applied sciences

MDPI

Review

Characteristics of the Colorectal Cancer Microenvironment—Role in Cancer Progression and Therapeutic Possibilities

Paulina Pieniądz [1,*], Mateusz Pięt [1] and Roman Paduch [1,2,*]

[1] Department of Virology and Immunology, Institute of Biological Sciences, Maria Curie-Skłodowska University, Akademicka 19, 20-033 Lublin, Poland; mateusz.piet@mail.umcs.pl
[2] Department of General and Pediatric Ophthalmology, Medical University, Chmielna 1, 20-079 Lublin, Poland
* Correspondence: paulina.pieniadz@mail.umcs.pl (P.P.); roman.paduch@mail.umcs.pl (R.P.)

Abstract: Colorectal cancer (CRC) is one of the most common and deadliest cancers worldwide. According to the GLOBOCAN (WHO) report in 2020, nearly 2 million patients were diagnosed globally. Despite the advances in cancer diagnosis and therapy, CRC remains a global challenge. Recently, attention has been paid to the tumor microenvironment (TME), which constitutes a significant part of the tumor and mainly includes various immune cells, fibroblasts, vascular cells, and extracellular elements, such as the extracellular matrix (ECM). Many components of the stroma initially exert an anti-tumor effect, but over time, they undergo functional transformation into elements that promote tumor growth. As a result, conditions conducive to further cancer development, invasion into local tissues, and distant metastasis arise. The microenvironment of colorectal cancer (CRC) may be an important direction in the search for therapeutic targets, but it requires further understanding. The main purpose of our review is to explain the role of the complex CRC microenvironment in the progression of this cancer and highlight the potential of targeted therapy directed at the TME. Therefore, continued research into its components and typical biomarkers is necessary to improve therapy and enhance the quality of life for patients.

Keywords: colorectal cancer; tumor microenvironment; therapeutic targets; intercellular communication

Citation: Pieniądz, P.; Pięt, M.; Paduch, R. Characteristics of the Colorectal Cancer Microenvironment—Role in Cancer Progression and Therapeutic Possibilities. *Appl. Sci.* **2024**, *14*, 2930. https://doi.org/10.3390/app14072930

Academic Editors: Bhanwar Lal Puniya and Rada Amin

Received: 20 February 2024
Revised: 26 March 2024
Accepted: 27 March 2024
Published: 30 March 2024

1. Introduction

The constant bidirectional communication between cancer cells and stromal cells shapes the complex and dynamic tumor microenvironment (TME). The interactions occurring within the TME are complicated because they involve a wide spectrum of cells, both normal and cancerous, as well as extracellular components. The diversity of TME elements makes it challenging to clearly determine the functions of individual components. However, the microenvironment, as a cohesive entity, may either provide protective effects against the tumor or even promote its malignancy. The effective functioning of the niche relies on efficient intercellular communication, which can occur directly through physical connections or indirectly through soluble mediators, such as the transfer of cytokines, growth factors, and enzymes and the diffusion of metabolites [1,2]. Both types of communication are inseparable, and there are feedback loops between them. In these loops, direct cell-to-cell interaction can induce cytokine production, and those cytokines can induce the appearance of specific molecules on cell surfaces (e.g., during inflammation) [3].

This review focused on colorectal cancer because it is one of the deadliest and most frequently occurring cancers in humans. According to data from 2020, nearly 2 million patients worldwide have been diagnosed [4].

Understanding the basic mechanisms of intercellular communication in the TME and ensuring the growth and development of transformed cells may be a step to limit the malignancy of cancer. Therefore, it is important to search for therapeutic targets among elements involved in the transport of active molecules within tumor mass.

2. Direct Communication in the Tumor Microenvironment

Direct interactions between cells include gap junctions, which connect cells located in close proximity. Hemichannels (connexons) made of connexin proteins connect each other within the intercellular space, facilitating the transport of small molecules (approx. 1 kDa) and ions. This mechanism in the tumor microenvironment also involves RNA exchange among interacting cells [5,6]. Primarily, gap junctions can easily regulate intercellular communication within the tumor microenvironment. This is because the direct transport between the cytoplasm of adjacent cells allows a rapid exchange of substances and a quick cell response [7].

Connexins are subject to multifactorial regulation, which affects the number and function of gap junctions. While the homeostasis between their degradation and synthesis is maintained in normal cells, it may be disrupted in the tumor microenvironment [8]. Initially, connexin proteins were classified as cancer suppressors [9]; however, an increasing number of studies suggest their significant role in tumor progression through the induction of cell migration.

In colorectal cancer (CRC), heterogeneity in gap junction connections has been identified. The site of their occurrence between stromal cells determines the prognosis. Their modulating role in carcinogenesis was thus indicated. The progression of CRC has been linked to the expression of connexin Cx37 on fibroblasts present in the TME [10]. Additionally, cancer cells can influence the expression of connexins, as well as the endothelium of blood vessels, suggesting the involvement of connexins in pathological angiogenesis [11].

Direct interactions between TME cells also include the interaction of ligands with membrane receptors, which involves various types of cells. While several interactions between two cell types (ligand–receptor pairs) have been identified, the complex interactions still remain unclear [12]. Recent studies have shown the impact of ligand–receptor interactions on the infiltration of immune cells in the CRC microenvironment. Specifically, two ligand–receptor pairs (intercellular adhesion molecule 1, ICAM-1, and interleukin 2 receptor subunit alpha, IL-2RA; ICAM-1 and integrin subunit alpha M, ITGAM) have been identified as driving the infiltration of tumor mass by dendritic cells (DCs). This effect does not necessarily correlate with immune response support, as, similar to other types of immune cells in the tumor microenvironment, DCs may exhibit impaired functions [12,13]. Another immunotherapeutic target is immune checkpoint inhibitors (ICI), such as programmed death receptor-1 (PD-1), programmed cell death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [14,15]. Elevated levels of thymocyte selection-associated high-mobility group box (TOX), T-cell immunoglobulin and mucin domain-3 mRNA (TIM-3 mRNA), CTLA-4, V-domain Ig-containing suppressor of T cell activation (VISTA), T cell immunoreceptor with Ig and ITIM domains (TIGIT), killer cell lectin-like receptor subfamily G member 1 (KLRG1), TOX2, silent information regulator 1 (SIRT1), proliferation marker (Ki-67), and T cell activation and proliferation marker (Helios) have also been demonstrated in advanced CRC tissue, indicating them as potential biomarkers [15].

Adhesive molecules such as integrins, selectins, and cadherins mediate cell–cell and cell–extracellular matrix interactions. The migratory ability of cells is closely associated with the regulation of these proteins, specifically integrins, which may occur at the transcriptional level in CRC [16–18]. The main role of such connections is to maintain interactions between neighboring cells, resulting in changes in the expression of these molecules under the influence of environmental factors. Also, restructuring of the cytoskeleton occurs, leading to a change in the cell structure. However, due to the cytoskeletal remodeling associated with adhesive molecules, they are also responsible for changing the cell structure. This can result in epithelial–mesenchymal transition (EMT), which is closely associated with metastasis induction. Additionally, changing the organization of the cytoskeleton is a mechanism limiting the effectiveness of tumor-infiltrating immune cells. The loss or increase in the quantity of connections based on adhesive complexes in cancer cells can also lead to excessive proliferation, resulting from the loss of contact inhibition. Specifically,

loss of E-cadherins in cancer is associated with a poor prognosis [3,16,17,19]. On the other hand, the presence of ICAM, in particular ICAM-1, promotes an increase in the density of tumor-infiltrating lymphocytes (TILs) in colorectal cancer [20]; as in the case of dendritic cells, it may have an ambiguous effect.

Direct long-distance communication in the TME takes place through tunneling nanotubes, known as intercellular bridges. Due to the extension of the cytoplasm formed by F-actin fibers, these structures form thin conduits, transporting larger particles and even cellular organelles (such as mitochondria and lysosomes) [21,22]. They ensure communication not only between normal cells, such as macrophages [23] or T lymphocytes [24], but also between immune cells and cancer cells, initiating metastatic phenotype in tumors [25]. Cancer cells also develop these communication structures. A study by Desir et al. demonstrated that hypoxia promotes the formation of tunneling nanotubes in ovarian cancer [26]. This was also proved in colon cancer cells, and hypoxia-induced connections were observed between SW480, HCT-116, and DLD-1 cells. The results confirm that hypoxia, which is typical for tumors, determines new communication pathways, enhancing tumor progression [27].

3. Indirect Communication in the Tumor Microenvironment

3.1. Extracellular Vesicles (EVs)

Extracellular vesicles (EVs) were first described in 1967 by Wolf. He observed small coagulants among the products of human blood platelets, which are now known as EVs [28,29]. EVs are structures surrounded by a lipid bilayer and released by cells [30]. Due to the differences in their size and biogenesis, they are divided into exosomes with a diameter of 30–100 nm, microvesicles with a diameter of 50–1000 nm, and apoptotic bodies with a diameter of 1–5 μm [31]. They mediate the transport of nucleic acids, proteins, lipids, and metabolites through paracrine communication [32]. They can participate in cancer invasion by inducing the formation of blood vessels [33], avoiding the immune system [34], and regulating resistance to 5-fluorouracil [35,36], mitomycin [37], or oxaliplatin [38]. They are also involved in the formation of a premetastatic niche and metastasis [39]. They cause immunosuppressive effects [40], primarily due to the presence of the exosomal ligand PD-L1, which can bind to receptors on the surface of CD8+ T lymphocytes, blocking their functions and allowing the tumor to escape immune surveillance [41,42].

In the TME, cancer cells use EVs to interact with tumor-infiltrating fibroblasts (CAFs), macrophages, and endothelial cells to ensure their survival and facilitate further expansion into healthy tissue [43]. Studies by Giusti et al. confirmed the ability of EVs to modulate the phenotype of TME fibroblasts by activating their transformation into CAFs. These CAFs can initiate pro-tumor behaviors in both normal and cancer cells [44]. This indicates the involvement of EVs in multifaceted communication occurring not only in the direction of cancer–microenvironment or cancer–cancer but also microenvironment–cancer [45]. Therefore, cancer cells also receive EVs produced by stromal cells, delivering crucial components for their development. Exosomes released by CAFs support the growth of cancer cells by providing nutrients [46]. Moreover, they are also strong inducers of M1 to M2 macrophage polarization. M2 macrophages are known to be pro-tumorigenic [47].

The acidic environment and hypoxia in the TME particularly favor the secretion of cancer-derived EVs. Therefore, the information flows along the cancer-cell pathway and can effectively deepen the anaplasia and malignancy of tumor cells [45,48]. Moreover, EVs released by hypoxic cancer cells act as messengers delivering miRNA to normoxic cancer cells, initiating EMT and promoting the metastatic phenotype [49]. There is a positive feedback loop in which mesenchymal CRC cells release more exosomes than CRC cells with proper polarization, determining subsequent transformations [50].

3.2. Soluble Mediators

Soluble mediators, such as cytokines, chemokines, and signaling molecules, similar to EVs, facilitate multifaceted communication in the CRC microenvironment [51]. Depending on their composition and proportions, their actions in the TME may induce both pro- and

anti-tumor effects [52]. By controlling biological functions in the TME, they influence the differentiation, proliferation, and migration of cells. Therefore, the disruption of the balance between these soluble mediators can be one of the determinants of CRC progression [51,53].

The tumor microenvironment includes signaling molecules released from both cancer cells and infiltrating tumor-associated cells, making their actions dependent on their origin. The goal of cancer cells is obvious: to autocrinally drive proliferation and recruit new niches to increase tumor mass. However, mediators released by tumor-infiltrating cells are initially an important weapon in the fight against cancer, but their long-term action may have the opposite effect [54,55]. Among the main pro-inflammatory cytokines in the TME are interleukins (IL), e.g., IL-1β, IL-6, and IL-8 (CXCL-8) and tumor necrosis factor α (TNF-α) [56].

Increased production of IL-1β is common in many types of cancer (including lung and breast cancer), but it is not fully known which specific niche cells are responsible for its increased production [57–59]. IL-1β has been attributed to regulating processes such as proliferation, differentiation, and apoptosis of cells. Additionally, it stimulates the production of inflammatory mediators, i.e., TNF-α, IL-6, IL-8, IL-17, cyclooxygenase-2 (COX-2), and (prostaglandin E2) PGE2. However, its role in the CRC requires further research [60]. It is known that IL-1β can promote the mesenchymal phenotype of CRC through EMT and stimulate the self-renewal of colorectal cancer stem cells [61]. Studies on CRC patient samples confirm its increasing levels up to stage III, which then decrease in stage IV. This indicates that its level is dependent on the advancement of cancer (up to stage III) and makes it a prognostic marker until metastasis occurs [62]. Furthermore, the role of IL-1β in some tumor invasions (like breast cancer) is supported by studies where inhibiting its production correlates with a lower likelihood of metastasis and an improvement in the anti-tumor immune response. Its operation in this respect should also be checked in the CRC [63,64]. In CRC, IL-1β is also associated with chemoresistance [65].

IL-6 is a pleiotropic pro-inflammatory cytokine that also plays a role in promoting cancer. Patients with colorectal cancer show increased levels of IL-6 compared to healthy individuals. This may be due to its production by cancer cells themselves as well as macrophages, CAFs, and T lymphocytes induced by cancer. Its action is associated with the IL-6/STAT3 (signal transducer and activator of transcription 3) pathway, which in CRC is linked to cell proliferation, the inhibition of apoptosis, invasion, metastasis, angiogenesis, and chemotherapy resistance. Additionally, IL-6 activates the proliferation of CAFs, which are also its source, maintaining a pro-tumor microenvironment in cancer and enhancing the metastatic phenotype of CRC [66–68]. Studies by Zeng et al. demonstrated a correlation between the level of IL-6 and the occurrence of metastasis to lymph nodes in CRC [69].

TNF-α, i.e., a promoter of inflammation, is responsible for the initiation and maintenance of the production of many cytokines, participation in leukocyte recruitment, and contribution to angiogenesis. However, these functions make it a factor that promotes tumor development in the tumor microenvironment. TNF-α is mainly produced by macrophages and monocytes, but also by cancer cells, aiming to escape immune surveillance [70,71]. It can not only inhibit the anti-tumor action of lymphocytes but also promote the tumor phenotype, which is more difficult for the immune system to recognize [72]. Its elevated levels in tumors and serum of CRC patients correlate with poor prognosis, explained by the increased migratory and invasive capabilities of tumor cells. This effect may be associated with an upregulation of the calcium-associated tumor transducer 2 (TROP-2) signaling protein. Studies on colorectal cancer cells have shown an elevated level of TROP-2, dependent on the TNF-α concentration [73]. Another study showed a significant increase in TNF-α mRNA and TNF-α levels in the serum of patients with advanced colorectal cancer compared to earlier stages. All these data point to the role of TNF-α in promoting colorectal cancer invasion [74,75]. In general, IL-1β, IL-6, and TNF-α can be useful significant diagnostic markers in CRC and potential therapeutic targets. However, their application in CRC therapy requires further research. So far, several drugs targeting these proinflammatory

cytokines have been approved (e.g., canakinumab, etanercept, and tocilizumab), but mainly in therapies for inflammatory diseases rather than cancer [62,76–78].

IL-8 (CXCL-8) is a pro-inflammatory cytokine that has an affinity for the C-X-C motif chemokine receptor (CXCR). It is produced by the epithelium and most immune cells, but it also acts as a chemoattractant for many of these cells (including acute inflammatory neutrophils) as well as endothelial cells, thus mediating the angiogenesis process. Its level increases in response to specific conditions, such as hypoxia or the presence of other pro-inflammatory cytokines (including TNF-α and IL-1β) [60,79,80]. In CRC, elevated levels of IL-8 are associated with cancer invasion [81]. IL-8 is involved in the progression of colorectal cancer, mainly through the development of liver metastases and resistance to chemotherapy. By binding to membrane receptors on the surface of cancer stem cells (CSCs), IL-8 mediates the migration and invasion of CSCs and the production of EMT inducers [82]. The use of specific IL-8 antagonists is a promising strategy for cancer treatment, as increased sensitivity of CRC cells to cytostatic agents has been observed after introducing the CXCR-2 antagonist SCH-527123 into treatment [83].

The pro-inflammatory cytokines of the CRC microenvironment also include the IL-17, IL-1, and IL-12 families. Anti-inflammatory cytokines include IL-4, IL-10, and IL-13. Moreover, a number of pleiotropic cytokines have both pro- and anti-inflammatory effects (e.g., interferon γ IFN-γ) [60]. In the CRC microenvironment, most cytokines are associated with tumor-promoting effects [52].

Indirect mediators also include chemokines, which constitute the most numerous subgroup of cytokines. Similar to other cytokines, they exhibit a wide range of actions specific to different types of cancer [52]. Initially, they were correlated only with the ability to target immune cells, but recent discoveries suggest that chemokines are also involved in controlling reprogrammed cells to maintain tumor progression. In CRC, the C–C motif chemokine ligand 2 (CCL-2) is the pro-tumor chemokine, and its presence correlates with poor prognosis. This effect is the result of action mainly on niche cells that maintain a suppressive environment for normal immune cells. It has been shown that the chemokine CCL-2 may be associated with the infiltration of unfavorable M2 macrophages. In turn, chemokines from the group of C-X-C motif chemokines (CXC) are strong chemoattractants for neutrophils [52,84]. The chemokines involved in CRC include the following ligands: C-X-C motif chemokine ligand 5 (CXCL-5), CXCL-8, CXCL-9, CXCL-10, CXCL-12, CXCL-15, and CCL-20, and the following receptors: CXCR-1, CXCR-2, CXCR-3, CXCR-4, CXCR-7, and C-C motif chemokine receptor 6 (CCR-6), the levels of which were increased in CRC patients and were associated with metastases, mainly to the lymph nodes and liver [84,85]. Some in vivo studies confirm the role of chemokines and their receptors (CCL20-CCR6) in CRC, with particular emphasis on their role in the recruitment of niche cells (i.e., macrophages) and the maintenance of the invasive cancer phenotype [86].

4. Cellular Component of the CRC Microenvironment

The colorectal cancer mass consists of approximately 60–90% of stromal cells located in the extracellular matrix [87]. These include mainly cells of the immune system as well as vascular endothelial cells and fibroblasts, which regulate the development of cancer [88]. It is important to distinguish the classical action of these cells from the action dictated by the conditions prevailing in the tumor environment, because chronic exposure to factors released by the tumor may induce functional changes in infiltrating cells. Phenotypically transformed cells and a wide range of their products maintain the conditions for further development of cancer (Table 1 and Figure 1) [89,90].

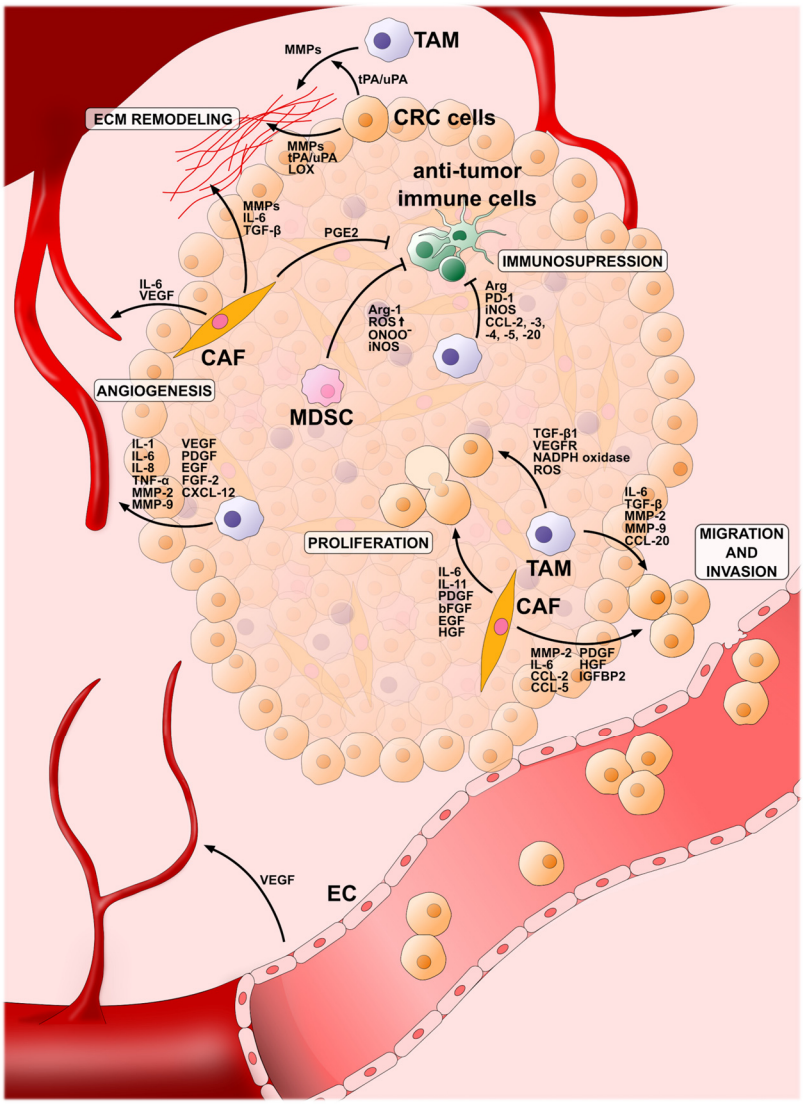

Figure 1. Interactions between CRC cells and TME components. Arg: arginase; bFGF: basic fibroblast growth factor; CAF: cancer-associated fibroblast; CCL: C–C motif chemokine ligand; CXCL−12: C−X−C motif chemokine ligand−12; EC: endothelial cell; EGF: epidermal growth factor; FGF: fibroblast growth factor; HGF: hepatocyte growth factor; IGFBP2: insulin−like growth factor binding protein−2; IL: interleukin; iNOS: inducible nitric oxide synthase; LOX: lysyl oxidase; MMP: matrix metalloproteinase; NADPH oxidase: nicotinamide adenine dinucleotide phosphate oxidase; ONOO−: peroxynitrite; PDGF: platelet−derived growth factor; PGE2: prostaglandin E2; ROS: reactive oxygen species; TAM: tumor−associated macrophage; TGF−β: transforming growth factor β; TIL: tumor−infiltrating lymphocyte; TNF: tumor necrosis factor; tPA: tissue plasminogen activator; uPA: urokinase plasminogen activator; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

4.1. Tumor-Associated Macrophages (TAMs)

Macrophages are immune cells with diverse phenotypes and functions. Their primary role involves the maintenance of homeostasis, tissue repair, and contribution to the non-specific immune response against pathogens [91]. These functions are attributed to their phagocytic abilities and the ability to activate and recruit immune-competent cells [92]. In the TME, TAMs play a complex role that is different from primary macrophages. Due to their plasticity, TAMs can undergo polarization that changes their phenotype and functions [93]. This means that they have a dualistic nature. Adoption of the M1 phenotype (considered anti-cancer) to the pro-cancer M2 phenotype depends on the stage of the tumor

and factors present in its microenvironment [94]. According to the current paradigm, M1 macrophages are associated with anti-tumor functions such as phagocytosis or antibody-dependent cell-mediated cytotoxicity (ADCC) [95]. Their actions include the production of various pro-inflammatory cytokines, mainly IL-1β, IL-6, IL-23, IL-12, IL-1, and TNF-α, which are responsible for the inflammation induced to fight cancer [93,96,97]. As the tumor develops, TAMs polarize towards a phenotype similar to M2, promoting the more invasive features of the cancer [98]. The actions of these macrophages are associated with the production of such cytokines as IL-10, IL-13, and IL-4 and transforming growth factor (TGF-β), which support the suppression of inflammation [1,96]. Moreover, among M2 macrophages, there are M2a, M2b, M2c, and M2d variants varying in the type of inducer and activation pathway. Therefore, the significant diversity of TAMs creates a challenge to clearly confirm the effects of their actions [99,100].

So far, several pro-tumor products of TAMs have been characterized; they include the following proangiogenic factors: vascular endothelial growth factor (VEGF), IL-8, angiopoietin 2 (Ang-2), fibroblast growth factor (FGF), and matrix metalloproteinase 9 (MMP-9); factors involved in the remodeling of the ECM: MMP-9 and MMP-12; growth factors: epidermal growth factor (EGF), FGF, and platelet-derived growth factor (PDGF); the following immunosuppressive factors: arginase (Arg), PD-L1, Fas ligand (FasL), IL-10, and TGF; and the following factors responsible for the recruitment of new cells: CXCL-17, CXCL-22, and CXCL-24. On the other hand, TAMs contribute to anti-tumor effects through the activation of T helper 1 (Th1) cells and natural killer (NK) cells, phagocytosis, and the release of reactive oxygen species (ROS) [88].

In the case of many solid tumors, such as ovarian cancer [101], pancreatic cancer [102], glioblastoma [103], breast cancer [104], and bladder cancer [105], the presence of TAMs is associated with a poor prognosis. In CRC, there are also studies indicating a tumor-promoting influence of macrophages [106–108]. However, numerous studies, particularly those based on patient samples, also demonstrate their suppressive actions [97,109,110]. In CRC, macrophages can induce apoptosis through the interaction of the Fas ligand with tumor cells [111]. This indicates that macrophages effectively fight the tumor through direct contact [98], but dependently on the tumor stage. In a study by Edin et al., a high percentage of M1 macrophages, dependent on the CRC stage, gave a higher likelihood of patient survival, and this was not disrupted even by the accompanying infiltration of M2 macrophages [94]. In turn, recent in vitro studies have shown that cancer cells promote the polarization of macrophages towards M2 to inhibit inflammation and escape from immune surveillance. Lactate secreted by cancer cells was found to be involved in this process, confirming the immunosuppressive role of the acidic tumor microenvironment [112]. Other mediators of M2 polarization include IL-4, IL-6, IL-10, TGF-β, EGF, and cancer-derived exosomes, which mediate the exchange of malignant traits within the tumor [88,113].

TAMs are considered inducers of angiogenesis in CRC for two main reasons. First, TAMs themselves secrete vascular factors like VEGF [98,114]. Second, they can stimulate colorectal cancer cells to release VEGF-A, recognized as the most potent inducer of angiogenesis and lymphangiogenesis [95,114]. VEGF-A is acknowledged as a mitogen for vascular endothelial cells, promoting their proliferation and mediating the regeneration of blood vessels during embryonic development. However, in cancer, VEGF serves as a supportive factor for tumor vascularization, leading to metastasis to distant sites. Additionally, angiogenesis is enhanced by the characteristic hypoxic tumor environment, which increases as the tumor develops [114–116]. Macrophages also increase the level of pro-angiogenic IL-8 through the production of TNF-α and IL-1α [117,118]. The angiogenic effect of TAMs in CRC was confirmed by studies on patient samples, which showed that macrophage infiltration is associated with an increase in the production of angiogenic growth factors, such as VEGF. Furthermore, TAM infiltration correlates with the density of blood vessels in tumors. This means that, under the influence of TAMs–cancer interactions, the number of microvessels increases, which facilitates further cancer invasion and distant metastases [104,119].

4.1.1. Metabolic Profile of TAMs

The functions of TAMs are closely associated with the type of metabolism they engage in. Various stimuli from the TME lead to their differentiation into various subtypes, with functions shaped by specific metabolic profiles. Several factors contribute to the polarization of macrophages, inducing changes in their metabolism. These include pro-inflammatory inducers such as lipopolysaccharides (LPS) and IFN-γ associated with classically activated M1 macrophages and IL-4 and IL-10 linked to the anti-inflammatory subtype M2 [120,121]. Classically, activated M1 macrophages are characterized by intense glycolysis, where glucose is converted to lactic acid and the pentose phosphate pathway (PPP), which is a source of NADPH. The result of this metabolic adaptation is the production of inflammatory inducers and reactive oxygen species. M1 also differs from M2 in arginine metabolism. Due to the presence of nitric oxide synthase 2 (NOS2, iNOS), they produce NO, serving as a weapon in the fight against cancer cells [96,120]. However, long-term exposure to the products of this type of metabolism in the TME may also have the opposite effect, increasing oncogenic mutations.

In contrast to M1, M2 macrophages primarily derive energy from oxidative phosphorylation, the tricarboxylic acid (TCA) cycle, and β-oxidation, resulting in the promotion of tumor invasion [122]. Studies confirm that alterations in the metabolism of TAMs regulate their functions and, consequently, the course of the disease [123]. The high metabolic flexibility of TAMs can also be explained by the fact that they must compete for nutrients with transformed TME cells [121].

Recently, the following eight enzymes: acyl-CoA dehydrogenase medium chain (ACADM), acyl-CoA dehydrogenase short chain (ACADS), glutathione peroxidase 4 (GPX4), glutathione-disulfide reductase (GSR), hydroxyacyl-CoA dehydrogenase (HADH), 3-hydroxy-3-methylglutaryl-CoA lyase (HMGCL), 3-hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1), and isocitrate dehydrogenase (NADP(+)) 1 (IDH1) associated with the characteristic amino acid metabolism of colorectal TAMs have been identified. The loss of one of them—ACADS—influenced the polarization of TAMs to M2, indicating the role of this protein in modifying the CRC microenvironment [124].

4.1.2. TAMs as Potential Therapeutic Targets

The activity of macrophages significantly regulates the growth and metastatic properties of cancer cells through a broad modification of the local TME [95]. So far, several molecular targets (IL-6, IL-1β, TGF-β, VEGF, and several chemokines) regulating the action of macrophages in metastatic CRC have been identified. A detailed characterization has been conducted by Zhang et al. Nevertheless, further investigations are necessary to explore the molecular mechanisms explaining how changes in the macrophage phenotype influence cancer at different stages [95,96].

There are several potential therapeutic strategies involving TAMs. These include blocking the recruitment of monocytes and TAM infiltration, blocking polarization to M2, or repolarizing M2 to M1 [14,125]. In the context of interference with infiltration and differentiation of macrophages, Xu et al. observed that the protein Six1 (sine oculis homeobox 1), overproduced by CRC cells, induces TAM infiltration by chemotaxis. This results in tumor development and cell mobility induction. Silencing the Six1 gene limited the proliferation and mobility of CRC cells associated with increased expression of factors recruiting macrophages, e.g., colony stimulating factor 1 (CSF-1), CCL-2/5, and VEG [126,127]. Furthermore, blocking the chemotactic axis CCL-2/CCR-2 can limit the recruitment of monocytes and, consequently, TAM infiltration into the inflammatory site [128]. CCL-2, produced by both cancer cells and stromal cells, strongly enhances the infiltration of monocytes or macrophages expressing CCR-2. Therefore, limiting its role seems to be a significant direction for targeting the TME [129]. The importance of the CCL-2/CCR-2 axis was also demonstrated by older studies in a mouse model, where CCR-2 knockout disrupted the targeted recruitment of monocytes [130]. On the other hand, the CCL-2/CCR-2 axis has been shown to play a significant role in the activation of T lymphocytes that participate in

the fight against cancer. Therefore, a closer look at these elements of the microenvironment and an assessment of the potential impact of targeting thereof seems to be necessary [131]. Studies by Wang et al. pointed to CXCL-12/CXCR-4 binding as mediating increased M2 polarization, which promoted CRC liver metastases [132]. Conversely, other authors report the induction of the M2 phenotype through the Wnt5a pathway [133]. These findings suggest targeting the polarization of macrophages to avoid negative transformation into M2. Other potential strategies include the inhibitor of signal regulatory protein α (SIRP1α), ICI, toll-like receptor (TLR) agonists, CD40 agonists, histone deacetylase (HDAC) inhibitors, phosphoinositide 3-kinases (PI3K) inhibitors, and siRNA/miRNA [134–136].

4.2. Cancer-Associated Fibroblasts (CAFs)

Tumor-infiltrating fibroblasts, known as CAFs, are an important component of the TME. Currently, they are increasingly being paid attention to in the context of cancer progression because they extensively infiltrate cancerous tumors, which is connected with a bad prognosis [137,138]. CAFs are a valuable source of extracellular matrix components and proteolytic enzymes (metalloproteinases). Therefore, in the tumor environment, they can impact the structure of the tumor extracellular matrix and induce metabolic reprogramming of malignant cells [139]. The key markers of CAFs typical for CRC include α-smooth muscle actin (α-SMA), fibroblast-specific protein 1 (FSP1), fibroblast activation protein (FAP), podoplanin, and S100A4 [140–143].

In CRC, CAFs mainly originate from fibroblasts. However, precursors such as mesenchymal stem cells (MSCs) or endothelial cells (ECs) have also been identified [140]. In the case of tumor epithelial origin, fibroblasts provide tumor cells with numerous factors promoting their development. This occurs through direct connections and also via EVs [88,143,144]. Additionally, as they are naturally involved in the wound healing process, these cells intensively infiltrate the tumor, sustaining its structure and promoting volumetric development. The conditions of hypoxia and acidification in the TME also favor the production of factors inducing tumor progression. The secretome of CAFs in CRC mainly includes metalloproteinases, proangiogenic factors such as VEGF, proliferation-stimulating factors such as EGF, PDGF, hepatocyte growth factor (HGF), and basic fibroblast growth factor (bFGF), interleukins inhibiting the immune response, and genetic material in the form of miRNA [17,143,145–148].

In the process of metastasis, CAFs play a significant role through several closely related actions. One of them is the initiation of the migratory phenotype (EMT) and angiogenesis through TGF-β, of which CAFs are a valuable source. Their high percentage in the CRC microenvironment and, consequently, the production of TGF-β enhance the metastatic phenotype and the expansion of cancer. Moreover, TGF-β mediates the recruitment of additional CAFs from the pool of MSCs, intensifying fibroblast infiltration and the autocrine production of this pro-tumorigenic factor. The strong pro-tumorigenic properties of TGF-β released by CAFs are evidenced by the reduced metastatic ability of CRC cells after knockdown of its gene in a mouse model [1,145,149]. The role of transforming growth factor β (TGF-β) is indeed highly dependent on the stage of cancer. While this factor inhibits further tumor development in the early stages, in advanced disease, it promotes further progression [150,151].

CRC-derived CAFs are a valuable source of IL-6, which induces the production of VEGF by these cells and further enhances angiogenesis [66]. Another process involves the release of metalloproteinases, which induce the dissociation of intercellular connections (E-cadherin digestion). This results in the loosening of the tumor structure and invasion of the local environment as well as distant sites [1,140]. CAFs are also strong producers of fibronectin, whose deposits are localized in the tumor microenvironment and can influence its modification. Moreover, the presence of fibronectin in the premetastatic niche is a strong chemotactic signal for cancer cells. Therefore, an elevated level of this marker in samples collected from CRC patients is associated with a poor prognosis and shorter survival [152,153].

CAFs, alongside vascular cells and inflammation in the CRC microenvironment, contribute to the malignant phenotype of cancer as well as drug resistance (chemoresistance) and disease recurrence [145,154]. Particularly, CAFs expressing the transcription factor-snail family zinc finger 1 (Snai1), which may be a cause of CRC resistance to oxaliplatin and cetuximab, are considered highly unfavorable in this tumor microenvironment. This is probably an effect of ECM modification, including a change in the orientation, degradation, or deposition of fibers. Therefore, SNAI1 is suspected to be an inducer of CRC resistance to chemotherapy, through the fibrosis of the ECM and the EMT process [155]. Another example of the protective action of CAFs is the exosomal transfer of miRNA (miR-93-5p), which induces resistance in CRC cells to radiation treatment. Additionally, CAFs produce more miR-93-5p than normal fibroblasts, emphasizing their protective role against the tumor [156,157].

CAFs are strong immunomodulators because they can regulate the action of cytotoxic T lymphocytes, monocytes, and NK cells [140,158,159]. The action of CAFs isolated from colorectal cancer has been studied in relation to NK cells. It appears that CAFs suppressed the expression of NK cell receptors and the production of granzymes and perforins, which are the main weapons of these cells. Moreover, their secretory role was also limited, as CAFs inhibited the production of the anti-tumor cytokines TNF-α and IFN-γ. This example of the action of tumor stroma fibroblasts reflects their crucial role in immune surveillance and immunoediting. This also suggests that they may be potential therapeutic targets in the fight against CRC [157].

CAFs as Potential Therapeutic Targets

The diversity of fibroblasts in the CRC microenvironment, resulting from their different origins, makes it difficult to define their role. Nevertheless, being the most numerous infiltrating cells in the tumor, fibroblasts exhibit potential in anti-cancer therapy. Therefore, it is crucial to continue the exploration of therapeutic possibilities, taking into account the quantities and diversity of particles secreted by CAFs [160,161].

IL-6, which promotes cancer by stimulating proliferation, migration, and angiogenesis, is abundantly produced not only by CRC cells but also by CAFs [66]. In the case of cancers such as ovarian tumors, the efficacy of IL-6-targeted therapy has been confirmed in preclinical and clinical studies [162]. There is limited evidence for the effectiveness of this approach in CRC; however, Nagasaki et al. observed that blocking the IL-6 receptor limits its transfer between stromal cells and CRC, thereby limiting further steps of invasion [66]. Attention was also paid to IL-11, which belongs to the IL-6 family. This cytokine produced by fibroblasts worsened the prognosis of CRC patients and promoted tumor progression. Its action led to the recruitment of additional IL-11-positive fibroblasts, initiating the division of cancer cells. Therefore, directing synthetic inhibitors towards these cytokines may have a beneficial effect in cancer therapy [163].

It has been shown that CAF products, such as fatty acids, initiate the movement of CRC cells in vitro. Fatty acid synthase, responsible for their production, is therefore another element that may influence cancer progression [164].

CAFs participate in the migration process of CRC cells. Phenotypically altered cells increase the production of metabolites that stimulate the migratory phenotype of CRC cells. Fibroblasts associated with CRC metastasis have been isolated and called metastasis-associated fibroblasts (MAFs). They differ from CAFs in surface proteins and secreted products. The presence of CD38 and the expression of the IGFBP2 gene were considered characteristic for MAFs [165,166].

4.3. Tumor-Infiltrating Lymphocytes (TILs)

Tumor-infiltrating lymphocytes (TILs) play one of the main roles in the fight against cancer. They induce apoptosis and express cytotoxic-dependent immune response, thereby limiting the proliferation and migration of abnormal cells [167,168]. In the cancer microenvironment, there is a mixture of cytotoxic T lymphocytes (Tc, CD8+), helper T cells (Th,

CD4+), B lymphocytes, and NK cells classified as cytotoxic cells. The homeostasis between these lymphocyte populations is crucial because, in the tumor microenvironment, effector T lymphocytes are assigned an anti-tumor role, while some helper cells (e.g., Th17) have partially immunosuppressive functions. Therefore, disruption of this balance may result in tumor progression [169–171]. After antigen recognition in the induction phase, cytotoxic lymphocytes and NK enter the effector phase, which is the actual stage of fighting cancer and involves the release of cytolytic granules containing granzymes, perforin, cytotoxic cytokines (IL-2, IL-12, IFN-γ), TNF-α, and FasL [170,172]. Studies have confirmed that high infiltration of CD8+ lymphocytes correlates with the longer survival of patients, including those with colorectal cancer. Histopathological analyses of CRC suggest that the infiltration of TILs into the tumor area has a protective effect on patients, especially those with microsatellite instability (MSI) tumors. This also indicates the dependence of the effectiveness of the immune system on the genetic background of cancer [165,168].

NK cells are characterized by a high diversity and a wide range of surface markers. Generally, they are considered similar to effector lymphocytes, but they exhibit greater cytotoxicity and faster reaction times, especially towards tumors [170]. Their presence in the microenvironment of colorectal cancer is associated with higher patient survival rates [173]. This may be due to the fact that, as producers of IFN-γ, NK cells regulate the function of cytotoxic lymphocytes, mainly by participating in the maturation of dendritic cells, supporting the immune reaction, and driving a direct cytotoxic reaction against cancer cells [174]. Moreover, the main mechanism of the NK fight against transformed cells is antibody-dependent cellular cytotoxicity. This property has been used in studies on the treatment of CRC using NK cells and radiotherapy combined with cetuximab. NK cells irradiated or combined with antibodies have been shown to effectively fight cancer. Additionally, their high infiltration increased the likelihood of the effective action of modified NK cells in the treatment of CRC [175].

The population of Th cells includes a wide range of those classified into subtypes based on the factors they produce: Th1, Th2, Th17, and follicular helper T cells (TFH). Th lymphocytes are mainly responsible for the elimination of cancer cells by activating the immune system during an immune response. However, the action of this lymphocyte group shows some inconsistency due to their diversity. Th1 cells, expressing IFN-γ and TNF-α, are attributed to anti-tumor activity in colorectal cancer, while other subpopulations show varied effects depending on the type and stage of the tumor. Some subsets of CD4+ T cells also have the potential for direct fighting against tumors through the acquisition of cytotoxic abilities. Such abilities have been observed in in vivo models [170,174,176–179]. Th17 lymphocytes, expressing IL-17, have been classified as predictors of poor prognosis not only in CRC [180,181] but also in ovarian cancer [182]. The negative impact of IL-17 is associated with IL-6 derived from cancer cells, whose production in the tumor microenvironment increases under the influence of IL-17, promoting tumor growth and the polarization of subsequent Th17 lymphocytes. Therefore, Th17 lymphocytes in CRC are mainly considered pro-tumorigenic [174,183]. The group of TFH lymphocytes, in the case of non-lymphocytic tumors, supports the immune response and enhances the effectiveness of therapy. TFH cells participate in the maturation and activation of B lymphocytes through the chemokine CXCL-13 and can support the infiltration of both normal and malignant B lymphocytes. However, the activation of negative B lymphocytes by TFH is mainly associated with lymphomas. In the case of solid tumors such as CRC, TFH supports the development of anti-tumor responses. These functions are mainly explained by the production of IL-21, which activates B lymphocytes [184,185].

Regulatory T cells (Treg) are a subpopulation of CD4+ lymphocytes. They are responsible for regulating the immune system and contribute to silencing inflammation, suppressing immune responses, and impeding immune surveillance, thereby promoting tumor progression. In many types of tumors, high Treg infiltration has been characterized and shown to be driven by the presence of chemokines such as CCL-17, CCL-22, CCL-1, CCL-28, CCL-9, CCL-10, and CCL-11, which are associated with poor patient progno-

sis. Therefore, treatment strategies targeting Treg and their products hold promise for immunotherapy [177,186–190].

B cells can exhibit dual functions in the tumor microenvironment. As antigen-presenting cells, cytokine producers, or participants in direct killing, they may demonstrate anti-tumor activity. On the other hand, regulatory B cells (Bregs), a subpopulation acting immunosuppressively through the secretion of cytokines (IL-10, TGF-β, and IL-35), regulation of anti-tumor functions of immune cells, and direct interaction with tumor cells, can exert pro-tumor effects [191–193]. Some results indicate that the infiltration of CD20+ B cells correlated with an improvement in patients' conditions and additionally activated the anti-tumor activity of T lymphocytes [191,194,195]. However, this largely depends on the stage of cancer. While initially the action of B cells was considered to have anti-tumor effects, in advanced stages, infiltrations of unfavorable Bregs were also observed [196].

Lymphocytes in Immunotherapy

Immunotherapy associated with T lymphocytes in CRC is primarily based on supporting the action of cytotoxic lymphocytes. It involves manipulating immune checkpoints, such as PD-1/PD-L1, CTLA-4/B7, and MHC I/TCR (major histocompatibility complex I/T-cell receptor), using specific antibodies that block either negative costimulatory receptors on T cells or their ligands on the surface of tumor cells. This approach prevents the exhaustion of cytotoxic cells and inhibits the apoptosis induced by cancer cells [170]. In CRC immunotherapy, the blockade of PD-1, PD-L1, and CTLA-4 has been found to be effective [197]. As reported by the FDA (Food and Drug Administration), it is possible to use immune checkpoint inhibitors, e.g., nivolumab (targeting PD-1) and ipilimumab (targeting CTLA-4) in CRC treatment [198–200].

4.4. Myeloid-Derived Suppressor Cells (MDSCs)

Myeloid suppressor cells (MDSCs) are a diverse population of immature cells that regulate the immune system [201]. This population includes two main subsets: monocytic cells (monocytes, macrophages, and dendritic cells) and granulocytic cells (neutrophils, eosinophils, basophils, and mast cells). Their presence is characteristic of the cancer microenvironment, as they are strongly activated in pathological conditions by injury, transformed cells, or pathogens. The removal of the threat allows them to return to homeostasis. However, the prolonged impact of inflammatory mediators or chemokines, even at low concentrations, maintains the expansion of MDSCs. This may result in strong immunosuppression of the local immune response because immature cells are much more easily recruited and immunomodulated than pro-tumor cells. On the one hand, the persistent level of MDSCs in a pathological state is an emergency mechanism in situations where the threat is not effectively eliminated. However, in the cancer microenvironment, such an effect may block an effective immune response. MDSCs exhibit suppressive effects, mainly against cytotoxic T lymphocytes, but this has also been extended to immunosuppression against NK cells and B lymphocytes [202,203]. The suppressive role of MDSCs is mainly attributed to their high ROS and $ONOO^-$ (peroxynitrite) production [201], which can block TCR, preventing the activation of T lymphocytes. Additionally, MDSCs are characterized by the activity of arginase-1 (Arg-1) and inducible nitric oxide synthase, whose presence results in a decrease in the level of L-arginine necessary for the proper functioning of T cells [204,205].

In CRC, the presence of MDSCs has been attributed to advanced stages of the tumor. The action of tumor-associated MDSCs has been defined as blocking the expansion of T lymphocytes. Furthermore, the metabolic profile of these cells has been defined as oxidative, which is associated with the production of reactive oxygen species and nitric oxide [206]. While high concentrations of these particles induce anti-tumor effects (through apoptosis induction), the persistent low level of these mediators generates damage to genetic material, enhancing mutations and the instability of cancer cells. Therefore, the presence of oxidative MDSCs may favor CRC progression [207]. The development of

MDSCs in the cancer microenvironment is associated with the chemokine CCL-2 level, which drives the expansion of MDSCs. Studies conducted on samples from CRC patients showed that the level of CCL-2 increased with the cancer stage. Blocking the production of CCL-2 in a mouse model resulted in a reduction of this chemokine and, consequently, a decrease in the infiltration of immunosuppressive MDSCs [204,208]. MDSCs also mediate the resistance of colorectal cancer to chemotherapy. It has been demonstrated that bacteria, such as *Peptostreptococcus anaerobius,* typical of the gut flora of CRC patients, recruit MDSCs that can participate in resistance to oxaliplatin treatment. This effect indicates the broad spectrum of pro-tumorigenic activity of MDSCs and their ease of differentiation into cells with a malignancy-promoting phenotype [209].

Autophagy, often described as cellular recycling, is considered a process that promotes the development of less malignant MDSCs. It is induced in hypoxic conditions, which are typical for tumors. Therefore, myeloid suppressor cells present in the hypoxic tumor environment are also exposed to autophagy. The induction of autophagy weakens their immunosuppressive activity. Redirecting MDSCs towards the autophagy pathway could be an effective alternative to immunotherapy [210,211]. However, no results confirming this effect have been found in the case of colorectal cancer.

In the context of therapy targeted at MDSCs, recent studies by Kang et al. report the effective action of metformin, an anti-diabetic drug with anti-tumor properties, which limits undesirable infiltration of MDSCs in CRC [212]. A comprehensive review of the role of MDSCs in colorectal cancer and the targeting of MDSCs in therapy has been conducted by Siemińska and Baran, as well as Al-Mterin and Elkord [204,213].

4.5. Vascular Cells

The vascular cells include blood endothelial cells (BECs), lymphatic endothelial cells (LECs), and pericytes (characteristic only for blood vessels). These cells build transport pathways that maintain homeostasis in physiological processes by regulating vessel permeability and tension. However, their primary functions can be exploited by tumors for survival and invasion [214–216]. Tumor progression involves proliferation and the growth of the tumor mass. Substance exchange through diffusion only affects the external layers of the tumor mass, leading to strong hypoxia and acidosis in the growing pathological tissue. In such conditions, hypoxia-inducible factor (HIF) is activated, regulating the behavior of endothelial cells towards the formation of microvessels. Proangiogenic factors secreted by the malignancy-promoting phenotype of endothelial cells participate in this process, leading to vasculogenesis (formation of blood vessels from endothelial cell precursors) or angiogenesis (using existing blood vessels), resulting in tumor vascularization [1,11,217–219].

In the tumor microenvironment, vascular cells are referred to as tumor-associated endothelial cells (TECs). They have different morphology and functions compared to normal vascular cells, resulting in the formation of mostly dysfunctional vessels. These vessels may be blind-ended, and their irregular arrangement and abnormal connections can slow down blood flow. This increases the malignancy of the tumor by maintaining compensatory mechanisms around the dysfunction of vessels, such as the production of proangiogenic factors and the activation of HIF, allowing energy acquisition in limited oxygen conditions [216,219,220]. On the other hand, partially dysfunctional vessels mediate substance exchange. Although this process does not guarantee full transport, it ensures the continued functioning and migration of cancer cells. Therefore, increased vessel density in the tumor niche correlates with a poor prognosis [216,221]. The tumor vascularization process also depends on the location and type of tumor invasion, influencing the expression of such angiogenic factors as VEGF-A [222]. In patients with CRC, a high level of lymphangiogenic markers (VEGF-C and VEGFR-3) has been identified. In a mouse model, the VEGF-C/VEGFR-3 axis initiated the formation of lymphatic vessels. Therefore, Tacconi C. et al. identified these factors as molecular targets for preventing metastasis [223]. Moreover, factors released by endothelial cells can stimulate tumor growth and resistance to chemotherapy [224,225].

Table 1. Cellular elements of the CRC microenvironment and the pro-tumor factors they produce.

Cellular Elements of the CRC TME	Pro-Tumor Effect	Factors	References
TAMs	Proliferation	TGF-β1, NADPH Oxidase, ROS, VEGFR3	[98]
	Immunosupression	Arg-1, iNOS, IL-10, PD-1, CCL-2, CCL-3, CCL-4, CCL-5, CCL-20	[96,98]
	Invasion and migration	MMP-9, MMP-2, IL-6, TGF- β, CCL-20	[98,226]
	Angiogenesis	VEGF, PDGF, EGF, FGF-2, IL-8, IL-1, IL-6, TNF-α, CXCL-12, MMP-9, MMP-2	[96,98,226,227]
CAFs	Proliferation	EGF, PDGF, HGF, bFGF, IL-11, IL-6	[140,147,163]
	Immunosupression	PGE2	[228]
	Invasion and migration	MMP-2, CCL-5, CCL-2, PDGF, HGF, IGFBP2, IL-6	[140,166,228,229]
	Angiogenesis	VEGF, IL-6	[140,228]
MDSCs	Immunosupression	high ROS, ONOO−, iNOS, Arg-1	[204]
Vascular cells	Angiogenesis	VEGF	[216]

5. Extracellular Components of the CRC Microenvironment

5.1. Extracellular Matrix (ECM)

The extracellular matrix is an integral component of the tumor microenvironment, serving structural functions as a scaffold for tissue cells and acting as a rich source of proteins and sugars involved in cellular processes [230,231]. The ECM is a dynamic structure that remodels itself as needed, such as during tissue development [232]. The main components of the ECM include basement membranes, fibers (such as fibronectin, laminin, collagen, tenascin, and elastin), and soluble components (heparin, cytokines, growth factors, and mediators). However, the composition of the ECM varies depending on the location and is specific to each tissue [233–235].

5.1.1. Degradation of the Extracellular Matrix in the CRC Microenvironment and Its Impact on Cancer Progression

In the tumor microenvironment, the ECM undergoes structural changes due to strong exposure to the actions of cancer cells and niche conditions (hypoxia, reduced pH, free radicals, and stromal cells), contributing to cancer progression by facilitating the proliferation of cancer cells, local invasion, and migration to distant sites [234,236]. First, the physical barrier that limits proliferating cells is broken. Second, bioactivators are released into the extracellular environment, and many binding sites for cell receptors are exposed [218].

There are two pathways of tumor invasion involving ECM remodeling. One is the degradation of the ECM, mediated by MMPs, which are proteins with proteolytic activity. They influence the loss of cell adhesion by mediating the dissociation of intercellular and cell-ECM connections, resulting in the loosening of the primary tumor structure and release from the primary niche. MMPs include collagenases (MMP-1, MMP-8, MMP-13, and MMP-18), gelatinases (MMP-2 and MMP-9), matrilysins (MMP-26 and MMP-7), stromelysins (MMP-3 and MMP-10), membrane-type (MT-MMP), and unclassified MMPs. Cancer cells are not the main producers of metalloproteinases but release interleukins, growth factors, or extracellular matrix metalloproteinase inducer (EMMPRIN), which stimulate other stromal cells to MMP production [218,237]. Studies conducted on samples taken from CRC patients have shown increased levels of MMPs. The impact of the CRC niche on MMP production was examined using M2 macrophages, and it was found that CRC cells isolated from a late-stage tumor (SW480 cell line) showed increased gene expression encoding MMP-9 when treated with medium derived from M2 macrophages [238]. MMP-7 has been classified as a prognostic marker in CRC [239], and MMP-25 (MT6-MMP) has shown increased expression, correlating with the invasive phenotype of CRC [240]. However, the action of MMPs depends on activators, such as tissue plasminogen activator (tPA) and

urokinase plasminogen activator (uPA) [218], which mediate the processes of migration, invasion, proliferation, and angiogenesis. Increased expression of uPA has been observed in in vitro CRC models, and the use of uPA inhibitors (including ATN-658) resulted in reduced migratory capabilities of model cells and inhibited tumor growth in the liver, the most common site of metastasis, in a mouse model [241].

CAFs within the tumor are responsible for remodeling the ECM through the production of MMPs and TGF-β. Their role includes maintaining hypoxia in the TME and cross-linking collagen fibers, causing ECM stiffness and, consequently, its degradation. The consequence is the proliferation of cancer cells, their release from the niche, and migration [242,243]. The ECM reorganization induced by reduced elasticity of fibers is mainly a consequence of reprogrammed niche cells depositing larger amounts of collagen, primarily type I as well as II, III, IV, and IX. Additionally, lysyl oxidase (LOX), an enzyme involved in ECM remodeling in physiological conditions, cross-links collagen fibers in the TME, leading to the formation of thick collagen bundles that serve as pathways for cancer cell transport [244]. In studies conducted on tissues from CRC patients, increased expression of one of the LOX family oxidases (specifically LOX2) was shown to correlate with the likelihood of distant metastases. This effect was also verified using LOX2-positive and LOX2-knockdown cell lines, revealing that the presence of LOX2 promoted the migratory potential by initiating the EMT process [245].

In another study, an elevated level of collagen and its crosslinking were observed in the invasive phenotype of CRC, and the stiffness of the ECM was 9.4 times higher than in the case of ECM derived from normal colorectal cells. In the same study, it was noted that this effect additionally correlated with increased vascularization, indicating the regulation of angiogenesis by the remodeled ECM [246].

The composition of the ECM in CRC differs from that in normal colorectal cells and correlates with increased cell proliferation. The quantity of extracellular matrix components and factors involved in its remodeling change depending on the stage of CRC advancement. The content of collagen I and MMP-2 in later stages is higher than in the initial ones. Conversely, for collagen IV and tissue inhibitor of metalloproteinase-3 (TIMP-3), a decreasing trend was observed with the progression of CRC [247].

5.1.2. Targeting Therapy at the ECM

A detailed characterization of the ECM in CRC, especially metastatic stroma, is a challenge due to the shortage of biological samples. On the other hand, in vitro and in vivo studies do not fully capture the real disease mechanisms. This leads to difficulties in designing therapies targeted at the ECM [248].

Somewhat distant in vitro studies focusing on serine proteases (such as uPA) in tumor invasion drew attention to inhibitors of these factors as potential therapeutics [249]. However, other studies questioned their effectiveness, as continued cancer development was observed [250]. Since a variety of cellular components and particles are involved in ECM remodeling, Liang et al. proposed a model/suggestion for therapy that takes into account the ECM characteristics for different stages of cancer:

Early stage: maintaining the proper elasticity of the ECM by limiting fiber deposition; targeting MMPs to restrict early metastasis.

Intermediate stages: reversing ECM modifications induced by tumor progression and inhibiting further fibrosis; improving chemotherapy effectiveness by facilitating drug transport.

Advanced stages: regulating ECM degradation, limiting neo-vascularization and metastasis, enabling drug transport, improving quality of life.

To normalize the state of the extracellular matrix, the researchers proposed the use of natural substances, such as flavonoids, phenols, polysaccharides, saponins, terpenoids, alkaloids, and quinones. Their action has been demonstrated in reducing the deposition of ECM components, reversing potential modifications, inhibiting ECM degradation, and targeting cancer-associated fibroblasts (CAFs) [251].

6. Conclusions

The interactions between cancer and the tumor microenvironment are very complex because they involve a wide spectrum of cells, both normal and cancerous, as well as extracellular elements (Figure 1). This review focused solely on the most important components, such as immune cells, fibroblasts, vascular cells, and the extracellular matrix. However, the TME includes many more cells and factors secreted by these cells, making further research in this direction extremely important, especially as there have been increasing reports in recent decades suggesting that the TME effectively supports cancer development. Moreover, most of the cells in the TME include undifferentiated cells, which makes their recruitment and immunoediting much easier. Therefore, the question arises whether depriving the tumor of its microenvironment would be an effective way to enhance immunotherapy. This seems to be the right direction; however, the complexity of intercellular interactions in the TME complicates targeting its elements.

So far, in the treatment of CRC, therapies targeting the immunological checkpoints of the microenvironment (PD-1/PD-L1, CTLA-4) and proteins associated with tumor angiogenesis (VEGFR) have been approved. However, the genetic diversity of CRC means that this therapy is effective only in specific subtypes, such as dMMR–MSI-H CRC. In addition to the genetic background, elements of the TME, such as immune cells, fibroblasts, vascular cells, and their products, may mediate resistance to immunotherapy. Therefore, it is necessary to further understand the interactions between tumor microenvironment cells and verify biomarkers to better understand tumor function.

First of all, efforts should be focused on blocking the infiltration of normal cells, which have been shown in several studies to play a protective role against the tumor. They support further growth and the avoidance of the immune response. Indeed, initial infiltration and induction of inflammation in some cases correlate with patient survival chances, but this process evolves over time and favors the tumor. Therefore, another approach is to try to inhibit the transformation of normal cells into cells with pro-tumor potential. In the case of immune cells, high plasticity may also be an advantage for restoring the normal phenotype of immune cells.

Developing targeted therapies focused on the TME is becoming a less distant direction in cancer treatment, but it certainly requires a more holistic approach, taking into account all the intercellular networks of this complex system.

Author Contributions: Conceptualization, P.P., M.P. and R.P.; methodology, P.P.; validation, P.P., M.P. and R.P.; formal analysis, P.P., M.P. and R.P.; investigation, P.P.; resources, P.P., M.P. and R.P.; data curation, P.P., M.P. and R.P.; writing—original draft preparation, P.P.; writing—review and editing, P.P., M.P. and R.P.; visualization, M.P. and P.P.; supervision, R.P. and M.P.; project administration, P.P., M.P. and R.P.; funding acquisition, R.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting this study are available within the article. Data supporting this study are also available from the corresponding author on justified request.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Anderson, N.M.; Simon, M.C. Tumor Microenvironment. *Curr. Biol.* **2020**, *30*, R921–R925. [CrossRef] [PubMed]
2. Baghban, R.; Roshangar, L.; Jahanban-Esfahlan, R.; Seidi, K.; Ebrahimi-Kalan, A.; Jaymand, M.; Kolahian, S.; Javaheri, T.; Zare, P. Tumor Microenvironment Complexity and Therapeutic Implications at a Glance. *Cell Commun. Signal.* **2020**, *18*, 59. [CrossRef] [PubMed]

3. Harjunpää, H.; Llort Asens, M.; Guenther, C.; Fagerholm, S.C. Cell Adhesion Molecules and Their Roles and Regulation in the Immune and Tumor Microenvironment. *Front. Immunol.* **2019**, *10*, 1078. [CrossRef] [PubMed]
4. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* **2021**, *71*, 209–249. [CrossRef] [PubMed]
5. Kar, R.; Batra, N.; Riquelme, M.A.; Jiang, J.X. Biological Role of Connexin Intercellular Channels and Hemichannels. *Arch. Biochem. Biophys.* **2012**, *524*, 2–15. [CrossRef] [PubMed]
6. Brücher, B.L.D.M.; Jamall, I.S. Cell-Cell Communication in the Tumor Microenvironment, Carcinogenesis, and Anticancer Treatment. *Cell. Physiol. Biochem.* **2014**, *34*, 213–243. [CrossRef] [PubMed]
7. Nielsen, M.S.; Axelsen, L.N.; Sorgen, P.L.; Verma, V.; Delmar, M.; Holstein-Rathlou, N.-H. Gap Junctions. *Compr. Physiol.* **2012**, *2*, 1981–2035. [CrossRef] [PubMed]
8. Zhou, M.; Zheng, M.; Zhou, X.; Tian, S.; Yang, X.; Ning, Y.; Li, Y.; Zhang, S. The Roles of Connexins and Gap Junctions in the Progression of Cancer. *Cell Commun. Signal.* **2023**, *21*, 8. [CrossRef] [PubMed]
9. Momiyama, M.; Omori, Y.; Ishizaki, Y.; Nishikawa, Y.; Tokairin, T.; Ogawa, J.; Enomoto, K. Connexin26-Mediated Gap Junctional Communication Reverses the Malignant Phenotype of MCF-7 Breast Cancer Cells. *Cancer Sci.* **2003**, *94*, 501–507. [CrossRef] [PubMed]
10. Liu, Y.; Han, M.; Li, J.; Zeng, S.; Ye, Q.; Yin, Z.; Liu, S.; Zou, X. An Analysis Regarding the Association Between Connexins and Colorectal Cancer (CRC) Tumor Microenvironment. *J. Inflamm. Res.* **2022**, *15*, 2461–2476. [CrossRef] [PubMed]
11. Thuringer, D.; Berthenet, K.; Cronier, L.; Solary, E.; Garrido, C. Primary tumor- and metastasis-derived colon cancer cells differently modulate connexin expression and function in human capillary endothelial cells. *Oncotarget* **2015**, *6*, 28800–28815. [CrossRef] [PubMed]
12. Lin, H.; Xia, L.; Lian, J.; Chen, Y.; Zhang, Y.; Zhuang, Z.; Cai, H.; You, J.; Guan, G. Delineation of Colorectal Cancer Ligand-Receptor Interactions and Their Roles in the Tumor Microenvironment and Prognosis. *J. Transl. Med.* **2021**, *19*, 497. [CrossRef] [PubMed]
13. Legitimo, A.; Consolini, R.; Failli, A.; Orsini, G.; Spisni, R. Dendritic Cell Defects in the Colorectal Cancer. *Hum. Vaccin. Immunother.* **2014**, *10*, 3224–3235. [CrossRef] [PubMed]
14. Geng, Y.; Feng, J.; Huang, H.; Wang, Y.; Yi, X.; Wei, S.; Zhang, M.; Li, Z.; Wang, W.; Hu, W. Single-Cell Transcriptome Analysis of Tumor Immune Microenvironment Characteristics in Colorectal Cancer Liver Metastasis. *Ann. Transl. Med.* **2022**, *10*, 1170. [CrossRef] [PubMed]
15. Saleh, R.; Taha, R.Z.; Toor, S.M.; Sasidharan Nair, V.; Murshed, K.; Khawar, M.; Al-Dhaheri, M.; Petkar, M.A.; Abu Nada, M.; Elkord, E. Expression of Immune Checkpoints and T Cell Exhaustion Markers in Early and Advanced Stages of Colorectal Cancer. *Cancer Immunol. Immunother.* **2020**, *69*, 1989–1999. [CrossRef] [PubMed]
16. Hou, S.; Wang, J.; Li, W.; Hao, X.; Hang, Q. Roles of Integrins in Gastrointestinal Cancer Metastasis. *Front. Mol. Biosci.* **2021**, *8*, 708779. [CrossRef] [PubMed]
17. AlMusawi, S.; Ahmed, M.; Nateri, A.S. Understanding Cell-Cell Communication and Signaling in the Colorectal Cancer Microenvironment. *Clin. Transl. Med.* **2021**, *11*, e308. [CrossRef] [PubMed]
18. Sinyuk, M.; Mulkearns-Hubert, E.E.; Reizes, O.; Lathia, J. Cancer Connectors: Connexins, Gap Junctions, and Communication. *Front. Oncol.* **2018**, *8*, 646. [CrossRef] [PubMed]
19. Dominiak, A.; Chełstowska, B.; Olejarz, W.; Nowicka, G. Communication in the Cancer Microenvironment as a Target for Therapeutic Interventions. *Cancers* **2020**, *12*, 1232. [CrossRef] [PubMed]
20. Maeda, K.; Kang, S.-M.; Sawada, T.; Nishiguchi, Y.; Yashiro, M.; Ogawa, Y.; Ohira, M.; Ishikawa, T.; Hirakawa-YS Chung, K. Expression of Intercellular Adhesion Molecule-1 and Prognosis in Colorectal Cancer. *Oncol. Rep.* **2002**, *9*, 511–514. [CrossRef]
21. Lou, E. A Ticket to Ride: The Implications of Direct Intercellular Communication via Tunneling Nanotubes in Peritoneal and Other Invasive Malignancies. *Front. Oncol.* **2020**, *10*, 559548. [CrossRef] [PubMed]
22. Melwani, P.K.; Pandey, B.N. Tunneling Nanotubes: The Intercellular Conduits Contributing to Cancer Pathogenesis and Its Therapy. *Biochim. Biophys. Acta BBA-Rev. Cancer* **2023**, *1878*, 189028. [CrossRef] [PubMed]
23. Önfelt, B.; Nedvetzki, S.; Benninger, R.K.P.; Purbhoo, M.A.; Sowinski, S.; Hume, A.N.; Seabra, M.C.; Neil, M.A.A.; French, P.M.W.; Davis, D.M. Structurally Distinct Membrane Nanotubes between Human Macrophages Support Long-Distance Vesicular Traffic or Surfing of Bacteria1. *J. Immunol.* **2006**, *177*, 8476–8483. [CrossRef] [PubMed]
24. Arkwright, P.D.; Luchetti, F.; Tour, J.; Roberts, C.; Ayub, R.; Morales, A.P.; Rodríguez, J.J.; Gilmore, A.; Canonico, B.; Papa, S.; et al. Fas Stimulation of T Lymphocytes Promotes Rapid Intercellular Exchange of Death Signals via Membrane Nanotubes. *Cell Res.* **2010**, *20*, 72–88. [CrossRef] [PubMed]
25. Hanna, S.J.; McCoy-Simandle, K.; Leung, E.; Genna, A.; Condeelis, J.; Cox, D. Tunneling Nanotubes, a Novel Mode of Tumor Cell–Macrophage Communication in Tumor Cell Invasion. *J. Cell Sci.* **2019**, *132*, jcs223321. [CrossRef] [PubMed]
26. Desir, S.; Dickson, E.L.; Vogel, R.I.; Thayanithy, V.; Wong, P.; Teoh, D.; Geller, M.A.; Steer, C.J.; Subramanian, S.; Lou, E. Tunneling Nanotube Formation Is Stimulated by Hypoxia in Ovarian Cancer Cells. *Oncotarget* **2016**, *7*, 43150–43161. [CrossRef] [PubMed]
27. Lou, E.; Zhai, E.; Sarkari, A.; Desir, S.; Wong, P.; Iizuka, Y.; Yang, J.; Subramanian, S.; McCarthy, J.; Bazzaro, M.; et al. Cellular and Molecular Networking Within the Ecosystem of Cancer Cell Communication via Tunneling Nanotubes. *Front. Cell Dev. Biol.* **2018**, *6*, 95. [CrossRef] [PubMed]

28. Wolf, P. The Nature and Significance of Platelet Products in Human Plasma. *Br. J. Haematol.* **1967**, *13*, 269–288. [CrossRef]
29. Couch, Y.; Buzàs, E.I.; Vizio, D.D.; Gho, Y.S.; Harrison, P.; Hill, A.F.; Lötvall, J.; Raposo, G.; Stahl, P.D.; Théry, C.; et al. A Brief History of Nearly EV-erything—The Rise and Rise of Extracellular Vesicles. *J. Extracell. Vesicles* **2021**, *10*, e12144. [CrossRef] [PubMed]
30. Bian, X.; Xiao, Y.-T.; Wu, T.; Yao, M.; Du, L.; Ren, S.; Wang, J. Microvesicles and Chemokines in Tumor Microenvironment: Mediators of Intercellular Communications in Tumor Progression. *Mol. Cancer* **2019**, *18*, 50. [CrossRef] [PubMed]
31. Wang, Y.; Khan, H.M.; Zhou, C.; Liao, X.; Tang, P.; Song, P.; Gui, X.; Li, H.; Chen, Z.; Liu, S.; et al. Apoptotic Cell-Derived Micro/Nanosized Extracellular Vesicles in Tissue Regeneration. *Nanotechnol. Rev.* **2022**, *11*, 957–972. [CrossRef]
32. Zhao, H.; Achreja, A.; Iessi, E.; Logozzi, M.; Mizzoni, D.; Di Raimo, R.; Nagrath, D.; Fais, S. The Key Role of Extracellular Vesicles in the Metastatic Process. *Biochim. Biophys. Acta BBA-Rev. Cancer* **2018**, *1869*, 64–77. [CrossRef] [PubMed]
33. Zeng, Z.; Li, Y.; Pan, Y.; Lan, X.; Song, F.; Sun, J.; Zhou, K.; Liu, X.; Ren, X.; Wang, F.; et al. Cancer-Derived Exosomal miR-25-3p Promotes Pre-Metastatic Niche Formation by Inducing Vascular Permeability and Angiogenesis. *Nat. Commun.* **2018**, *9*, 5395. [CrossRef]
34. Ma, Y.-S.; Wu, T.-M.; Ling, C.-C.; Yu, F.; Zhang, J.; Cao, P.-S.; Gu, L.-P.; Wang, H.-M.; Xu, H.; Li, L.; et al. M2 Macrophage-Derived Exosomal microRNA-155-5p Promotes the Immune Escape of Colon Cancer by Downregulating ZC3H12B. *Mol. Ther. Oncolytics* **2021**, *20*, 484–498. [CrossRef] [PubMed]
35. Sun, L.-H.; Tian, D.; Yang, Z.-C.; Li, J.-L. Exosomal miR-21 Promotes Proliferation, Invasion and Therapy Resistance of Colon Adenocarcinoma Cells through Its Target PDCD4. *Sci. Rep.* **2020**, *10*, 8271. [CrossRef] [PubMed]
36. Zhang, Q.; Liu, R.-X.; Chan, K.-W.; Hu, J.; Zhang, J.; Wei, L.; Tan, H.; Yang, X.; Liu, H. Exosomal Transfer of P-STAT3 Promotes Acquired 5-FU Resistance in Colorectal Cancer Cells. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 320. [CrossRef] [PubMed]
37. Chen, X.; Liu, Y.; Zhang, Q.; Liu, B.; Cheng, Y.; Zhang, Y.; Sun, Y.; Liu, J.; Gen, H. Exosomal Long Non-Coding RNA HOTTIP Increases Resistance of Colorectal Cancer Cells to Mitomycin via Impairing MiR-214-Mediated Degradation of KPNA3. *Front. Cell Dev. Biol.* **2020**, *8*, 582723. [CrossRef] [PubMed]
38. Xu, Y.; Zhu, M. Novel Exosomal miR-46146 Transfer Oxaliplatin Chemoresistance in Colorectal Cancer. *Clin. Transl. Oncol.* **2020**, *22*, 1105–1116. [CrossRef] [PubMed]
39. Zhao, S.; Mi, Y.; Zheng, B.; Wei, P.; Gu, Y.; Zhang, Z.; Xu, Y.; Cai, S.; Li, X.; Li, D. Highly-metastatic Colorectal Cancer Cell Released miR-181a-5p-rich Extracellular Vesicles Promote Liver Metastasis by Activating Hepatic Stellate Cells and Remodelling the Tumour Microenvironment. *J. Extracell. Vesicles* **2022**, *11*, e12186. [CrossRef] [PubMed]
40. Yin, Y.; Liu, B.; Cao, Y.; Yao, S.; Liu, Y.; Jin, G.; Qin, Y.; Chen, Y.; Cui, K.; Zhou, L.; et al. Colorectal Cancer-Derived Small Extracellular Vesicles Promote Tumor Immune Evasion by Upregulating PD-L1 Expression in Tumor-Associated Macrophages. *Adv. Sci.* **2022**, *9*, 2102620. [CrossRef] [PubMed]
41. Chen, G.; Huang, A.C.; Zhang, W.; Zhang, G.; Wu, M.; Xu, W.; Yu, Z.; Yang, J.; Wang, B.; Sun, H.; et al. Exosomal PD-L1 Contributes to Immunosuppression and Is Associated with Anti-PD-1 Response. *Nature* **2018**, *560*, 382–386. [CrossRef]
42. Liu, J.; Peng, X.; Yang, S.; Li, X.; Huang, M.; Wei, S.; Zhang, S.; He, G.; Zheng, H.; Fan, Q.; et al. Extracellular Vesicle PD-L1 in Reshaping Tumor Immune Microenvironment: Biological Function and Potential Therapy Strategies. *Cell Commun. Signal.* **2022**, *20*, 14. [CrossRef] [PubMed]
43. Majood, M.; Rawat, S.; Mohanty, S. Delineating the Role of Extracellular Vesicles in Cancer Metastasis: A Comprehensive Review. *Front. Immunol.* **2022**, *13*, 966661. [CrossRef] [PubMed]
44. Giusti, I.; Di Francesco, M.; Poppa, G.; Esposito, L.; D'Ascenzo, S.; Dolo, V. Tumor-Derived Extracellular Vesicles Activate Normal Human Fibroblasts to a Cancer-Associated Fibroblast-Like Phenotype, Sustaining a Pro-Tumorigenic Microenvironment. *Front. Oncol.* **2022**, *12*, 839880. [CrossRef] [PubMed]
45. Bebelman, M.P.; Smit, M.J.; Pegtel, D.M.; Baglio, S.R. Biogenesis and Function of Extracellular Vesicles in Cancer. *Pharmacol. Ther.* **2018**, *188*, 1–11. [CrossRef] [PubMed]
46. 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] [PubMed]
47. Tang, Y.; Hu, S.; Li, T.; Qiu, X. Tumor Cells-Derived Exosomal circVCP Promoted the Progression of Colorectal Cancer by Regulating Macrophage M1/M2 Polarization. *Gene* **2023**, *870*, 147413. [CrossRef] [PubMed]
48. Chen, Q.Y.; Gao, B.; Tong, D.; Huang, C. Crosstalk between Extracellular Vesicles and Tumor-Associated Macrophage in the Tumor Microenvironment. *Cancer Lett.* **2023**, *552*, 215979. [CrossRef] [PubMed]
49. Li, L.; Li, C.; Wang, S.; Wang, Z.; Jiang, J.; Wang, W.; Li, X.; Chen, J.; Liu, K.; Li, C.; et al. Exosomes Derived from Hypoxic Oral Squamous Cell Carcinoma Cells Deliver miR-21 to Normoxic Cells to Elicit a Prometastatic Phenotype. *Cancer Res.* **2016**, *76*, 1770–1780. [CrossRef] [PubMed]
50. Yang, C.; Dou, R.; Wei, C.; Liu, K.; Shi, D.; Zhang, C.; Liu, Q.; Wang, S.; Xiong, B. Tumor-Derived Exosomal microRNA-106b-5p Activates EMT-Cancer Cell and M2-Subtype TAM Interaction to Facilitate CRC Metastasis. *Mol. Ther.* **2021**, *29*, 2088–2107. [CrossRef] [PubMed]
51. Bhat, A.A.; Nisar, S.; Singh, M.; Ashraf, B.; Masoodi, T.; Prasad, C.P.; Sharma, A.; Maacha, S.; Karedath, T.; Hashem, S.; et al. Cytokine- and Chemokine-induced Inflammatory Colorectal Tumor Microenvironment: Emerging Avenue for Targeted Therapy. *Cancer Commun.* **2022**, *42*, 689–715. [CrossRef] [PubMed]

52. Braumüller, H.; Mauerer, B.; Andris, J.; Berlin, C.; Wieder, T.; Kesselring, R. The Cytokine Network in Colorectal Cancer: Implications for New Treatment Strategies. *Cells* **2023**, *12*, 138. [CrossRef] [PubMed]
53. Nengroo, M.A.; Verma, A.; Datta, D. Cytokine Chemokine Network in Tumor Microenvironment: Impact on CSC Properties and Therapeutic Applications. *Cytokine* **2022**, *156*, 155916. [CrossRef] [PubMed]
54. Singh, N.; Baby, D.; Rajguru, J.P.; Patil, P.B.; Thakkannavar, S.S.; Pujari, V.B. Inflammation and Cancer. *Ann. Afr. Med.* **2019**, *18*, 121–126. [CrossRef] [PubMed]
55. Klampfer, L. Cytokines, Inflammation and Colon Cancer. *Curr. Cancer Drug Targets* **2011**, *11*, 451–464. [CrossRef] [PubMed]
56. Fryczkowski, M.; Hejmo, T.; Bułdak, M.; Stachowska, M.; Żwirska-Korczala, K.; Rokicka, J. Impact of selected pro-inflammatory cytokines and oxidative stress on carcinogenesis and progression of prostate and colorectal adenocarcinomas. *Ann. Acad. Med. Siles.* **2019**, *73*, 182–193. [CrossRef]
57. Kiss, M.; Vande Walle, L.; Saavedra, P.H.V.; Lebegge, E.; Van Damme, H.; Murgaski, A.; Qian, J.; Ehling, M.; Pretto, S.; Bolli, E.; et al. IL1β Promotes Immune Suppression in the Tumor Microenvironment Independent of the Inflammasome and Gasdermin D. *Cancer Immunol. Res.* **2021**, *9*, 309–323. [CrossRef] [PubMed]
58. Wu, T.-C.; Xu, K.; Martinek, J.; Young, R.R.; Banchereau, R.; George, J.; Turner, J.; Kim, K.I.; Zurawski, S.; Wang, X.; et al. IL1 Receptor Antagonist Controls Transcriptional Signature of Inflammation in Patients with Metastatic Breast Cancer. *Cancer Res.* **2018**, *78*, 5243–5258. [CrossRef] [PubMed]
59. Colasante, A.; Mascetra, N.; Brunetti, M.; Lattanzio, G.; Diodoro, M.; Caltagirone, S.; Musiani, P.; Aiello, F.B. Transforming Growth Factor β 1, Interleukin-8 and Interleukin-1, in Non–Small-Cell Lung Tumors. *Am. J. Respir. Crit. Care Med.* **1997**, *156*, 968–973. [CrossRef] [PubMed]
60. Borowczak, J.; Szczerbowski, K.; Maniewski, M.; Kowalewski, A.; Janiczek-Polewska, M.; Szylberg, A.; Marszałek, A.; Szylberg, Ł. The Role of Inflammatory Cytokines in the Pathogenesis of Colorectal Carcinoma—Recent Findings and Review. *Biomedicines* **2022**, *10*, 1670. [CrossRef] [PubMed]
61. Li, Y.; Wang, L.; Pappan, L.; Galliher-Beckley, A.; Shi, J. IL-1β Promotes Stemness and Invasiveness of Colon Cancer Cells through Zeb1 Activation. *Mol. Cancer* **2012**, *11*, 87. [CrossRef] [PubMed]
62. Florescu, D.N.; Boldeanu, M.-V.; Șerban, R.-E.; Florescu, L.M.; Serbanescu, M.-S.; Ionescu, M.; Streba, L.; Constantin, C.; Vere, C.C. Correlation of the Pro-Inflammatory Cytokines IL-1β, IL-6, and TNF-α, Inflammatory Markers, and Tumor Markers with the Diagnosis and Prognosis of Colorectal Cancer. *Life* **2023**, *13*, 2261. [CrossRef] [PubMed]
63. Kaplanow, I.; Carmi, Y.; Kornetsky, R.; Shemesh, A.; Shurin, G.V.; Shurin, M.R.; Dinarello, C.A.; Voronov, E.; Apte, R.N. Blocking IL-1β Reverses the Immunosuppression in Mouse Breast Cancer and Synergizes with Anti–PD-1 for Tumor Abrogation. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 1361–1369. [CrossRef] [PubMed]
64. Pradhan, A.K.; Maji, S.; Bhoopathi, P.; Talukdar, S.; Mannangatti, P.; Guo, C.; Wang, X.-Y.; Cartagena, L.C.; Idowu, M.; Landry, J.W.; et al. Pharmacological Inhibition of MDA-9/Syntenin Blocks Breast Cancer Metastasis through Suppression of IL-1β. *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2103180118. [CrossRef] [PubMed]
65. Spagnardi, M.; Paredes, J.; Zabaleta, J.; Garai, J.; Reyes, T.; Martello, L.A.; Williams, J.L. IL-1β Enhances Cell Viability and Decreases 5-FU Sensitivity in Novel Colon Cancer Cell Lines Derived from African American Patients. *Front. Oncol.* **2022**, *12*, 1010380. [CrossRef] [PubMed]
66. Nagasaki, T.; Hara, M.; Nakanishi, H.; Takahashi, H.; Sato, M.; Takeyama, H. Interleukin-6 Released by Colon Cancer-Associated Fibroblasts Is Critical for Tumour Angiogenesis: Anti-Interleukin-6 Receptor Antibody Suppressed Angiogenesis and Inhibited Tumour–Stroma Interaction. *Br. J. Cancer* **2014**, *110*, 469–478. [CrossRef] [PubMed]
67. Lin, Y.; He, Z.; Ye, J.; Liu, Z.; She, X.; Gao, X.; Liang, R. Progress in Understanding the IL-6/STAT3 Pathway in Colorectal Cancer. *Onco Targets Ther.* **2020**, *13*, 13023–13032. [CrossRef] [PubMed]
68. Knüpfer, H.; Preiss, R. Serum Interleukin-6 Levels in Colorectal Cancer Patients—A Summary of Published Results. *Int. J. Color. Dis.* **2010**, *25*, 135–140. [CrossRef] [PubMed]
69. Zeng, J.; Tang, Z.-H.; Liu, S.; Guo, S.-S. Clinicopathological Significance of Overexpression of Interleukin-6 in Colorectal Cancer. *World J. Gastroenterol.* **2017**, *23*, 1780–1786. [CrossRef] [PubMed]
70. Stanilov, N.; Miteva, L.; Dobreva, Z.; Stanilova, S. Colorectal Cancer Severity and Survival in Correlation with Tumour Necrosis Factor-Alpha. *Biotechnol. Biotechnol. Equip.* **2014**, *28*, 911–917. [CrossRef] [PubMed]
71. Terzić, J.; Grivennikov, S.; Karin, E.; Karin, M. Inflammation and Colon Cancer. *Gastroenterology* **2010**, *138*, 2101–2114.e5. [CrossRef] [PubMed]
72. Montfort, A.; Colacios, C.; Levade, T.; Andrieu-Abadie, N.; Meyer, N.; Ségui, B. The TNF Paradox in Cancer Progression and Immunotherapy. *Front. Immunol.* **2019**, *10*, 1818. [CrossRef] [PubMed]
73. Zhao, P.; Zhang, Z. TNF-α Promotes Colon Cancer Cell Migration and Invasion by Upregulating TROP-2. *Oncol. Lett.* **2018**, *15*, 3820–3827. [CrossRef] [PubMed]
74. Warsinggih; Limanu, F.; Labeda, I.; Lusikooy, R.E.; Mappincara; Faruk, M. The Relationship of Tumor Necrosis Factor Alpha Levels in Plasma toward the Stage and Differentiation Degree in Colorectal Cancer. *Med. Clínica Práctica* **2021**, *4*, 100224. [CrossRef]
75. Obeed, O.A.A.; Alkhayal, K.A.; Sheikh, A.A.; Zubaidi, A.M.; Vaali-Mohammed, M.-A.; Boushey, R.; Mckerrow, J.H.; Abdulla, M.-H. Increased Expression of Tumor Necrosis Factor-α Is Associated with Advanced Colorectal Cancer Stages. *World J. Gastroenterol.* **2014**, *20*, 18390–18396. [CrossRef]

76. Olayinka, T.; Okoye, C.; Amarachi, O. A Review of the Role of Canakinumab—An Anti-Inflammatory Agent in CAD. *Int. J. Health Sci. Res.* **2023**, *13*, 48–52. [CrossRef]
77. Pan, A.; Gerriets, V. Etanercept. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
78. Preuss, C.V.; Anjum, F. Tocilizumab. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
79. Matsushima, K.; Yang, D.; Oppenheim, J.J. Interleukin-8: An Evolving Chemokine. *Cytokine* **2022**, *153*, 155828. [CrossRef]
80. Li, J.; Huang, L.; Zhao, H.; Yan, Y.; Lu, J. The Role of Interleukins in Colorectal Cancer. *Int. J. Biol. Sci.* **2020**, *16*, 2323–2339. [CrossRef] [PubMed]
81. Ha, H.; Debnath, B.; Neamati, N. Role of the CXCL8-CXCR1/2 Axis in Cancer and Inflammatory Diseases. *Theranostics* **2017**, *7*, 1543–1588. [CrossRef] [PubMed]
82. Conciatori, F.; Bazzichetto, C.; Falcone, I.; Ferretti, G.; Cognetti, F.; Milella, M.; Ciuffreda, L. Colorectal Cancer Stem Cells Properties and Features: Evidence of Interleukin-8 Involvement. *Cancer Drug Resist.* **2019**, *2*, 968–979. [CrossRef] [PubMed]
83. Ning, Y.; Labonte, M.J.; Zhang, W.; Bohanes, P.O.; Gerger, A.; Yang, D.; Benhaim, L.; Paez, D.; Rosenberg, D.O.; Nagulapalli Venkata, K.C.; et al. The CXCR2 Antagonist, SCH-527123, Shows Antitumor Activity and Sensitizes Cells to Oxaliplatin in Preclinical Colon Cancer Models. *Mol. Cancer Ther.* **2012**, *11*, 1353–1364. [CrossRef] [PubMed]
84. Pączek, S.; Łukaszewicz-Zając, M.; Mroczko, B. Chemokines—What Is Their Role in Colorectal Cancer? *Cancer Control* **2020**, *27*, 1073274820903384. [CrossRef] [PubMed]
85. Braoudaki, M.; Ahmad, M.S.; Mustafov, D.; Seriah, S.; Siddiqui, M.N.; Siddiqui, S.S. Chemokines and Chemokine Receptors in Colorectal Cancer; Multifarious Roles and Clinical Impact. *Semin. Cancer Biol.* **2022**, *86*, 436–449. [CrossRef] [PubMed]
86. Nandi, B.; Pai, C.; Huang, Q.; Prabhala, R.H.; Munshi, N.C.; Gold, J.S. CCR6, the Sole Receptor for the Chemokine CCL20, Promotes Spontaneous Intestinal Tumorigenesis. *PLoS ONE* **2014**, *9*, e97566. [CrossRef] [PubMed]
87. Powell, D.W.; Adegboyega, P.A.; Di Mari, J.F.; Mifflin, R.C. Epithelial Cells and Their Neighbors I. Role of Intestinal Myofibroblasts in Development, Repair, and Cancer. *Am. J. Physiol.-Gastrointest. Liver Physiol.* **2005**, *289*, G2–G7. [CrossRef] [PubMed]
88. Farc, O.; Cristea, V. An Overview of the Tumor Microenvironment, from Cells to Complex Networks (Review). *Exp. Ther. Med.* **2021**, *21*, 96. [CrossRef]
89. Li, J.; Chen, D.; Shen, M. Tumor Microenvironment Shapes Colorectal Cancer Progression, Metastasis, and Treatment Responses. *Front. Med.* **2022**, *9*, 869010. [CrossRef] [PubMed]
90. Wu, X.; Yan, H.; Qiu, M.; Qu, X.; Wang, J.; Xu, S.; Zheng, Y.; Ge, M.; Yan, L.; Liang, L. Comprehensive Characterization of Tumor Microenvironment in Colorectal Cancer via Molecular Analysis. *eLife* **2023**, *12*, e86032. [CrossRef]
91. Wynn, T.A.; Chawla, A.; Pollard, J.W. Origins and Hallmarks of Macrophages: Development, Homeostasis, and Disease. *Nature* **2013**, *496*, 445–455. [CrossRef] [PubMed]
92. Lendeckel, U.; Venz, S.; Wolke, C. Macrophages: Shapes and Functions. *ChemTexts* **2022**, *8*, 12. [CrossRef] [PubMed]
93. Lu, L.; Liu, Y.-J.; Cheng, P.-Q.; Hu, D.; Xu, H.-C.; Ji, G. Macrophages Play a Role in Inflammatory Transformation of Colorectal Cancer. *World J. Gastrointest. Oncol.* **2021**, *13*, 2013–2028. [CrossRef] [PubMed]
94. Edin, S.; Wikberg, M.L.; Dahlin, A.M.; Rutegård, J.; Öberg, Å.; Oldenborg, P.-A.; Palmqvist, R. The Distribution of Macrophages with a M1 or M2 Phenotype in Relation to Prognosis and the Molecular Characteristics of Colorectal Cancer. *PLoS ONE* **2012**, *7*, e47045. [CrossRef] [PubMed]
95. Zhang, Y.; Zhao, Y.; Li, Q.; Wang, Y. Macrophages, as a Promising Strategy to Targeted Treatment for Colorectal Cancer Metastasis in Tumor Immune Microenvironment. *Front. Immunol.* **2021**, *12*, 685978. [CrossRef] [PubMed]
96. Zhong, X.; Chen, B.; Yang, Z. The Role of Tumor-Associated Macrophages in Colorectal Carcinoma Progression. *Cell. Physiol. Biochem.* **2018**, *45*, 356–365. [CrossRef]
97. Koelzer, V.H.; Canonica, K.; Dawson, H.; Sokol, L.; Karamitopoulou-Diamantis, E.; Lugli, A.; Zlobec, I. Phenotyping of Tumor-Associated Macrophages in Colorectal Cancer: Impact on Single Cell Invasion (Tumor Budding) and Clinicopathological Outcome. *OncoImmunology* **2016**, *5*, e1106677. [CrossRef] [PubMed]
98. Wang, H.; Tian, T.; Zhang, J. Tumor-Associated Macrophages (TAMs) in Colorectal Cancer (CRC): From Mechanism to Therapy and Prognosis. *Int. J. Mol. Sci.* **2021**, *22*, 8470. [CrossRef] [PubMed]
99. Kiseleva, V.; Vishnyakova, P.; Elchaninov, A.; Fatkhudinov, T.; Sukhikh, G. Biochemical and Molecular Inducers and Modulators of M2 Macrophage Polarization in Clinical Perspective. *Int. Immunopharmacol.* **2023**, *122*, 110583. [CrossRef] [PubMed]
100. Pan, Y.; Yu, Y.; Wang, X.; Zhang, T. Tumor-Associated Macrophages in Tumor Immunity. *Front. Immunol.* **2020**, *11*, 583084. [CrossRef]
101. Ko, S.Y.; Ladanyi, A.; Lengyel, E.; Naora, H. Expression of the Homeobox Gene HOXA9 in Ovarian Cancer Induces Peritoneal Macrophages to Acquire an M2 Tumor-Promoting Phenotype. *Am. J. Pathol.* **2014**, *184*, 271–281. [CrossRef] [PubMed]
102. Hu, H.; Hang, J.-J.; Han, T.; Zhuo, M.; Jiao, F.; Wang, L.-W. The M2 Phenotype of Tumor-Associated Macrophages in the Stroma Confers a Poor Prognosis in Pancreatic Cancer. *Tumor Biol.* **2016**, *37*, 8657–8664. [CrossRef] [PubMed]
103. Xiao, Y.; Yang, K.; Wang, Z.; Zhao, M.; Deng, Y.; Ji, W.; Zou, Y.; Qian, C.; Liu, Y.; Xiao, H.; et al. CD44-Mediated Poor Prognosis in Glioma Is Associated With M2-Polarization of Tumor-Associated Macrophages and Immunosuppression. *Front. Surg.* **2022**, *8*, 775194. [CrossRef] [PubMed]
104. Dong, F.; Ruan, S.; Wang, J.; Xia, Y.; Le, K.; Xiao, X.; Hu, T.; Wang, Q. M2 Macrophage-Induced lncRNA PCAT6 Facilitates Tumorigenesis and Angiogenesis of Triple-Negative Breast Cancer through Modulation of VEGFR2. *Cell Death Dis.* **2020**, *11*, 728. [CrossRef] [PubMed]

105. Hanada, T.; Nakagawa, M.; Emoto, A.; Nomura, T.; Nasu, N.; Nomura, Y. Prognostic Value of Tumor-Associated Macrophage Count in Human Bladder Cancer. *Int. J. Urol.* **2000**, *7*, 263–269. [CrossRef] [PubMed]
106. Wei, C.; Yang, C.; Wang, S.; Shi, D.; Zhang, C.; Lin, X.; Liu, Q.; Dou, R.; Xiong, B. Crosstalk between Cancer Cells and Tumor Associated Macrophages Is Required for Mesenchymal Circulating Tumor Cell-Mediated Colorectal Cancer Metastasis. *Mol. Cancer* **2019**, *18*, 64. [CrossRef] [PubMed]
107. Zhang, Y.; Sime, W.; Juhas, M.; Sjölander, A. Crosstalk between Colon Cancer Cells and Macrophages via Inflammatory Mediators and CD47 Promotes Tumour Cell Migration. *Eur. J. Cancer* **2013**, *49*, 3320–3334. [CrossRef] [PubMed]
108. Kang, J.-C.; Chen, J.-S.; Lee, C.-H.; Chang, J.-J.; Shieh, Y.-S. Intratumoral Macrophage Counts Correlate with Tumor Progression in Colorectal Cancer. *J. Surg. Oncol.* **2010**, *102*, 242–248. [CrossRef] [PubMed]
109. Forssell, J.; Öberg, Å.; Henriksson, M.L.; Stenling, R.; Jung, A.; Palmqvist, R. High Macrophage Infiltration along the Tumor Front Correlates with Improved Survival in Colon Cancer. *Clin. Cancer Res.* **2007**, *13*, 1472–1479. [CrossRef] [PubMed]
110. Ålgars, A.; Irjala, H.; Vaittinen, S.; Huhtinen, H.; Sundström, J.; Salmi, M.; Ristamäki, R.; Jalkanen, S. Type and Location of Tumor-Infiltrating Macrophages and Lymphatic Vessels Predict Survival of Colorectal Cancer Patients. *Int. J. Cancer* **2012**, *131*, 864–873. [CrossRef] [PubMed]
111. Sugita, J.; Ohtani, H.; Mizoi, T.; Saito, K.; Shiiba, K.; Sasaki, I.; Matsuno, S.; Yagita, H.; Miyazawa, M.; Nagura, H. Close Association between Fas Ligand (FasL; CD95L)-Positive Tumor-Associated Macrophages and Apoptotic Cancer Cells along Invasive Margin of Colorectal Carcinoma: A Proposal on Tumor-Host Interactions. *Jpn. J. Cancer Res.* **2002**, *93*, 320–328. [CrossRef] [PubMed]
112. Gao, X.; Zhou, S.; Qin, Z.; Li, D.; Zhu, Y.; Ma, D. Upregulation of HMGB1 in Tumor-Associated Macrophages Induced by Tumor Cell-Derived Lactate Further Promotes Colorectal Cancer Progression. *J. Transl. Med.* **2023**, *21*, 53. [CrossRef]
113. Lian, G.; Chen, S.; Ouyang, M.; Li, F.; Chen, L.; Yang, J. Colon Cancer Cell Secretes EGF to Promote M2 Polarization of TAM Through EGFR/PI3K/AKT/mTOR Pathway. *Technol. Cancer Res. Treat.* **2019**, *18*, 1533033819849068. [CrossRef]
114. Riabov, V.; Gudima, A.; Wang, N.; Mickley, A.; Orekhov, A.; Kzhyshkowska, J. Role of Tumor Associated Macrophages in Tumor Angiogenesis and Lymphangiogenesis. *Front. Physiol.* **2014**, *5*, 75. [CrossRef]
115. Łojko, A.; Komarnicki, M. Vascular Endothelial Growth Factor in Tumor Angiogenesis. *Contemp. Oncol.* **2004**, *8*, 1–4.
116. Schito, L. Hypoxia-Dependent Angiogenesis and Lymphangiogenesis in Cancer. In *Hypoxia and Cancer Metastasis*; Gilkes, D.M., Ed.; Advances in Experimental Medicine and Biology; Springer International Publishing: Cham, Switzerland, 2019; pp. 71–85. ISBN 978-3-030-12734-3.
117. Yao, P.-L.; Lin, Y.-C.; Wang, C.-H.; Huang, Y.-C.; Liao, W.-Y.; Wang, S.-S.; Chen, J.J.W.; Yang, P.-C. Autocrine and Paracrine Regulation of Interleukin-8 Expression in Lung Cancer Cells. *Am. J. Respir. Cell Mol. Biol.* **2005**, *32*, 540–547. [CrossRef] [PubMed]
118. Yang, Q.; Guo, N.; Zhou, Y.; Chen, J.; Wei, Q.; Han, M. The Role of Tumor-Associated Macrophages (TAMs) in Tumor Progression and Relevant Advance in Targeted Therapy. *Acta Pharm. Sin. B* **2020**, *10*, 2156–2170. [CrossRef] [PubMed]
119. Badawi, M.A.; Abouelfadl, D.M.; El-Sharkawy, S.L.; El-Aal, W.E.A.; Abbas, N.F. Tumor-Associated Macrophage (TAM) and Angiogenesis in Human Colon Carcinoma. *Open Access Maced. J. Med. Sci.* **2015**, *3*, 209–214. [CrossRef] [PubMed]
120. Mazzone, M.; Menga, A.; Castegna, A. Metabolism and TAM Functions—It Takes Two to Tango. *FEBS J.* **2018**, *285*, 700–716. [CrossRef] [PubMed]
121. Crezee, T.; Rabold, K.; de Jong, L.; Jaeger, M.; Netea-Maier, R.T. Metabolic Programming of Tumor Associated Macrophages in the Context of Cancer Treatment. *Ann. Transl. Med.* **2020**, *8*, article 1028. [CrossRef] [PubMed]
122. Scheurlen, K.M.; Billeter, A.T.; O'Brien, S.J.; Galandiuk, S. Metabolic Dysfunction and Early-Onset Colorectal Cancer—How Macrophages Build the Bridge. *Cancer Med.* **2020**, *9*, 6679–6693. [CrossRef] [PubMed]
123. Wenes, M.; Shang, M.; Di Matteo, M.; Goveia, J.; Martín-Pérez, R.; Serneels, J.; Prenen, H.; Ghesquière, B.; Carmeliet, P.; Mazzone, M. Macrophage Metabolism Controls Tumor Blood Vessel Morphogenesis and Metastasis. *Cell Metab.* **2016**, *24*, 701–715. [CrossRef] [PubMed]
124. Jiang, M.; Cui, H.; Liu, Z.; Zhou, X.; Zhang, L.; Cao, L.; Wang, M. The Role of Amino Acid Metabolism of Tumor Associated Macrophages in the Development of Colorectal Cancer. *Cells* **2022**, *11*, 4106. [CrossRef]
125. Panni, R.Z.; Linehan, D.C.; DeNardo, D.G. Targeting Tumor-Infiltrating Macrophages to Combat Cancer. *Immunotherapy* **2013**, *5*, 1075–1087. [CrossRef] [PubMed]
126. Xu, H.; Zhang, Y.; Peña, M.M.; Pirisi, L.; Creek, K.E. Six1 Promotes Colorectal Cancer Growth and Metastasis by Stimulating Angiogenesis and Recruiting Tumor-Associated Macrophages. *Carcinogenesis* **2017**, *38*, 281–292. [CrossRef] [PubMed]
127. Song, W.; Ma, J.; Lei, B.; Yuan, X.; Cheng, B.; Yang, H.; Wang, M.; Feng, Z.; Wang, L. Sine Oculis Homeobox 1 Promotes Proliferation and Migration of Human Colorectal Cancer Cells through Activation of Wnt/B-catenin Signaling. *Cancer Sci.* **2019**, *110*, 608–616. [CrossRef] [PubMed]
128. Fei, L.; Ren, X.; Yu, H.; Zhan, Y. Targeting the CCL2/CCR2 Axis in Cancer Immunotherapy: One Stone, Three Birds? *Front. Immunol.* **2021**, *12*, 771210. [CrossRef] [PubMed]
129. Qian, B.-Z.; Li, J.; Zhang, H.; Kitamura, T.; Zhang, J.; Campion, L.R.; Kaiser, E.A.; Snyder, L.A.; Pollard, J.W. CCL2 Recruits Inflammatory Monocytes to Facilitate Breast Tumor Metastasis. *Nature* **2011**, *475*, 222–225. [CrossRef] [PubMed]
130. Boring, L.; Gosling, J.; Chensue, S.W.; Kunkel, S.L.; Farese, R.V.; Broxmeyer, H.E.; Charo, I.F. Impaired Monocyte Migration and Reduced Type 1 (Th1) Cytokine Responses in C-C Chemokine Receptor 2 Knockout Mice. *J. Clin. Investig.* **1997**, *100*, 2552–2561. [CrossRef] [PubMed]

131. Lança, T.; Costa, M.F.; Gonçalves-Sousa, N.; Rei, M.; Grosso, A.R.; Penido, C.; Silva-Santos, B. Protective Role of the Inflammatory CCR2/CCL2 Chemokine Pathway through Recruitment of Type 1 Cytotoxic Γδ T Lymphocytes to Tumor Beds. *J. Immunol.* **2013**, *190*, 6673–6680. [CrossRef]
132. Wang, D.; Wang, X.; Si, M.; Yang, J.; Sun, S.; Wu, H.; Cui, S.; Qu, X.; Yu, X. Exosome-Encapsulated miRNAs Contribute to CXCL12/CXCR4-Induced Liver Metastasis of Colorectal Cancer by Enhancing M2 Polarization of Macrophages. *Cancer Lett.* **2020**, *474*, 36–52. [CrossRef] [PubMed]
133. Liu, Q.; Yang, C.; Wang, S.; Shi, D.; Wei, C.; Song, J.; Lin, X.; Dou, R.; Bai, J.; Xiang, Z.; et al. Wnt5a-Induced M2 Polarization of Tumor-Associated Macrophages via IL-10 Promotes Colorectal Cancer Progression. *Cell Commun. Signal.* **2020**, *18*, 51. [CrossRef] [PubMed]
134. Khan, S.U.; Khan, M.U.; Azhar Ud Din, M.; Khan, I.M.; Khan, M.I.; Bungau, S.; Hassan, S.S. ul Reprogramming Tumor-Associated Macrophages as a Unique Approach to Target Tumor Immunotherapy. *Front. Immunol.* **2023**, *14*, 1166487. [CrossRef] [PubMed]
135. Zeng, Q.; Jewell, C.M. Directing Toll-like Receptor Signaling in Macrophages to Enhance Tumor Immunotherapy. *Curr. Opin. Biotechnol.* **2019**, *60*, 138–145. [CrossRef]
136. Sun, P.; Meng, L. Emerging Roles of Class I PI3K Inhibitors in Modulating Tumor Microenvironment and Immunity. *Acta Pharmacol. Sin.* **2020**, *41*, 1395–1402. [CrossRef] [PubMed]
137. Dominiak, A.; Nowicki, T.; Łacheta, D.; Nowicka, G. Cancer-Associated Fibroblasts as a Potential Target in Oncology Therapy. *Postep. Hig. Med. Dosw.* **2019**, *73*, 536–549. [CrossRef]
138. Wang, Y.; Chen, Z.; Zhao, G.; Li, Q. Cancer-Associated Fibroblast Risk Model for Prediction of Colorectal Carcinoma Prognosis and Therapeutic Responses. *Mediat. Inflamm.* **2023**, *2023*, 3781091. [CrossRef] [PubMed]
139. Nazemi, M.; Rainero, E. Cross-Talk Between the Tumor Microenvironment, Extracellular Matrix, and Cell Metabolism in Cancer. *Front. Oncol.* **2020**, *10*, 239. [CrossRef]
140. Deng, L.; Jiang, N.; Zeng, J.; Wang, Y.; Cui, H. The Versatile Roles of Cancer-Associated Fibroblasts in Colorectal Cancer and Therapeutic Implications. *Front. Cell Dev. Biol.* **2021**, *9*, 733270. [CrossRef] [PubMed]
141. Chen, L.; Qiu, X.; Wang, X.; He, J. FAP Positive Fibroblasts Induce Immune Checkpoint Blockade Resistance in Colorectal Cancer via Promoting Immunosuppression. *Biochem. Biophys. Res. Commun.* **2017**, *487*, 8–14. [CrossRef] [PubMed]
142. Son, G.M.; Kwon, M.-S.; Shin, D.-H.; Shin, N.; Ryu, D.; Kang, C.-D. Comparisons of cancer-associated fibroblasts in the intratumoral stroma and invasive front in colorectal cancer. *Medicine* **2019**, *98*, e15164. [CrossRef] [PubMed]
143. Dai, X.; Xie, Y.; Dong, M. Cancer-Associated Fibroblasts Derived Extracellular Vesicles Promote Angiogenesis of Colorectal Adenocarcinoma Cells through miR-135b-5p/FOXO1 Axis. *Cancer Biol. Ther.* **2022**, *23*, 76–88. [CrossRef] [PubMed]
144. Hu, J.L.; Wang, W.; Lan, X.L.; Zeng, Z.C.; Liang, Y.S.; Yan, Y.R.; Song, F.Y.; Wang, F.F.; Zhu, X.H.; Liao, W.J.; et al. CAFs Secreted Exosomes Promote Metastasis and Chemotherapy Resistance by Enhancing Cell Stemness and Epithelial-Mesenchymal Transition in Colorectal Cancer. *Mol. Cancer* **2019**, *18*, 91. [CrossRef] [PubMed]
145. Zafari, N.; Khosravi, F.; Rezaee, Z.; Esfandyari, S.; Bahiraei, M.; Bahramy, A.; Ferns, G.A.; Avan, A. The Role of the Tumor Microenvironment in Colorectal Cancer and the Potential Therapeutic Approaches. *J. Clin. Lab. Anal.* **2022**, *36*, e24585. [CrossRef] [PubMed]
146. Ding, X.; Ji, J.; Jiang, J.; Cai, Q.; Wang, C.; Shi, M.; Yu, Y.; Zhu, Z.; Zhang, J. HGF-Mediated Crosstalk between Cancer-Associated Fibroblasts and MET-Unamplified Gastric Cancer Cells Activates Coordinated Tumorigenesis and Metastasis. *Cell Death Dis.* **2018**, *9*, 867. [CrossRef] [PubMed]
147. Fotsitzoudis, C.; Koulouridi, A.; Messaritakis, I.; Konstantinidis, T.; Gouvas, N.; Tsiaoussis, J.; Souglakos, J. Cancer-Associated Fibroblasts: The Origin, Biological Characteristics and Role in Cancer—A Glance on Colorectal Cancer. *Cancers* **2022**, *14*, 4394. [CrossRef] [PubMed]
148. Gao, D.; Fang, L.; Liu, C.; Yang, M.; Yu, X.; Wang, L.; Zhang, W.; Sun, C.; Zhuang, J. Microenvironmental Regulation in Tumor Progression: Interactions between Cancer-Associated Fibroblasts and Immune Cells. *Biomed. Pharmacother.* **2023**, *167*, 115622. [CrossRef] [PubMed]
149. Calon, A.; Espinet, E.; Palomo-Ponce, S.; Tauriello, D.V.F.; Iglesias, M.; Céspedes, M.V.; Sevillano, M.; Nadal, C.; Jung, P.; Zhang, X.H.-F.; et al. Dependency of Colorectal Cancer on a TGF-Beta-Driven Programme in Stromal Cells for Metastasis Initiation. *Cancer Cell* **2012**, *22*, 571–584. [CrossRef] [PubMed]
150. Li, X.; Wu, Y.; Tian, T. TGF-β Signaling in Metastatic Colorectal Cancer (mCRC): From Underlying Mechanism to Potential Applications in Clinical Development. *Int. J. Mol. Sci.* **2022**, *23*, 14436. [CrossRef] [PubMed]
151. Itatani, Y.; Kawada, K.; Sakai, Y. Transforming Growth Factor-β Signaling Pathway in Colorectal Cancer and Its Tumor Microenvironment. *Int. J. Mol. Sci.* **2019**, *20*, 5822. [CrossRef] [PubMed]
152. Yi, W.; Xiao, E.; Ding, R.; Luo, P.; Yang, Y. High Expression of Fibronectin Is Associated with Poor Prognosis, Cell Proliferation and Malignancy via the NF-κB/P53-Apoptosis Signaling Pathway in Colorectal Cancer. *Oncol. Rep.* **2016**, *36*, 3145–3153. [CrossRef] [PubMed]
153. Spada, S.; Tocci, A.; Di Modugno, F.; Nisticò, P. Fibronectin as a Multiregulatory Molecule Crucial in Tumor Matrisome: From Structural and Functional Features to Clinical Practice in Oncology. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 102. [CrossRef] [PubMed]
154. Tardito, S.; Zocchi, M.R.; Benelli, R. The Stockholm Syndrome of Cancer: Fibroblasts as a Powerful Shield against Colorectal Cancer Therapy. *Cancers* **2023**, *15*, 491. [CrossRef] [PubMed]

155. Galindo-Pumariño, C.; Collado, M.; Castillo, M.E.; Barquín, J.; Romio, E.; Larriba, M.J.; Muñoz de Mier, G.J.; Carrato, A.; de la Pinta, C.; Pena, C. SNAI1-Expressing Fibroblasts and Derived-Extracellular Matrix as Mediators of Drug Resistance in Colorectal Cancer Patients. *Toxicol. Appl. Pharmacol.* **2022**, *450*, 116171. [CrossRef] [PubMed]
156. Chen, X.; Liu, J.; Zhang, Q.; Liu, B.; Cheng, Y.; Zhang, Y.; Sun, Y.; Ge, H.; Liu, Y. Exosome-Mediated Transfer of miR-93-5p from Cancer-Associated Fibroblasts Confer Radioresistance in Colorectal Cancer Cells by Downregulating FOXA1 and Upregulating TGFB3. *J. Exp. Clin. Cancer Res.* **2020**, *39*, 65. [CrossRef] [PubMed]
157. Li, T.; Yi, S.; Liu, W.; Jia, C.; Wang, G.; Hua, X.; Tai, Y.; Zhang, Q.; Chen, G. Colorectal Carcinoma-Derived Fibroblasts Modulate Natural Killer Cell Phenotype and Antitumor Cytotoxicity. *Med. Oncol.* **2013**, *30*, 663. [CrossRef] [PubMed]
158. Yao, L.; Hou, J.; Wu, X.; Lu, Y.; Jin, Z.; Yu, Z.; Yu, B.; Li, J.; Yang, Z.; Li, C.; et al. Cancer-Associated Fibroblasts Impair the Cytotoxic Function of NK Cells in Gastric Cancer by Inducing Ferroptosis via Iron Regulation. *Redox Biol.* **2023**, *67*, 102923. [CrossRef] [PubMed]
159. Cho, H.; Seo, Y.; Loke, K.M.; Kim, S.-W.; Oh, S.-M.; Kim, J.-H.; Soh, J.; Kim, H.S.; Lee, H.; Kim, J.; et al. Cancer-Stimulated CAFs Enhance Monocyte Differentiation and Protumoral TAM Activation via IL6 and GM-CSF Secretion. *Clin. Cancer Res.* **2018**, *24*, 5407–5421. [CrossRef] [PubMed]
160. Mukaida, N.; Sasaki, S. Fibroblasts, an Inconspicuous but Essential Player in Colon Cancer Development and Progression. *World J. Gastroenterol.* **2016**, *22*, 5301–5316. [CrossRef] [PubMed]
161. Glabman, R.A.; Choyke, P.L.; Sato, N. Cancer-Associated Fibroblasts: Tumorigenicity and Targeting for Cancer Therapy. *Cancers* **2022**, *14*, 3906. [CrossRef] [PubMed]
162. Coward, J.; Kulbe, H.; Chakravarty, P.; Leader, D.; Vassileva, V.; Leinster, D.A.; Thompson, R.; Schioppa, T.; Nemeth, J.; Vermeulen, J.; et al. Interleukin-6 as a Therapeutic Target in Human Ovarian Cancer. *Clin. Cancer Res.* **2011**, *17*, 6083–6096. [CrossRef] [PubMed]
163. Nishina, T.; Deguchi, Y.; Ohshima, D.; Takeda, W.; Ohtsuka, M.; Shichino, S.; Ueha, S.; Yamazaki, S.; Kawauchi, M.; Nakamura, E.; et al. Interleukin-11-Expressing Fibroblasts Have a Unique Gene Signature Correlated with Poor Prognosis of Colorectal Cancer. *Nat. Commun.* **2021**, *12*, 2281. [CrossRef] [PubMed]
164. Gong, J.; Lin, Y.; Zhang, H.; Liu, C.; Cheng, Z.; Yang, X.; Zhang, J.; Xiao, Y.; Sang, N.; Qian, X.; et al. Reprogramming of Lipid Metabolism in Cancer-Associated Fibroblasts Potentiates Migration of Colorectal Cancer Cells. *Cell Death Dis.* **2020**, *11*, 267. [CrossRef] [PubMed]
165. Fuchs, T.L.; Sioson, L.; Sheen, A.; Jafari-Nejad, K.; Renaud, C.J.; Andrici, J.; Ahadi, M.; Chou, A.; Gill, A.J. Assessment of Tumor-infiltrating Lymphocytes Using International TILs Working Group (ITWG) System Is a Strong Predictor of Overall Survival in Colorectal Carcinoma: A Study of 1034 Patients. *Am. J. Surg. Pathol.* **2020**, *44*, 536. [CrossRef] [PubMed]
166. Walterskirchen, N.; Müller, C.; Ramos, C.; Zeindl, S.; Stang, S.; Herzog, D.; Sachet, M.; Schimek, V.; Unger, L.; Gerakopoulos, V.; et al. Metastatic Colorectal Carcinoma-Associated Fibroblasts Have Immunosuppressive Properties Related to Increased IGFBP2 Expression. *Cancer Lett.* **2022**, *540*, 215737. [CrossRef] [PubMed]
167. Zhao, J.; Huang, W.; Wu, Y.; Luo, Y.; Wu, B.; Cheng, J.; Chen, J.; Liu, D.; Li, C. Prognostic Role of Pretreatment Blood Lymphocyte Count in Patients with Solid Tumors: A Systematic Review and Meta-Analysis. *Cancer Cell Int.* **2020**, *20*, 15. [CrossRef] [PubMed]
168. Idos, G.E.; Kwok, J.; Bonthala, N.; Kysh, L.; Gruber, S.B.; Qu, C. The Prognostic Implications of Tumor Infiltrating Lymphocytes in Colorectal Cancer: A Systematic Review and Meta-Analysis. *Sci. Rep.* **2020**, *10*, 3360. [CrossRef]
169. Aristin Revilla, S.; Kranenburg, O.; Coffer, P.J. Colorectal Cancer-Infiltrating Regulatory T Cells: Functional Heterogeneity, Metabolic Adaptation, and Therapeutic Targeting. *Front. Immunol.* **2022**, *13*, 903564. [CrossRef] [PubMed]
170. Bai, Z.; Zhou, Y.; Ye, Z.; Xiong, J.; Lan, H.; Wang, F. Tumor-Infiltrating Lymphocytes in Colorectal Cancer: The Fundamental Indication and Application on Immunotherapy. *Front. Immunol.* **2022**, *12*, 808964. [CrossRef] [PubMed]
171. Paijens, S.T.; Vledder, A.; de Bruyn, M.; Nijman, H.W. Tumor-Infiltrating Lymphocytes in the Immunotherapy Era. *Cell Mol. Immunol.* **2021**, *18*, 842–859. [CrossRef] [PubMed]
172. Ghazvinian, Z.; Abdolahi, S.; Tokhanbigli, S.; Tarzemani, S.; Piccin, A.; Reza Zali, M.; Verdi, J.; Baghaei, K. Contribution of Natural Killer Cells in Innate Immunity against Colorectal Cancer. *Front. Oncol.* **2023**, *12*, 1077053. [CrossRef] [PubMed]
173. Coca, S.; Perez-Piqueras, J.; Martinez, D.; Colmenarejo, A.; Saez, M.A.; Vallejo, C.; Martos, J.A.; Moreno, M. The Prognostic Significance of Intratumoral Natural Killer Cells in Patients with Colorectal Carcinoma. *Cancer* **1997**, *79*, 2320–2328. [CrossRef]
174. Ruffell, B.; DeNardo, D.G.; Affara, N.I.; Coussens, L.M. Lymphocytes in Cancer Development: Polarization towards pro-Tumor Immunity. *Cytokine Growth Factor. Rev.* **2010**, *21*, 3–10. [CrossRef]
175. Koh, E.-K.; Lee, H.-R.; Son, W.-C.; Park, G.-Y.; Bae, J.; Park, Y.-S. Antitumor Effects of NK Cells Expanded by Activation Pre-processing of Autologous Feeder Cells before Irradiation in Colorectal Cancer. *Oncol. Lett.* **2023**, *25*, 1–12. [CrossRef] [PubMed]
176. Tosolini, M.; Kirilovsky, A.; Mlecnik, B.; Fredriksen, T.; Mauger, S.; Bindea, G.; Berger, A.; Bruneval, P.; Fridman, W.-H.; Pagès, F.; et al. Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer. *Cancer Res.* **2011**, *71*, 1263–1271. [CrossRef] [PubMed]
177. Lee, J.; Lozano-Ruiz, B.; Yang, F.M.; Fan, D.D.; Shen, L.; González-Navajas, J.M. The Multifaceted Role of Th1, Th9, and Th17 Cells in Immune Checkpoint Inhibition Therapy. *Front. Immunol.* **2021**, *12*, 625667. [CrossRef] [PubMed]
178. Andreu-Sanz, D.; Kobold, S. Role and Potential of Different T Helper Cell Subsets in Adoptive Cell Therapy. *Cancers* **2023**, *15*, 1650. [CrossRef] [PubMed]

179. Kotov, D.I.; Kotov, J.A.; Goldberg, M.F.; Jenkins, M.K. Many Helper T Cell Subsets Have Fas Ligand-Dependent Cytotoxic Potential. *J. Immunol.* **2018**, *200*, 2004–2012. [CrossRef] [PubMed]
180. Wu, D.; Wu, P.; Huang, Q.; Liu, Y.; Ye, J.; Huang, J. Interleukin-17: A Promoter in Colorectal Cancer Progression. *Clin. Dev. Immunol.* **2013**, *2013*, 436307. [CrossRef] [PubMed]
181. Li, S.; Na, R.; Li, X.; Zhang, Y.; Zheng, T. Targeting Interleukin-17 Enhances Tumor Response to Immune Checkpoint Inhibitors in Colorectal Cancer. *Biochim. Biophys. Acta BBA-Rev. Cancer* **2022**, *1877*, 188758. [CrossRef]
182. Miyahara, Y.; Odunsi, K.; Chen, W.; Peng, G.; Matsuzaki, J.; Wang, R.-F. Generation and Regulation of Human CD4+ IL-17-Producing T Cells in Ovarian Cancer. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 15505–15510. [CrossRef] [PubMed]
183. De Simone, V.; Pallone, F.; Monteleone, G.; Stolfi, C. Role of TH17 Cytokines in the Control of Colorectal Cancer. *Oncoimmunology* **2013**, *2*, e26617. [CrossRef] [PubMed]
184. Gutiérrez-Melo, N.; Baumjohann, D. T Follicular Helper Cells in Cancer. *Trends Cancer* **2023**, *9*, 309–325. [CrossRef] [PubMed]
185. Wang, S.; Liu, W.; Ly, D.; Xu, H.; Qu, L.; Zhang, L. Tumor-Infiltrating B Cells: Their Role and Application in Anti-Tumor Immunity in Lung Cancer. *Cell Mol. Immunol.* **2019**, *16*, 6–18. [CrossRef] [PubMed]
186. Ohue, Y.; Nishikawa, H. Regulatory T (Treg) Cells in Cancer: Can Treg Cells Be a New Therapeutic Target? *Cancer Sci.* **2019**, *110*, 2080–2089. [CrossRef] [PubMed]
187. Mizukami, Y.; Kono, K.; Kawaguchi, Y.; Akaike, H.; Kamimura, K.; Sugai, H.; Fujii, H. CCL17 and CCL22 Chemokines within Tumor Microenvironment Are Related to Accumulation of Foxp3+ Regulatory T Cells in Gastric Cancer. *Int. J. Cancer* **2008**, *122*, 2286–2293. [CrossRef] [PubMed]
188. Kuehnemuth, B.; Piseddu, I.; Wiedemann, G.M.; Lauseker, M.; Kuhn, C.; Hofmann, S.; Schmoeckel, E.; Endres, S.; Mayr, D.; Jeschke, U.; et al. CCL1 Is a Major Regulatory T Cell Attracting Factor in Human Breast Cancer. *BMC Cancer* **2018**, *18*, 1278. [CrossRef] [PubMed]
189. Galgani, M.; Bruzzaniti, S.; La Rocca, C.; Micillo, T.; de Candia, P.; Bifulco, M.; Matarese, G. Immunometabolism of Regulatory T Cells in Cancer. *Mol. Asp. Med.* **2021**, *77*, 100936. [CrossRef] [PubMed]
190. Olguín, J.E.; Medina-Andrade, I.; Rodríguez, T.; Rodríguez-Sosa, M.; Terrazas, L.I. Relevance of Regulatory T Cells during Colorectal Cancer Development. *Cancers* **2020**, *12*, 1888. [CrossRef] [PubMed]
191. Milne, K.; Köbel, M.; Kalloger, S.E.; Barnes, R.O.; Gao, D.; Gilks, C.B.; Watson, P.H.; Nelson, B.H. Systematic Analysis of Immune Infiltrates in High-Grade Serous Ovarian Cancer Reveals CD20, FoxP3 and TIA-1 as Positive Prognostic Factors. *PLoS ONE* **2009**, *4*, e6412. [CrossRef] [PubMed]
192. Shen, M.; Sun, Q.; Wang, J.; Pan, W.; Ren, X. Positive and Negative Functions of B Lymphocytes in Tumors. *Oncotarget* **2016**, *7*, 55828–55839. [CrossRef] [PubMed]
193. Wei, X.; Jin, Y.; Tian, Y.; Zhang, H.; Wu, J.; Lu, W.; Lu, X. Regulatory B Cells Contribute to the Impaired Antitumor Immunity in Ovarian Cancer Patients. *Tumor Biol.* **2016**, *37*, 6581–6588. [CrossRef]
194. Edin, S.; Kaprio, T.; Hagström, J.; Larsson, P.; Mustonen, H.; Böckelman, C.; Strigård, K.; Gunnarsson, U.; Haglund, C.; Palmqvist, R. The Prognostic Importance of CD20+ B Lymphocytes in Colorectal Cancer and the Relation to Other Immune Cell Subsets. *Sci. Rep.* **2019**, *9*, 19997. [CrossRef] [PubMed]
195. Berntsson, J.; Nodin, B.; Eberhard, J.; Jirstrom, K. Prognostic Impact of Tumor-Associated B Cells and Plasma Cells in Colorectal Cancer. *JCO* **2016**, *34*, 587. [CrossRef]
196. Shimabukuro-Vornhagen, A.; Schlößer, H.A.; Gryschok, L.; Malcher, J.; Wennhold, K.; Garcia-Marquez, M.; Herbold, T.; Neuhaus, L.S.; Becker, H.J.; Fiedler, A.; et al. Characterization of Tumor-Associated B-Cell Subsets in Patients with Colorectal Cancer. *Oncotarget* **2014**, *5*, 4651–4664. [CrossRef] [PubMed]
197. Ganesh, K.; Stadler, Z.K.; Cercek, A.; Mendelsohn, R.B.; Shia, J.; Segal, N.H.; Diaz, L.A. Immunotherapy in Colorectal Cancer: Rationale, Challenges and Potential. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 361–375. [CrossRef] [PubMed]
198. Saad, P.; Kasi, A. Ipilimumab. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
199. Rendon, A.; Rayi, A. Nivolumab. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2024.
200. Chen, X.; Chen, L.-J.; Peng, X.-F.; Deng, L.; Wang, Y.; Li, J.-J.; Guo, D.-L.; Niu, X.-H. Anti-PD-1/PD-L1 Therapy for Colorectal Cancer: Clinical Implications and Future Considerations. *Transl. Oncol.* **2024**, *40*, 101851. [CrossRef] [PubMed]
201. Gabrilovich, D.I.; Nagaraj, S. Myeloid-Derived Suppressor Cells as Regulators of the Immune System. *Nat. Rev. Immunol.* **2009**, *9*, 162–174. [CrossRef] [PubMed]
202. Wu, Y.; Yi, M.; Niu, M.; Mei, Q.; Wu, K. Myeloid-Derived Suppressor Cells: An Emerging Target for Anticancer Immunotherapy. *Mol. Cancer* **2022**, *21*, 184. [CrossRef] [PubMed]
203. Yang, Y.; Li, C.; Liu, T.; Dai, X.; Bazhin, A.V. Myeloid-Derived Suppressor Cells in Tumors: From Mechanisms to Antigen Specificity and Microenvironmental Regulation. *Front. Immunol.* **2020**, *11*, 1371. [CrossRef] [PubMed]
204. Sieminska, I.; Baran, J. Myeloid-Derived Suppressor Cells in Colorectal Cancer. *Front. Immunol.* **2020**, *11*, 1526. [CrossRef] [PubMed]
205. Li, K.; Shi, H.; Zhang, B.; Ou, X.; Ma, Q.; Chen, Y.; Shu, P.; Li, D.; Wang, Y. Myeloid-Derived Suppressor Cells as Immunosuppressive Regulators and Therapeutic Targets in Cancer. *Signal Transduct. Target. Ther.* **2021**, *6*, 362. [CrossRef] [PubMed]
206. OuYang, L.-Y.; Wu, X.-J.; Ye, S.-B.; Zhang, R.; Li, Z.-L.; Liao, W.; Pan, Z.-Z.; Zheng, L.-M.; Zhang, X.-S.; Wang, Z.; et al. Tumor-Induced Myeloid-Derived Suppressor Cells Promote Tumor Progression through Oxidative Metabolism in Human Colorectal Cancer. *J. Transl. Med.* **2015**, *13*, 47. [CrossRef]

207. Sreevalsan, S.; Safe, S. Reactive Oxygen Species and Colorectal Cancer. *Curr. Color. Cancer Rep.* **2013**, *9*, 350–357. [CrossRef] [PubMed]
208. Chun, E.; Lavoie, S.; Michaud, M.; Gallini, C.A.; Kim, J.; Soucy, G.; Odze, R.; Glickman, J.N.; Garrett, W.S. CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function. *Cell Rep.* **2015**, *12*, 244–257. [CrossRef] [PubMed]
209. Gu, J.; Lv, X.; Li, W.; Li, G.; He, X.; Zhang, Y.; Shi, L.; Zhang, X. Deciphering the Mechanism of Peptostreptococcus Anaerobius-Induced Chemoresistance in Colorectal Cancer: The Important Roles of MDSC Recruitment and EMT Activation. *Front. Immunol.* **2023**, *14*, 1230681. [CrossRef] [PubMed]
210. Nie, J.; Wang, D.; Li, M. The Crosstalk between Autophagy and Myeloid-Derived Suppressor Cell Responses in Cancer. *Clin. Transl. Oncol.* **2023**, *25*, 2832–2840. [CrossRef] [PubMed]
211. Jin, Z.; Sun, X.; Wang, Y.; Zhou, C.; Yang, H.; Zhou, S. Regulation of Autophagy Fires up the Cold Tumor Microenvironment to Improve Cancer Immunotherapy. *Front. Immunol.* **2022**, *13*, 1018903. [CrossRef] [PubMed]
212. Kang, J.; Lee, D.; Lee, K.J.; Yoon, J.E.; Kwon, J.-H.; Seo, Y.; Kim, J.; Chang, S.Y.; Park, J.; Kang, E.A.; et al. Tumor-Suppressive Effect of Metformin via the Regulation of M2 Macrophages and Myeloid-Derived Suppressor Cells in the Tumor Microenvironment of Colorectal Cancer. *Cancers* **2022**, *14*, 2881. [CrossRef] [PubMed]
213. Al-Mterin, M.A.; Elkord, E. Myeloid-Derived Suppressor Cells in Colorectal Cancer: Prognostic Biomarkers and Therapeutic Targets. *Explor. Target. Antitumor Ther.* **2022**, *3*, 497–510. [CrossRef] [PubMed]
214. Ratajska, A.; Jankowska-Steifer, E.; Czarnowska, E.; Flaht, A.; Radomska-Leśniewska, D. Morphogenesis, structure and properties of lymphatic vessels. *Postep. Hig. Med. Dosw.* **2012**, *66*, 901–912. [CrossRef] [PubMed]
215. Berendam, S.J.; Koeppel, A.F.; Godfrey, N.R.; Rouhani, S.J.; Woods, A.N.; Rodriguez, A.B.; Peske, J.D.; Cummings, K.L.; Turner, S.D.; Engelhard, V.H. Comparative Transcriptomic Analysis Identifies a Range of Immunologically Related Functional Elaborations of Lymph Node Associated Lymphatic and Blood Endothelial Cells. *Front. Immunol.* **2019**, *10*, 816. [CrossRef] [PubMed]
216. Chen, W.-Z.; Jiang, J.-X.; Yu, X.-Y.; Xia, W.-J.; Yu, P.-X.; Wang, K.; Zhao, Z.-Y.; Chen, Z.-G. Endothelial Cells in Colorectal Cancer. *World J. Gastrointest. Oncol.* **2019**, *11*, 946–956. [CrossRef] [PubMed]
217. Dudley, A.C. Tumor Endothelial Cells. *Cold Spring Harb. Perspect. Med.* **2012**, *2*, a006536. [CrossRef] [PubMed]
218. Fink, K.; Boratyński, J. The role of metalloproteinases in modification of extracellular matrix in invasive tumor growth, metastasis and angiogenesis. *Postep. Hig. Med. Dosw.* **2012**, *66*, 609–628. [CrossRef] [PubMed]
219. Conway, E.M.; Collen, D.; Carmeliet, P. Molecular Mechanisms of Blood Vessel Growth. *Cardiovasc. Res.* **2001**, *49*, 507–521. [CrossRef]
220. Schellerer, V.S.; Croner, R.S.; Weinländer, K.; Hohenberger, W.; Stürzl, M.; Naschberger, E. Endothelial Cells of Human Colorectal Cancer and Healthy Colon Reveal Phenotypic Differences in Culture. *Lab. Investig.* **2007**, *87*, 1159–1170. [CrossRef] [PubMed]
221. Paduch, R. The Role of Lymphangiogenesis and Angiogenesis in Tumor Metastasis. *Cell Oncol.* **2016**, *39*, 397–410. [CrossRef] [PubMed]
222. Hutajulu, S.H.; Paramita, D.K.; Santoso, J.; Sani, M.I.A.; Amalia, A.; Wulandari, G.; Ghozali, A.; Kurnianda, J. Correlation between Vascular Endothelial Growth Factor-A Expression and Tumor Location and Invasion in Patients with Colorectal Cancer. *J. Gastrointest. Oncol.* **2018**, *9*, 1099–1108. [CrossRef]
223. Tacconi, C.; Correale, C.; Gandelli, A.; Spinelli, A.; Dejana, E.; D'Alessio, S.; Danese, S. Vascular Endothelial Growth Factor C Disrupts the Endothelial Lymphatic Barrier to Promote Colorectal Cancer Invasion. *Gastroenterology* **2015**, *148*, 1438–1451.e8. [CrossRef] [PubMed]
224. Wang, R.; Bhattacharya, R.; Ye, X.; Fan, F.; Boulbes, D.R.; Ellis, L.M. Endothelial Cells Promote Colorectal Cancer Cell Survival by Activating the HER3-AKT Pathway in a Paracrine Fashion. *Mol. Cancer Res.* **2019**, *17*, 20–29. [CrossRef] [PubMed]
225. Liu, Z.; Qi, L.; Li, Y.; Zhao, X.; Sun, B. VEGFR2 Regulates Endothelial Differentiation of Colon Cancer Cells. *BMC Cancer* **2017**, *17*, 593. [CrossRef] [PubMed]
226. Hou, S.; Zhao, Y.; Chen, J.; Lin, Y.; Qi, X. Tumor-Associated Macrophages in Colorectal Cancer Metastasis: Molecular Insights and Translational Perspectives. *J. Transl. Med.* **2024**, *22*, 62. [CrossRef] [PubMed]
227. Yahaya, M.A.F.; Lila, M.A.M.; Ismail, S.; Zainol, M.; Afizan, N.A.R.N.M. Tumour-Associated Macrophages (TAMs) in Colon Cancer and How to Reeducate Them. *J. Immunol. Res.* **2019**, *2019*, 2368249. [CrossRef] [PubMed]
228. Chen, Y.; Yu, Z.; Lv, M.; Cai, Z.; Zou, Y.; Lan, P.; Wu, X.; Gao, F. Cancer-Associated Fibroblasts Impact the Clinical Outcome and Treatment Response in Colorectal Cancer via Immune System Modulation: A Comprehensive Genome-Wide Analysis. *Mol. Med.* **2021**, *27*, 139. [CrossRef] [PubMed]
229. Peddareddigari, V.G.; Wang, D.; DuBois, R.N. The Tumor Microenvironment in Colorectal Carcinogenesis. *Cancer Microenviron.* **2010**, *3*, 149–166. [CrossRef] [PubMed]
230. Kular, J.K.; Basu, S.; Sharma, R.I. The Extracellular Matrix: Structure, Composition, Age-Related Differences, Tools for Analysis and Applications for Tissue Engineering. *J. Tissue Eng.* **2014**, *5*, 2041731414557112. [CrossRef] [PubMed]
231. Popova, N.V.; Jücker, M. The Functional Role of Extracellular Matrix Proteins in Cancer. *Cancers* **2022**, *14*, 238. [CrossRef] [PubMed]
232. Hu, M.; Ling, Z.; Ren, X. Extracellular Matrix Dynamics: Tracking in Biological Systems and Their Implications. *J. Biol. Eng.* **2022**, *16*, 13. [CrossRef] [PubMed]

233. Hynes, R.O. Extracellular Matrix: Not Just Pretty Fibrils. *Science* **2009**, *326*, 1216–1219. [CrossRef] [PubMed]
234. Yuan, Z.; Li, Y.; Zhang, S.; Wang, X.; Dou, H.; Yu, X.; Zhang, Z.; Yang, S.; Xiao, M. Extracellular Matrix Remodeling in Tumor Progression and Immune Escape: From Mechanisms to Treatments. *Mol. Cancer* **2023**, *22*, 48. [CrossRef] [PubMed]
235. Frantz, C.; Stewart, K.M.; Weaver, V.M. The Extracellular Matrix at a Glance. *J. Cell Sci.* **2010**, *123*, 4195–4200. [CrossRef] [PubMed]
236. Brassart-Pasco, S.; Brézillon, S.; Brassart, B.; Ramont, L.; Oudart, J.-B.; Monboisse, J.C. Tumor Microenvironment: Extracellular Matrix Alterations Influence Tumor Progression. *Front. Oncol.* **2020**, *10*, 397. [CrossRef] [PubMed]
237. Reunanen, N.; Kähäri, V. Matrix Metalloproteinases in Cancer Cell Invasion. In *Madame Curie Bioscience Database [Internet]*; Landes Bioscience: Austin, TX, USA, 2013.
238. Vinnakota, K.; Zhang, Y.; Selvanesan, B.C.; Topi, G.; Salim, T.; Sand-Dejmek, J.; Jönsson, G.; Sjölander, A. M2-like Macrophages Induce Colon Cancer Cell Invasion via Matrix Metalloproteinases. *J. Cell. Physiol.* **2017**, *232*, 3468–3480. [CrossRef] [PubMed]
239. Koskensalo, S.; Louhimo, J.; Nordling, S.; Hagström, J.; Haglund, C. MMP-7 as a Prognostic Marker in Colorectal Cancer. *Tumor Biol.* **2011**, *32*, 259–264. [CrossRef] [PubMed]
240. Sun, Q.; Weber, C.R.; Sohail, A.; Bernardo, M.M.; Toth, M.; Zhao, H.; Turner, J.R.; Fridman, R. MMP25 (MT6-MMP) Is Highly Expressed in Human Colon Cancer, Promotes Tumor Growth, and Exhibits Unique Biochemical Properties *. *J. Biol. Chem.* **2007**, *282*, 21998–22010. [CrossRef] [PubMed]
241. Van Buren, G.; Gray, M.J.; Dallas, N.A.; Xia, L.; Lim, S.J.; Fan, F.; Mazar, A.P.; Ellis, L.M. Targeting the Urokinase Plasminogen Activator Receptor With a Monoclonal Antibody Impairs the Growth of Human Colorectal Cancer in the Liver. *Cancer* **2009**, *115*, 3360–3368. [CrossRef] [PubMed]
242. Najafi, M.; Farhood, B.; Mortezaee, K. Extracellular Matrix (ECM) Stiffness and Degradation as Cancer Drivers. *J. Cell. Biochem.* **2019**, *120*, 2782–2790. [CrossRef] [PubMed]
243. Franchi, M.; Karamanos, K.-A.; Cappadone, C.; Calonghi, N.; Greco, N.; Franchi, L.; Onisto, M.; Masola, V. Substrate Type and Concentration Differently Affect Colon Cancer Cells Ultrastructural Morphology, EMT Markers, and Matrix Degrading Enzymes. *Biomolecules* **2022**, *12*, 1786. [CrossRef] [PubMed]
244. Brauchle, E.; Kasper, J.; Daum, R.; Schierbaum, N.; Falch, C.; Kirschniak, A.; Schäffer, T.E.; Schenke-Layland, K. Biomechanical and Biomolecular Characterization of Extracellular Matrix Structures in Human Colon Carcinomas. *Matrix Biol.* **2018**, *68–69*, 180–193. [CrossRef] [PubMed]
245. Park, P.-G.; Jo, S.J.; Kim, M.J.; Kim, H.J.; Lee, J.H.; Park, C.K.; Kim, H.; Lee, K.Y.; Kim, H.; Park, J.H.; et al. Role of LOXL2 in the Epithelial-Mesenchymal Transition and Colorectal Cancer Metastasis. *Oncotarget* **2017**, *8*, 80325–80335. [CrossRef]
246. Nebuloni, M.; Albarello, L.; Andolfo, A.; Magagnotti, C.; Genovese, L.; Locatelli, I.; Tonon, G.; Longhi, E.; Zerbi, P.; Allevi, R.; et al. Insight On Colorectal Carcinoma Infiltration by Studying Perilesional Extracellular Matrix. *Sci. Rep.* **2016**, *6*, 22522. [CrossRef]
247. Li, Z.-L.; Wang, Z.-J.; Wei, G.-H.; Yang, Y.; Wang, X.-W. Changes in Extracellular Matrix in Different Stages of Colorectal Cancer and Their Effects on Proliferation of Cancer Cells. *World J. Gastrointest. Oncol.* **2020**, *12*, 267–275. [CrossRef] [PubMed]
248. Karlsson, S.; Nyström, H. The Extracellular Matrix in Colorectal Cancer and Its Metastatic Settling—Alterations and Biological Implications. *Crit. Rev. Oncol./Hematol.* **2022**, *175*, 103712. [CrossRef] [PubMed]
249. Crowley, C.W.; Cohen, R.L.; Lucas, B.K.; Liu, G.; Shuman, M.A.; Levinson, A.D. Prevention of Metastasis by Inhibition of the Urokinase Receptor. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5021–5025. [CrossRef] [PubMed]
250. Baker, E.A.; Bergin, F.G.; Leaper, D.J. Plasminogen Activator System, Vascular Endothelial Growth Factor, and Colorectal Cancer Progression. *Mol. Pathol.* **2000**, *53*, 307–312. [CrossRef] [PubMed]
251. Liang, D.; Liu, L.; Zhao, Y.; Luo, Z.; He, Y.; Li, Y.; Tang, S.; Tang, J.; Chen, N. Targeting Extracellular Matrix through Phytochemicals: A Promising Approach of Multi-Step Actions on the Treatment and Prevention of Cancer. *Front. Pharmacol.* **2023**, *14*, 1186712. [CrossRef] [PubMed]