; et al. Targeting metabolic activity in high-risk neuroblastoma through Monocarboxylate Transporter 1 (MCT1) inhibition. *Oncogene* **2020**, *39*, 3555–3570. [CrossRef] [PubMed]
457. Tanis, S.P.; Parker, T.T.; Colca, J.R.; Fisher, R.M.; Kletzein, R.F. Synthesis and biological activity of metabolites of the antidiabetic, antihyperglycemic agent pioglitazone. *J. Med. Chem.* **1996**, *39*, 5053–5063. [CrossRef] [PubMed]
458. Wiemer, E.A.; Michels, P.A.; Opperdoes, F.R. The inhibition of pyruvate transport across the plasma membrane of the bloodstream form of Trypanosoma brucei and its metabolic implications. *Biochem. J.* **1995**, *312 Pt 2*, 479–484. [CrossRef]
459. Shi, Y.; Lim, S.K.; Liang, Q.; Iyer, S.V.; Wang, H.Y.; Wang, Z.; Xie, X.; Sun, D.; Chen, Y.J.; Tabar, V.; et al. Gboxin is an oxidative phosphorylation inhibitor that targets glioblastoma. *Nature* **2019**, *567*, 341–346. [CrossRef]
460. Schulte, M.L.; Fu, A.; Zhao, P.; Li, J.; Geng, L.; Smith, S.T.; Kondo, J.; Coffey, R.J.; Johnson, M.O.; Rathmell, J.C.; et al. Pharmacological blockade of ASCT2-dependent glutamine transport leads to antitumor efficacy in preclinical models. *Nat. Med.* **2018**, *24*, 194–202. [CrossRef]
461. Edwards, D.N.; Ngwa, V.M.; Raybuck, A.L.; Wang, S.; Hwang, Y.; Kim, L.C.; Cho, S.H.; Paik, Y.; Wang, Q.; Zhang, S.; et al. Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. *J. Clin. Investig.* **2021**, *131*, e140100. [CrossRef]
462. Wicker, C.A.; Hunt, B.G.; Krishnan, S.; Aziz, K.; Parajuli, S.; Palackdharry, S.; Elaban, W.R.; Wise-Draper, T.M.; Mills, G.B.; Waltz, S.E.; et al. Glutaminase inhibition with telaglenastat (CB-839) improves treatment response in combination with ionizing radiation in head and neck squamous cell carcinoma models. *Cancer Lett.* **2021**, *502*, 180–188. [CrossRef]
463. Varghese, S.; Pramanik, S.; Williams, L.J.; Hodges, H.R.; Hudgens, C.W.; Fischer, G.M.; Luo, C.K.; Knighton, B.; Tan, L.; Lorenzi, P.L.; et al. The Glutaminase Inhibitor CB-839 (Telaglenastat) Enhances the Antimelanoma Activity of T-Cell-Mediated Immunotherapies. *Mol. Cancer* **2021**, *20*, 500–511. [CrossRef]
464. Balog, A.; Lin, T.A.; Maley, D.; Gullo-Brown, J.; Kandoussi, E.H.; Zeng, J.; Hunt, J.T. Preclinical Characterization of Linrodostat Mesylate, a Novel, Potent, and Selective Oral Indoleamine 2,3-Dioxygenase 1 Inhibitor. *Mol. Cancer* **2021**, *20*, 467–476. [CrossRef]
465. Li, X.; Chen, Y.T.; Hu, P.; Huang, W.C. Fatostatin displays high antitumor activity in prostate cancer by blocking SREBP-regulated metabolic pathways and androgen receptor signaling. *Mol. Cancer* **2014**, *13*, 855–866. [CrossRef]
466. Kamisuki, S.; Mao, Q.; Abu-Elheiga, L.; Gu, Z.; Kugimiya, A.; Kwon, Y.; Shinohara, T.; Kawazoe, Y.; Sato, S.; Asakura, K.; et al. A small molecule that blocks fat synthesis by inhibiting the activation of SREBP. *Chem. Biol.* **2009**, *16*, 882–892. [CrossRef]
467. Lally, J.S.V.; Ghoshal, S.; DePeralta, D.K.; Moaven, O.; Wei, L.; Masia, R.; Erstad, D.J.; Fujiwara, N.; Leong, V.; Houde, V.P.; et al. Inhibition of Acetyl-CoA Carboxylase by Phosphorylation or the Inhibitor ND-654 Suppresses Lipogenesis and Hepatocellular Carcinoma. *Cell Metab.* **2019**, *29*, 174–182.e5. [CrossRef]
468. Svensson, R.U.; Parker, S.J.; Eichner, L.J.; Kolar, M.J.; Wallace, M.; Brun, S.N.; Lombardo, P.S.; Van Nostrand, J.L.; Hutchins, A.; Vera, L.; et al. Inhibition of acetyl-CoA carboxylase suppresses fatty acid synthesis and tumor growth of non-small-cell lung cancer in preclinical models. *Nat. Med.* **2016**, *22*, 1108–1119. [CrossRef]
469. Beloueche-Babari, M.; Casals Galobart, T.; Delgado-Goni, T.; Wantuch, S.; Parkes, H.G.; Tandy, D.; Harker, J.A.; Leach, M.O. Monocarboxylate transporter 1 blockade with AZD3965 inhibits lipid biosynthesis and increases tumour immune cell infiltration. *Br. J. Cancer* **2020**, *122*, 895–903. [CrossRef]

470. McNeillis, R.; Greystoke, A.; Walton, J.; Bacon, C.; Keun, H.; Siskos, A.; Petrides, G.; Leech, N.; Jenkinson, F.; Bowron, A.; et al. A case of malignant hyperlactaemic acidosis appearing upon treatment with the mono-carboxylase transporter 1 inhibitor AZD3965. *Br. J. Cancer* **2020**, *122*, 1141–1145. [CrossRef]
471. Silva, A.; Antunes, B.; Batista, A.; Pinto-Ribeiro, F.; Baltazar, F.; Afonso, J. In Vivo Anticancer Activity of AZD3965: A Systematic Review. *Molecules* **2021**, *27*, 181. [CrossRef]
472. Halford, S.E.R.; Walter, H.; McKay, P.; Townsend, W.; Linton, K.; Heinzmann, K.; Dragoni, I.; Brotherton, L.; Veal, G.; Siskos, A.; et al. Phase I expansion study of the first-in-class monocarboxylate transporter 1 (MCT1) inhibitor AZD3965 in patients with diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL). *J. Clin. Oncol.* **2021**, *39*, 3115. [CrossRef]
473. Zachar, Z.; Marecek, J.; Maturo, C.; Gupta, S.; Stuart, S.D.; Howell, K.; Schauble, A.; Lem, J.; Piramzadian, A.; Karnik, S.; et al. Non-redox-active lipoate derivates disrupt cancer cell mitochondrial metabolism and are potent anticancer agents in vivo. *J. Mol. Med.* **2011**, *89*, 1137–1148. [CrossRef]
474. Pardee, T.S.; Anderson, R.G.; Pladna, K.M.; Isom, S.; Ghiraldeli, L.P.; Miller, L.D.; Chou, J.W.; Jin, G.; Zhang, W.; Ellis, L.R.; et al. A Phase I Study of CPI-613 in Combination with High-Dose Cytarabine and Mitoxantrone for Relapsed or Refractory Acute Myeloid Leukemia. *Clin. Cancer Res.* **2018**, *24*, 2060–2073. [CrossRef] [PubMed]
475. Stuart, S.D.; Schauble, A.; Gupta, S.; Kennedy, A.D.; Keppler, B.R.; Bingham, P.M.; Zachar, Z. A strategically designed small molecule attacks alpha-ketoglutarate dehydrogenase in tumor cells through a redox process. *Cancer Metab.* **2014**, *2*, 4. [CrossRef] [PubMed]
476. Lee, K.C.; Maturo, C.; Perera, C.N.; Luddy, J.; Rodriguez, R.; Shorr, R. Translational assessment of mitochondrial dysfunction of pancreatic cancer from in vitro gene microarray and animal efficacy studies, to early clinical studies, via the novel tumor-specific anti-mitochondrial agent, CPI-613. *Ann. Transl. Med.* **2014**, *2*, 91. [CrossRef]
477. Philip, P.A.; Bahary, N.; Mahipal, A.; Kasi, A.; Lima, C.M.S.P.R.; Alistar, A.T.; Oberstein, P.E.; Golan, T.; Sahai, V.; Metges, J.P.; et al. Phase 3, multicenter, randomized study of CPI-613 with modified FOLFIRINOX (mFFX) versus FOLFIRINOX (FFX) as first-line therapy for patients with metastatic adenocarcinoma of the pancreas (AVENGER500). *J. Clin. Oncol.* **2022**, *40*, 4023. [CrossRef]
478. Yen, K.; Travins, J.; Wang, F.; David, M.D.; Artin, E.; Straley, K.; Padyana, A.; Gross, S.; DeLaBarre, B.; Tobin, E.; et al. AG-221, a First-in-Class Therapy Targeting Acute Myeloid Leukemia Harboring Oncogenic IDH2 Mutations. *Cancer Discov.* **2017**, *7*, 478–493. [CrossRef] [PubMed]
479. Saengboonmee, C.; Sanlung, T.; Wongkham, S. Repurposing Metformin for Cancer Treatment: A Great Challenge of a Promising Drug. *Anticancer Res.* **2021**, *41*, 5913–5918. [CrossRef]
480. Ahn, H.K.; Lee, Y.H.; Koo, K.C. Current Status and Application of Metformin for Prostate Cancer: A Comprehensive Review. *Int. J. Mol. Sci.* **2020**, *21*, 8540. [CrossRef]
481. Vial, G.; Detaille, D.; Guigas, B. Role of Mitochondria in the Mechanism(s) of Action of Metformin. *Front. Endocrinol.* **2019**, *10*, 294. [CrossRef]
482. Bilusic, M.; Toney, N.J.; Donahue, R.N.; Wroblewski, S.; Zibelman, M.; Ghatalia, P.; Ross, E.A.; Karzai, F.; Madan, R.A.; Dahut, W.L.; et al. A randomized phase 2 study of bicalutamide with or without metformin for biochemical recurrence in overweight or obese prostate cancer patients (BIMET-1). *Prostate Cancer Prostatic Dis.* 2022; *online ahead of print*. [CrossRef]
483. Ma, T.; Tian, X.; Zhang, B.; Li, M.; Wang, Y.; Yang, C.; Wu, J.; Wei, X.; Qu, Q.; Yu, Y.; et al. Low-dose metformin targets the lysosomal AMPK pathway through PEN2. *Nature* **2022**, *603*, 159–165. [CrossRef]
484. Molina, J.R.; Sun, Y.; Protopopova, M.; Gera, S.; Bandi, M.; Bristow, C.; McAfoos, T.; Morlacchi, P.; Ackroyd, J.; Agip, A.A.; et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. *Nat. Med.* **2018**, *24*, 1036–1046. [CrossRef]
485. Yap, T.A.; Ahnert, J.R.; Piha-Paul, S.A.; Fu, S.; Janku, F.; Karp, D.D.; Naing, A.; Dumbrava, E.E.I.; Pant, S.; Subbiah, V.; et al. Phase I trial of IACS-010759 (IACS), a potent, selective inhibitor of complex I of the mitochondrial electron transport chain, in patients (pts) with advanced solid tumors. *J. Clin. Oncol.* **2019**, *37*, 3014. [CrossRef]
486. Zhao, H.; Swanson, K.D.; Zheng, B. Therapeutic Repurposing of Biguanides in Cancer. *Trends Cancer* **2021**, *7*, 714–730. [CrossRef] [PubMed]
487. Izreig, S.; Gariepy, A.; Kaymak, I.; Bridges, H.R.; Donayo, A.O.; Bridon, G.; DeCamp, L.M.; Kitchen-Goosen, S.M.; Avizonis, D.; Sheldon, R.D.; et al. Repression of LKB1 by miR-17 approximately 92 Sensitizes MYC-Dependent Lymphoma to Biguanide Treatment. *Cell Rep. Med.* **2020**, *1*, 100014. [CrossRef] [PubMed]
488. Rha, S.Y.; Beom, S.-H.; Shin, Y.G.; Yim, D.-S.; Moon, Y.W.; Kim, T.W.; Kim, S.Y.; Kim, G.M.; Kim, H.S.; Cheong, J.-H.; et al. Phase I study of IM156, a novel potent biguanide oxidative phosphorylation (OXPHOS) inhibitor, in patients with advanced solid tumors. *J. Clin. Oncol.* **2020**, *38*, 3590. [CrossRef]
489. Okano, N.; Naruge, D.; Kawai, K.; Kobayashi, T.; Nagashima, F.; Endou, H.; Furuse, J. First-in-human phase I study of JPH203, an L-type amino acid transporter 1 inhibitor, in patients with advanced solid tumors. *Investig. New Drugs* **2020**, *38*, 1495–1506. [CrossRef]
490. Oda, K.; Hosoda, N.; Endo, H.; Saito, K.; Tsujihara, K.; Yamamura, M.; Sakata, T.; Anzai, N.; Wempe, M.F.; Kanai, Y.; et al. L-type amino acid transporter 1 inhibitors inhibit tumor cell growth. *Cancer Sci.* **2010**, *101*, 173–179. [CrossRef]
491. Hafliger, P.; Graff, J.; Rubin, M.; Stooss, A.; Dettmer, M.S.; Altmann, K.H.; Gertsch, J.; Charles, R.P. The LAT1 inhibitor JPH203 reduces growth of thyroid carcinoma in a fully immunocompetent mouse model. *J. Exp. Clin. Cancer Res.* **2018**, *37*, 234. [CrossRef]

492. Myint, Z.W.; Sun, R.C.; Hensley, P.J.; James, A.C.; Wang, P.; Strup, S.E.; McDonald, R.J.; Yan, D.; St Clair, W.H.; Allison, D.B. Evaluation of Glutaminase Expression in Prostate Adenocarcinoma and Correlation with Clinicopathologic Parameters. *Cancers* **2021**, *13*, 2157. [CrossRef]
493. Soth, M.J.; Le, K.; Di Francesco, M.E.; Hamilton, M.M.; Liu, G.; Burke, J.P.; Carroll, C.L.; Kovacs, J.J.; Bardenhagen, J.P.; Bristow, C.A.; et al. Discovery of IPN60090, a Clinical Stage Selective Glutaminase-1 (GLS-1) Inhibitor with Excellent Pharmacokinetic and Physicochemical Properties. *J. Med. Chem.* **2020**, *63*, 12957–12977. [CrossRef]
494. Yokoyama, Y.; Wild, R.; Estok, T.M. Sirpiglenastat (DRP-104) Induces Anti-tumor Efficacy Through Direct, Broad Antagonism of Glutamine Metabolism and Stimulation of the Innate & Adaptive Immune Systems. *Mol. Cancer Ther.* **2022**, *21*, 1561–1572. [CrossRef]
495. Komiya, T.; Huang, C.H. Updates in the Clinical Development of Epacadostat and Other Indoleamine 2,3-Dioxygenase 1 Inhibitors (IDO1) for Human Cancers. *Front. Oncol.* **2018**, *8*, 423. [CrossRef]
496. Kalev, P.; Hyer, M.L.; Gross, S.; Konteatis, Z.; Chen, C.C.; Fletcher, M.; Lein, M.; Aguado-Fraile, E.; Frank, V.; Barnett, A.; et al. MAT2A Inhibition Blocks the Growth of MTAP-Deleted Cancer Cells by Reducing PRMT5-Dependent mRNA Splicing and Inducing DNA Damage. *Cancer Cell* **2021**, *39*, 209–224.E11. [CrossRef]
497. Hung, M.H.; Lee, J.S.; Ma, C.; Diggs, L.P.; Heinrich, S.; Chang, C.W.; Ma, L.; Forgues, M.; Budhu, A.; Chaisaingmongkol, J.; et al. Tumor methionine metabolism drives T-cell exhaustion in hepatocellular carcinoma. *Nat. Commun.* **2021**, *12*, 1455. [CrossRef]
498. Yoon, H.; Luo, S.; Sanfilippo, K.M.; Linneman, T.; Whitmer, A.; Schoen, M.W. Statin type and survival of patients with metastatic castrate-resistant prostate cancer receiving abiraterone and enzalutamide: A nationwide retrospective cohort study. *J. Clin. Oncol.* **2022**, *40*, 50. [CrossRef]
499. Heuer, T.S.; Ventura, R.; Mordec, K.; Lai, J.; Fridlib, M.; Buckley, D.; Kemble, G. FASN Inhibition and Taxane Treatment Combine to Enhance Anti-tumor Efficacy in Diverse Xenograft Tumor Models through Disruption of Tubulin Palmitoylation and Microtubule Organization and FASN Inhibition-Mediated Effects on Oncogenic Signaling and Gene Expression. *eBioMedicine* **2017**, *16*, 51–62. [CrossRef]
500. Menendez, J.A.; Lupu, R. Fatty acid synthase (FASN) as a therapeutic target in breast cancer. *Expert Opin. Ther. Targets* **2017**, *21*, 1001–1016. [CrossRef]
501. Harriman, G.; Greenwood, J.; Bhat, S.; Huang, X.; Wang, R.; Paul, D.; Tong, L.; Saha, A.K.; Westlin, W.F.; Kapeller, R.; et al. Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis, improves insulin sensitivity, and modulates dyslipidemia in rats. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E1796–E1805. [CrossRef]
502. Alkhouri, N.; Lawitz, E.; Noureddin, M.; DeFronzo, R.; Shulman, G.I. GS-0976 (Firsocostat): An investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH). *Expert Opin. Investig. Drugs* **2020**, *29*, 135–141. [CrossRef]
503. Popovici-Muller, J.; Lemieux, R.M.; Artin, E.; Saunders, J.O.; Salituro, F.G.; Travins, J.; Cianchetta, G.; Cai, Z.; Zhou, D.; Cui, D.; et al. Discovery of AG-120 (Ivosidenib): A First-in-Class Mutant IDH1 Inhibitor for the Treatment of IDH1 Mutant Cancers. *ACS. Med. Chem. Lett.* **2018**, *9*, 300–305. [CrossRef]
504. Sussmuth, S.D.; Haider, S.; Landwehrmeyer, G.B.; Farmer, R.; Frost, C.; Tripepi, G.; Andersen, C.A.; Di Bacco, M.; Lamanna, C.; Diodato, E.; et al. An exploratory double-blind, randomized clinical trial with selisistat, a SirT1 inhibitor, in patients with Huntington's disease. *Br. J. Clin. Pharmacol.* **2015**, *79*, 465–476. [CrossRef] [PubMed]
505. Gertz, M.; Fischer, F.; Nguyen, G.T.; Lakshminarasimhan, M.; Schutkowski, M.; Weyand, M.; Steegborn, C. Ex-527 inhibits Sirtuins by exploiting their unique NAD+-dependent deacetylation mechanism. *Proc. Natl. Acad. Sci. USA* **2013**, *110*, E2772–E2781. [CrossRef] [PubMed]
506. Zhang, C.; Chu, M. Leflunomide: A promising drug with good antitumor potential. *Biochem. Biophys. Res. Commun.* **2018**, *496*, 726–730. [CrossRef] [PubMed]
507. Ozturk, S.; Mathur, D.; Zhou, R.W.; Mulholland, D.; Parsons, R. Leflunomide triggers synthetic lethality in PTEN-deficient prostate cancer. *Prostate Cancer Prostatic Dis.* **2020**, *23*, 718–723. [CrossRef]
508. Shukla-Dave, A.; Castillo-Martin, M.; Chen, M.; Lobo, J.; Gladoun, N.; Collazo-Lorduy, A.; Khan, F.M.; Ponomarev, V.; Yi, Z.; Zhang, W.; et al. Ornithine Decarboxylase Is Sufficient for Prostate Tumorigenesis via Androgen Receptor Signaling. *Am. J. Pathol.* **2016**, *186*, 3131–3145. [CrossRef]
509. Alexiou, G.A.; Lianos, G.D.; Ragos, V.; Galani, V.; Kyritsis, A.P. Difluoromethylornithine in cancer: New advances. *Future Oncol.* **2017**, *13*, 809–819. [CrossRef]
510. Randall, E.C.; Zadra, G.; Chetta, P.; Lopez, B.G.C.; Syamala, S.; Basu, S.S.; Agar, J.N.; Loda, M.; Tempany, C.M.; Fennessy, F.M.; et al. Molecular Characterization of Prostate Cancer with Associated Gleason Score Using Mass Spectrometry Imaging. *Mol. Cancer Res.* **2019**, *17*, 1155–1165. [CrossRef]
511. Seydel, C. Single-cell metabolomics hits its stride. *Nat. Methods* **2021**, *18*, 1452–1456. [CrossRef]