Review

Ferroptosis, Metabolic Rewiring, and Endometrial Cancer

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Abstract: Ferroptosis is a newly discovered form of regulated cell death. The main feature of ferroptosis is excessive membrane lipid peroxidation caused by iron-mediated chemical and enzymatic reactions. In normal cells, harmful lipid peroxides are neutralized by glutathione peroxidase 4 (GPX4). When GPX4 is inhibited, ferroptosis occurs. In mammalian cells, ferroptosis serves as a tumor suppression mechanism. Not surprisingly, in recent years, ferroptosis induction has gained attention as a potential anticancer strategy, alone or in combination with other conventional therapies. However, sensitivity to ferroptosis inducers depends on the metabolic state of the cell. Endometrial cancer (EC) is the sixth most common cancer in the world, with more than 66,000 new cases diagnosed every year. Out of all gynecological cancers, carcinogenesis of EC is mostly dependent on metabolic abnormalities. Changes in the uptake and catabolism of iron, lipids, glucose, and glutamine affect the redox capacity of EC cells and, consequently, their sensitivity to ferroptosis-inducing agents. In addition to this, in EC cells, ferroptosis-related genes are usually mutated and overexpressed, which makes ferroptosis a promising target for EC prediction, diagnosis, and therapy. However, for a successful application of ferroptosis, the connection between metabolic rewiring and ferroptosis in EC needs to be deciphered, which is the focus of this review.

Keywords: ferroptosis; metabolism; endometrial cancer; resistance

1. Introduction

Ferroptosis is an iron-dependent mode of cell death that is mechanistically different from apoptosis, necroptosis, pyroptosis, and other regulated cell death types. Discovered in 2012 by Dixon et al., ferroptosis quickly gained attention in the context of cardiovascular, neurodegenerative diseases, and cancer [1]. One of the hallmarks of ferroptosis is membrane lipid peroxidation. Lipid peroxides and peroxyl radicals are constantly produced as byproducts of normal cellular homeostasis in Fenton reactions and by enzymes that use iron as a cofactor, such as lipoxygenases. Typically, toxic oxidized lipid species are neutralized by an enzyme glutathione peroxidase 4 (GPX4). When GPX4 is inactivated, ferroptosis occurs [2]. Many of the currently used ferroptosis inducers deplete cells of cysteine, inhibit GPX4 enzymatic activity, or lower GPX4 protein level, whereas ferroptosis is inhibited by lipophilic antioxidants and iron chelators [3]. However, recently, additional proteins (FSP1, DHODH, and GCH1) responsible for the defense against ferroptosis have been identified [4–7]. Also, although at first plasma membrane was believed to be the main site of lipid peroxidation, recent evidence shows that endoplasmic reticulum (ER) [8], mitochondria [4], lysosomes [9], Golgi complex [10], and peroxisomes [11] are involved as well. It has been shown that certain conditions predispose cells to ferroptosis. For example, mesenchymal cells are more sensitive to ferroptosis induction than epithelial cells due to an increased amount of easily oxidized polyunsaturated fatty acids in cellular membranes [12]. In detached cells, a loss of α6β4 integrin signaling promotes ferroptosis by upregulation of ACSL4 and a decreased expression of GPX4 [13]. Thus, ferroptosis might be a potential strategy to eliminate metastatic cancer cells. In addition, immunotherapy-resistant dedifferentiated melanoma cell subtypes exhibit vulnerability to ferroptosis due to a decreased level of reduced glutathione [14]. A reduced level of glutathione and NADPH was also observed

in drug-resistant tumor cell populations, thus making them a target of ferroptosis-inducing agents [15]. Finally, cancer stem cells have an increased labile iron pool in their cytosol and are very susceptible to ferroptosis [16]. Thus, ferroptosis can be used to eliminate tumor cell subpopulations responsible for cancer recurrence. To increase the anticancer effect, ferroptosis can be coupled with chemotherapy [17], radiation therapy [18], photodynamic therapy [19], and, being an immunogenic cell death, with immunotherapy [20].

Endometrial carcinoma (EC) is the sixth most common cancer among women worldwide [21]. Carcinogenesis of EC is highly dependent on metabolic factors. Three metabolic abnormalities, namely, obesity, hyperglycemia, and hormone exposure, increase the risk of EC [22]. Metabolic rewiring is a common trait of cancer cells. Not only does it make them addicted to certain nutrients, such as glucose and glutamine, but it also influences cellular antioxidant defense [23–26]. Consequently, cell sensitivity to ferroptosis is altered. Thus, the outcome of therapeutic strategies involving ferroptosis inducers critically depends on the metabolic state of the cell. In comparison to normal tissue, EC genes of ferroptosis-related proteins and lncRNAs are mutated, epigenetically modified, and, as a result, differentially expressed. Commonly, a higher expression of ferroptosis genes correlates positively with immune cell infiltration into tumor mass, highlighting the importance of ferroptosis immunogenicity. Not surprisingly, ferroptosis gene signatures are used to create prognostic models for EC patient survival [27].

This review summarizes the current knowledge of ferroptosis, metabolic rewiring in cancer cells, and its relationship to ferroptosis sensitivity, with a particular focus on EC.

2. Discovery of Ferroptosis

Cell death is the inevitable fate of all living organisms. For a long time, the classification of cell death was based solely on morphologic characteristics. Three cell death types were defined: (a) apoptosis, accompanied by rounding up and shrinkage of the cell, retraction of pseudopodia, chromatin condensation, and fragmentation of the nucleus; (b) autophagy, characterized by the formation of autophagosomes; and (c) necrosis, that results in cell swelling and the rupture of the plasma membrane (Figure 1) [28]. Although morphologic classification is still widely used, cell death can also be broadly divided into accidental and regulated. According to the Nomenclature Committee on Cell Death, accidental cell death is induced by various external stresses: extreme temperatures, pH variations, and osmotic and mechanical shock. In contrast, regulated cell death is governed by molecular mechanisms and, therefore, can be intervened by pharmacologic and genetic approaches. When regulated cell death accompanies natural physiological processes (embryogenesis, tissue homeostasis, immune reaction), it is called programmed cell death. However, environmental stress can also induce regulated cell death [29]. According to biochemical processes and morphological features of programmed cell death, it is further divided into twelve types: extrinsic and intrinsic apoptosis, immunogenic cell death, autophagy-dependent cell death, lysosome-dependent cell death, netotic cell death, entotic cell death, parthanatos, necroptosis, mitochondrial permeability transition-driven necrosis, pyroptosis, and ferroptosis [30]. New cell death types, such as methuosis [31], paraptosis [32], autosis [33], alkaliptosis [34], oxeiptosis [35], cuproptosis [36], and erebosis [37], are also emerging.

In 2003, while screening the library of new antitumor agents, Dolma et al. discovered a compound that was selectively lethal to cancer cells expressing oncogenic RAS and Small T oncoprotein. The compound was named erastin (eradicator of RAS and ST) [38]. Interestingly, cell death induced by erastin did not exhibit any biochemical and morphological features of apoptosis and could not be inhibited by apoptosis inhibitors. Eventually, it was shown that this atypical cell death could be prevented by iron chelators. Other compounds, RSL3 (RAS Selective Lethal 3) and RSL5 (RAS Selective Lethal 5), with similar properties to erastin, were discovered in 2008 [39]. RSL3 induced ROS accumulation inside the cell [40]. In the same year, Seiler et al. discovered that inactivation of GPX4 drives lipid peroxidation that can be suppressed by antioxidant α-tocopherol

or by inhibition of lipoxygenases [41]. In addition, xCT was identified as a mediator of oxidative stress resistance upon GSH depletion [42]. In 2012, Dixon et al. named the new cell death type "ferroptosis", based on the Latin ferrum meaning "iron" and Greek ptôsis meaning "fall" [43]. More ferroptosis-mediating compounds, including ferroptosis inducers sulfasalazine, sorafenib, FIN56, FINO2, and inhibitors ferrostatin-1 and liprostatin-1, were discovered in several years [44]. [43]. New antioxidant systems, FSP1, DHODH, and GCH1, which are responsible for ferroptosis resistance, have been actively studied recently [5–7]. However, it is worth mentioning that features of ferroptotic cell death had been noticed earlier by other researchers. For example, when neurons are deprived of cysteine, reduced GSH synthesis leads to oxidative stress and cell death, called oxytosis [45]. Oxytosis and ferroptosis are similar from a mechanistic perspective, and sometimes the terms are used interchangeably [46]. However, in the context of cancer, the term ferroptosis is more relevant. Also, there are some differences between oxytosis and ferroptosis; for example, oxytosis is strongly dependent on the uptake of calcium [47], while ferroptosis is caused by cellular iron accumulation [43].
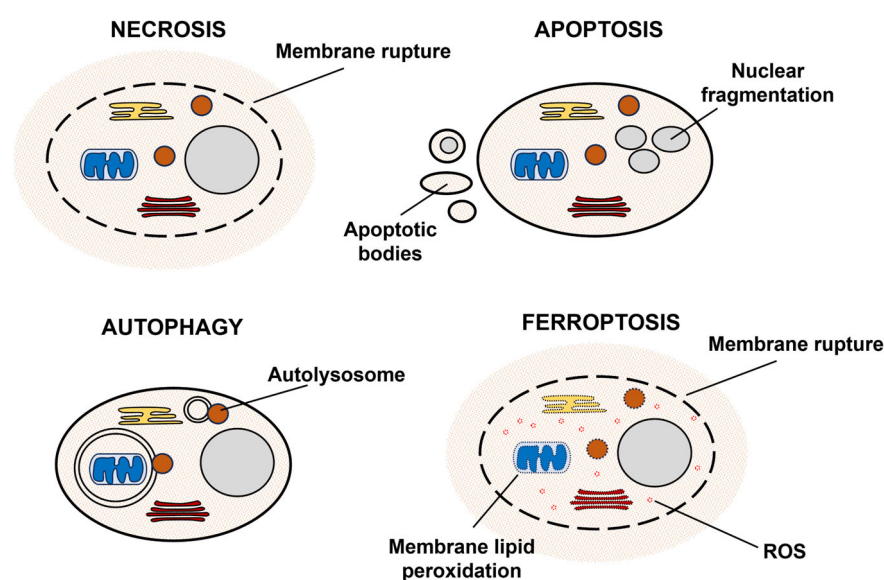

Figure 1. A scheme illustrating different modes of cell death.

3. Inducers and Inhibitors of Ferroptosis

Ferroptosis is a regulated cell death that is caused by excessive membrane lipid peroxidation [2]. Normally, the oxidative damage of the cell membrane is prevented by glutathione peroxidase 4 (GPX4). Ferroptosis occurs when GPX4 becomes dysfunctional (Figure 2). It can be caused by several factors: inactivation of GPX4 due to GSH depletion, reduced GPX4 activity, and reduced GPX4 protein level. Based on this, four classes of ferroptosis inducers are distinguished (Figure 3A). Class I ferroptosis inducers inhibit cystine/glutamate antiporter x_C^-. x_C^- is a transmembrane protein that exchanges one molecule of glutamate to one molecule of cystine, an oxidized form of cysteine. The incorporation of cysteine into GSH is a rate-limiting step of GSH synthesis. When x_C^- is inhibited, the cell is deprived of GSH, and GPX4 activity is reduced. Consequently, oxidative damage to cell membranes is no longer prevented [48]. The main class I ferroptosis inducers are erastin and its analogs imidazole ketone erastin and piperazine erastin. In comparison to erastin, imidazole ketone erastin and piperazine erastin have better water solubility and have more potential to be used in vivo [49]. In addition, class I ferroptosis inducers include repurposed drugs sulfasalazine [50] and sorafenib [51]. Class II ferroptosis inducers inhibit the enzymatic activity of GPX4. One of the most widely used class II ferroptosis inducers is RSL3, which covalently binds to selenocysteine in the active center of GPX4 [52]. Class III ferroptosis inducers, FIN56 (Ferroptosis Inducer 56) and CIN56 (Caspase-Independent

Lethal 56), lower the protein level of GPX4 (indirectly activate its degradation) and inhibit the synthesis of endogenic lipophilic antioxidant coenzyme Q [53,54]. Class IV ferroptosis inducers, such as $FINO_2$ oxidize iron, indirectly inhibit GPX4 enzymatic activity and induce lipid peroxidation [55]. Out of the mentioned compounds, only imidazole ketone erastin, piperazine erastin, FIN56, sulfasalazine, and sorafenib are suitable for clinical use. However, unlike erastin, its analogs, RSL3 and FIN56, sulfasalazine, and sorafenib, are not specific ferroptosis inducers [56,57].
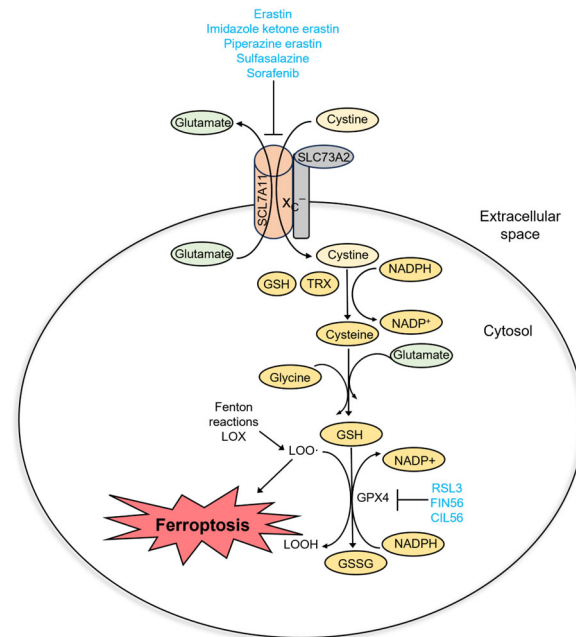

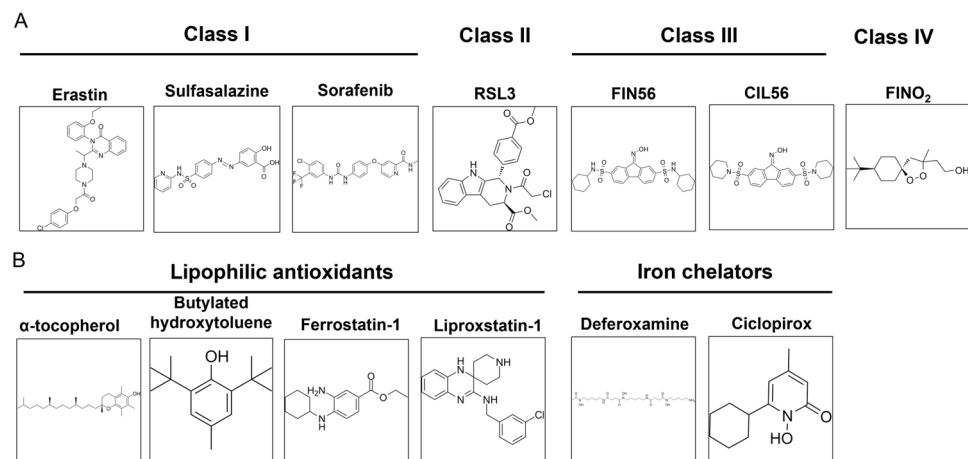**Figure 2.** Molecular pathway of ferroptosis.

Figure 3. Commonly used ferroptosis inducers (**A**) and inhibitors (**B**).

As ferroptosis is an iron-dependent form of cell death, it can be inhibited by iron chelators (deferoxamine, ciclopirox) and lipophilic antioxidants (α-tocopherol, butylated hydroxytoluene, ferrostatin-1, and liproxstatin-1) (Figure 3B). Iron chelators prevent lipid peroxidation by inhibiting lipoxygenases and Fenton reactions, while lipophilic antioxidants neutralize lipid radicals [48]. The third type of ferroptosis inhibitors are deuterated polyunsaturated fatty acids (D-PUFA, for example, D_4-arachidonic acid) that stop the initiation and propagation steps of membrane lipid peroxidation. Ferroptosis is also suppressed by inhibitors of lipoxygenases (LOX). Nonspecific ferroptosis inhibitors include cycloheximide (inhibits translation) [40], β-mercaptoethanol (reduces extracellular cystine

to cysteine) [43], dopamine (inhibits GPX4 degradation) [58], GPX4 cofactor selenium [59], and vildagliptin (impedes DPP4-dependent lipid peroxidation) [60].

4. Molecular Mechanism of Ferroptosis

Mammalian cell membranes are composed of phospholipids, acylated with at least one polyunsaturated fatty acid (PUFA). In contrast to saturated and monounsaturated fatty acids, PUFA bisalylic hydrogen atoms are easily oxidized by free radicals formed in Fenton reactions and by enzymes that use iron as a cofactor: cyclooxygenases, cytochrome P450, and lipoxygenases [61]. Out of the three, lipoxygenases are mostly studied in the context of ferroptosis, and their inhibition suppresses ferroptosis in cancer cells. However, the impact of Fenton and enzymatic reactions is hardly discriminated in ferroptosis, as inhibitors of lipoxygenases also scavenge peroxyl radicals that are formed in Fenton reactions [62].

Although the plasma membrane was believed to be the primary target of lipid peroxidation, recent evidence shows that the rupture of the plasma membrane might be the final step of ferroptosis rather than the first. Oxidation of other organelles, such as endoplasmic reticulum (ER), mitochondria, lysosomes, Golgi complex, and peroxisomes, might be more important in the initiation and propagation of ferroptosis (Figure 4). According to some authors, ER is believed to be the main site of lipid peroxidation. This is supported by the fact that ferroptosis inhibitors primarily accumulate in ER. Changes in ER morphology, such as increased viscosity, are observed during ferroptosis [2]. However, mitochondria are a primary source of ROS in the cell. During ferroptotic cell death, a decrease in mitochondria cristae is present, as well as the rupture of the mitochondrial outer membrane [63]. However, it seems that the role of mitochondria in ferroptosis is cell-type-dependent. For example, cancer cells lacking functional mitochondria are also capable of RSL-3-induced cell death, which indicates that mitochondria are not crucial for ferroptosis [64]. However, in neuronal cells and mouse embryonic fibroblasts, mitochondrial ROS scavenging and preservation of mitochondrial function abolish RSL-3-induced cell death even when plasma membrane lipid peroxidation is evident [65]. Mitochondria also accumulate iron in the form of mitochondrial ferritin (FtMt). Overexpression of FtMt reduces the labile iron pool and prevents ferroptosis in neuroblastoma cells [66]. Lysosomes accumulate ROS and iron as well as mitochondria. Iron overload leads to lysosome membrane oxidation and induces ferroptosis and lysosome-dependent cell death [9]. Also, ferritin and GPX4 degradation in the lysosomes increases the level of ROS in the cell [67]. [64]. Golgi complex and peroxisomes might stimulate iron uptake and ferroptosis by accumulating the transferrin receptor that is transported to the cell membrane and peroxidation of ether lipids, respectively [10,11].
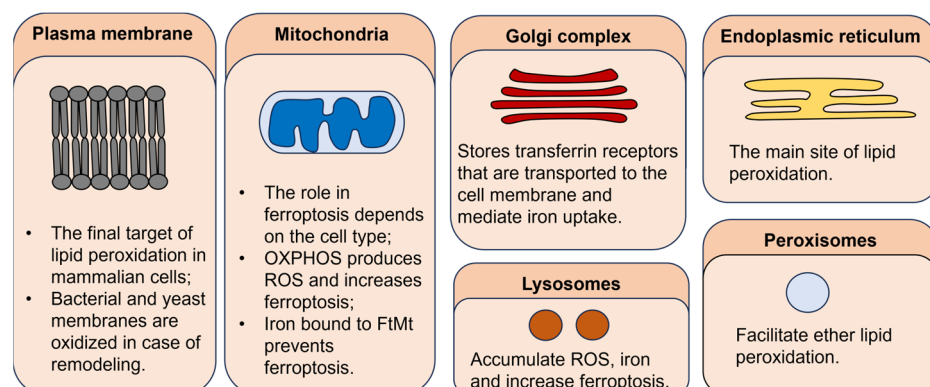

Figure 4. The role of different cellular organelles in ferroptosis.

In addition, cell death can be triggered not only by the membrane oxidation itself but also by the toxic side products of lipid peroxidation. Malondialdehyde and 4-hydroxinonenal are toxic byproducts of lipid peroxidation that damage cell proteins and DNA [68,69].

Four cellular antioxidant systems take part in the defense against ferroptosis: GPX4, FSP1, DHODH, and GCH1. The main enzyme responsible for the neutralization of harmful lipid peroxides is GPX4 [70]. GPX4 uses two cofactors: selenocysteine and GSH. In the first step of the GPX4 reaction, selenocysteine attacks lipid peroxide; selenic acid and a neutral lipid hydroxide are formed. The active site of GPX4 is regenerated by two molecules of GSH that reduce selenic acid to selenocysteine [61]. Some cancers, like diffuse large B cell lymphomas and renal cell carcinomas, are very sensitive to GPX4-mediated ferroptosis, whereas others do not require functional GPX4 to survive, mostly due to upregulated antioxidant defense and decreased amount of fatty acids in cellular membranes [71]. Two other proteins, FSP1 (Ferroptosis Suppressor Protein 1), previously known as AIFM2 (Apoptosis-Inducing Factor Mitochondrial 2), and DHODH, prompt coenzyme Q regeneration and inhibit ferroptosis as well [4–6]. The third ferroptosis suppressor is GTP cyclohydrolase 1 (GCH1). GCH1 synthesizes tetrahydrobiopterin (BH_4), a cofactor used by NO synthases (NOS) [72]. An increased level of BH_4 leads to NOS activation and attenuation of ROS. Not surprisingly, GCH1 expression negatively correlates with cancer cell sensitivity to ferroptosis [7].

5. Ferroptosis and Immunity

It has been shown that the cells undergoing ferroptosis secrete DAMPs (damage-associated molecular patterns) and other molecules that attract immune cells and elicit immune responses. Thus, ferroptosis is an immunogenic cell death. This additional tumor suppression mechanism could be successfully exploited in immunotherapy [20]. For example, nanoparticles charged with RSL-3 not only initiated T lymphocyte activation and antitumoral response but also increased resistance to lipid damage repair in tumor cells, leading to accumulation of ROS [73] and sensitivity to radiotherapy [74]. Upon ferroptosis induction, murine fibrosarcoma and glioma cells secrete DAMPs ATP and HMGB1 in vitro and in vivo and promote the maturation of dendritic cells. Some of these DAMPs, such as HMGB1, can further promote ferroptosis. However, studies showed that only early but not late ferroptotic cells display immunogenic properties [75]. On the contrary, another research indicated that early ferroptotic cells decrease antigen cross-presentation in dendritic cells and suppress the proliferation of cytotoxic T lymphocytes [76]. This means that the immunogenicity of ferroptotic cells is time and condition-dependent. In addition, the cells undergoing ferroptosis accumulate oxidized phosphatidylethanolamine and its derivatives, which are the main "eat me" signals for macrophages [77,78]. Dying cells also release prostaglandins, eicosanoids (5-hydroxyeicosatetraenoic acid (5-HETE), 12-HETE, and 15-HETE), and oxidized amino acids that attract immune cells [79]. Lipid oxidation itself can also negatively impact the maturation of dendritic cells [80] and the antitumor properties of $CD8^+$ T cells [81]. For example, in pancreatic cancer, ferroptotic cells release 8-hydroxy-2'-deoxyguanosine and activate interferon signaling in tumor-associated macrophages to promote their activation and cancer initiation [82]. An interesting mechanism was proposed by Dai et al., in which pancreatic cancer cells undergoing autophagy-dependent ferroptosis secreted exosomes containing oncogenic KRAS protein that induced macrophage polarization and elicited tumor-promoting effect [83]. Overall, these results indicate that ferroptosis can either induce or suppress immune response. This must be considered when ferroptosis induction is combined with immunotherapeutic agents as antitumor therapy [84].

6. The Nature of Ferroptosis

To understand the nature of ferroptosis, we must investigate similar cell death types in evolutionarily distant species. Although all cell membranes are composed of phospholipids (PL), not all PLs contain polyunsaturated fatty acids, which are the main target of ROS. For example, in the membranes of archaea and bacteria, saturated and monounsaturated fatty acids are abundant. The unique composition of cellular membranes allows microorganisms to survive harsh environmental conditions—extreme pH, temperature, and pressure [85]. Thus, bacteria and archaea are usually resistant to ferroptosis. However, some bacteria

like *Shewanella* and *Vibrio* utilize polyunsaturated fatty acids to increase membrane fluidity, biofilm formation, and resistance to antibiotics [86,87]. Yeast, as well as bacteria, typically do not synthesize polyunsaturated fatty acids but can accumulate them from the environment and integrate them into their membranes. It was shown that *Saccharomyces cerevisiae* growing in a medium containing polyunsaturated fatty acids are susceptible to oxidative stress [88]. Thus, most likely, ferroptosis is not innate to microorganisms. However, susceptibility to ferroptosis can be gained in certain stressful conditions that require membrane remodeling.

ROS signaling is highly expressed in plants. When *Arabidopsis thaliana* roots are exposed to 55 °C temperature, cell death occurs. It can be prevented by cyclopyrox, ferrostatin-1, or by immersing roots into the solution supplemented with deuterated fatty acids, whose bisalylic carbon cannot be readily oxidized [89]. Although ROS mediate signaling in plants, oxidative stress can be detrimental to plant cells. On the other hand, ferroptosis can be utilized to eliminate the cells that have ROS overload.

In mammalian cells, ferroptosis functions as a mechanism of tumor suppression. It was demonstrated that cancer cells possessing a defective p53 (p533KR) are susceptible to ferroptosis, although cell cycle progression, senescence, and apoptosis are defective. In these cells, the level of SLC7A11, a component of cystine/glutamate antiporter x_C^-, is decreased [90]. Additional p53 point mutation K98 eliminates the suppressor function [91]. Tumor suppressor BAP1 (BRCA1-associated protein 1) promotes ferroptosis and inhibits tumor development via a similar mechanism [92]. The third tumor suppressor linked to ferroptosis is fumarase. Fumarase converts fumarate to malate. Inhibition of fumarase leads to fumarate build-up, slowing down the tricarboxylic acid cycle and oxidative phosphorylation. Inactive mitochondria produce less ROS, and ferroptosis is inhibited. When fumarase is active, oxidative phosphorylation progresses and ferroptosis is initiated [93]. Overall, ferroptosis is a rather simple process that does not require sophisticated signaling, transcription, or translation steps. Thus, ferroptosis could be a form of natural selection regulated by the level of only one amino acid, cysteine, in the cellular microenvironment [94]. Furthermore, unlike apoptosis, ferroptosis is an immunogenic cell death and could be used to induce an immune response to eliminate tumors or pathogen infections [95].

7. Detection of Ferroptosis: Markers and Methods

To date, the best-studied genetic markers of ferroptosis are *PTGS2* (prostaglandin-endoperoxide synthase 2), *CHAC1* (glutathione specific gamma-glutamylcyclotransferase 1), *SCL7A11* (a component of system x_C^-), *ACSL4* (fatty acid-CoA ligase 4), and *RGS4* (regulator of G protein signaling 4). Except for *RGS4*, the expression of all these genes is upregulated in cells undergoing ferroptosis [2]. However, the database of ferroptosis regulators and markers FerrDb V2 (http://www.zhounan.org/ferrdb/, accessed on 6 November 2023) currently annotates nearly fifty positive and negative markers of ferroptosis, i.e., proteins and non-coding RNAs, whose expression changes after ferroptosis induction (Table 1). Most of these proteins are involved in lipid and iron homeostasis, signal transduction, and the regulation of transcription.

Table 1. Biomarkers of ferroptosis.

Gene	Gene Product	Expression Change	PMID
ARRDC3	Arrestin domain-containing protein 3	↑	24844246
ASNS	Asparagine synthetase	↑	24844246
ATF3	Cyclic AMP-dependent transcription factor ATF-3	↑	24844246
ATF4	Cyclic AMP-dependent transcription factor ATF-4	↑	24844246
ATP6V1G2	V-type proton ATPase subunit E	↑	24844246
BLOC1S5-TXNDC5	Biogenesis of lysosome-related organelles complex 1 subunit 5	↓	24844246

Table 1. *Cont.*

Gene	Gene Product	Expression Change	PMID
CAPG	Macrophage-capping protein	↓	31108460
CBS	Cystathionine beta-synthase	↑	24844246
CEBPG	CCAAT/enhancer-binding protein gamma	↑	24844246
DDIT3	DNA damage-inducible transcript 3 protein	↑	24844246
DDIT4	DNA damage-inducible transcript 4 protein	↑	24844246
DRD5	D(1B) dopamine receptor	↑	27793671
DUSP1	Dual specificity protein phosphatase 1	↑	24439385
FTH1	Ferritin heavy chain	↓	27514700
GABPB1	GA-binding protein subunit beta-1	↓	31700067
GDF15	Growth/differentiation factor 15	↑	24844246
GPT2	G patch domain-containing protein 2	↑	24844246
GPX4	Phospholipid hydroperoxide glutathione peroxidase	↓	27773819
HBA1	Hemoglobin subunit alpha	↑	31108460
HERPUD1	Homocysteine inducible ER protein with ubiquitin-like domain 1	↑	24844246
HMOX1	Heme oxygenase 1	↑	26097885
JDP2	Jun dimerization protein 2	↑	24844246
KLHL24	Kelch-like protein 24	↑	24844246
LOC284561	Long non-coding RNA	↑	24844246
LOC390705	Long non-coding RNA	↓	24844246
LURAP1L	Leucine-rich adaptor protein 1-like	↑	24844246
MT3	Metallothionein-3	↑	24439385
NCF2	Neutrophil cytosol factor 2	↑	24439385
NNMT	Nicotinamide N-methyltransferase	↑	31108460
NOS2	Nitric oxide synthase, inducible	↑	24439385
OXSR1	Serine/threonine-protein kinase OSR1	↑	24439385
PCK2	Phosphoenolpyruvate carboxykinase (GTP)	↑	24844246
PLIN4	Perilipin-4	↑	31108460
PSAT1	Phosphoserine aminotransferase	↑	24844246
RGS4	Regulator of G-protein signaling 4	↓	24844246
RRM2	rRNA methyltransferase 2	↓	31108460
SELENOS	Selenoprotein S	↑	24439385
SESN2	Sestrin-2	↑	24844246
SLC1A4	Neutral amino acid transporter A	↑	24844246
SLC3A2	Amino acid transporter heavy chain SLC3A2	↑	24844246
SLC7A5	Large neutral amino acids transporter small subunit 1	↑	24844246
SNORA16A	Small nucleolar RNA	↓	24844246
SRXN1	Sulfiredoxin-1	↑	24439385
STMN1	Stathmin	↓	31108460
TRIB3	Tribbles homolog 3	↑	24844246
TSC22D3	TSC22 domain family protein 3	↑	24844246
TUBE1	Tubulin epsilon chain	↑	24844246
TXNIP	Thioredoxin-interacting protein	↑	24844246
TXNRD1	Thioredoxin reductase 1	↑	24439385
UBC	Polyubiquitin-C	↑	24439385
VEGFA	Vascular endothelial growth factor A	↑	24844246
VLDLR	Very low-density lipoprotein receptor	↑	24844246
XBP1	X-box-binding protein 1	↑	24844246
ZFP69B	Zinc finger protein 69 homolog B	↑	24844246
ZNF419	Zinc finger protein 419	↑	24844246

In addition to the detection of gene expression changes, ferroptosis can be monitored by other methods. Cell death after the treatment with ferroptosis inducers can be determined by the loss of integrity of the plasma membrane. Propidium iodide is usually used to determine the proportion of dead cells in the population, as it only stains the cells with ruptured membranes. For the quantification, propidium iodide staining can be coupled with flow cytometry. Also, in parallel, cells can be treated with specific ferroptosis inhibitors

to prove that the loss of membrane integrity was caused by ferroptosis and no other types of cell death. Another hallmark of ferroptosis is membrane lipid peroxidation, which can be detected with fluorescent dies that react with lipid peroxides or peroxyl radicals, such as C11-BODIPY, Click-It LAA, and LiperFluo [96]. For example, when fluorescent lipid peroxidation reporter C11-BODIPY 581/591 is oxidized, its fluorescence changes from red to green. A fluorescent microscope or flow cytometer then detects a decrease in red fluorescence intensity (the amount of reduced membrane lipids is decreased) and an increase in green fluorescence intensity (the amount of oxidized membrane lipids is increased) [97]. Also, the oxidation of lipid membranes can be detected indirectly by measuring the formation of the reaction side products, such as malondialdehyde and 4-hydroxynonenal, by LC-MS/MS and with antibodies, for example, anti-HNE FerAb antibody, the HNEJ-1 antibody or the anti-malondialdehyde (MDA) adduct 1F83 antibody [2]. Ferroptosis can be monitored by spectrophotometrically assessing the levels of GSH/GSSG and Fe^{2+}/Fe^{3+}. New fluorescent probes are being developed for the purpose of imaging ferroptosis in live cells [98,99].

8. Starvation-Induced Metabolic Rewiring in Cancer Cells

During carcinogenesis, tumor cells are constantly exposed to starvation. At the beginning of carcinogenesis, the need for nutrients and energy is increased due to rapid cell proliferation. Only the cells that adapt to nutrient deprivation survive. In a growing tumor, nutrient gradients are formed that limit cell capacity to utilize them. During metastasis cancer cells are constantly facing nutrient deprivation in different microenvironment niches. In all these cases, the limitation of nutrients rewires cell metabolism and induces cancer cell addiction to certain types of nutrients [100]. For example, tumor cells become addicted to glutamine, arginine, or serine [101–103]. A gain of certain addiction depends on the nutrients in the bloodstream, tissue type, tumor heterogeneity, interactions among cancer and stromal cells, and functional needs of certain types of cancer cells [104]. It is not clear whether metabolic changes required for carcinogenesis are innate or adaptive. On the one hand, primary tumors can be composed of phenotypically identical clones that change with regard to nutrient and oxygen availability. Clones that adapt more rapidly proliferate and metastasize. In other models, all tumor cells exhibit different metabolic phenotypes. Although this metabolic heterogeneity can be useless at the beginning of carcinogenesis, it can be utilized by cancer cells during metastasis formation [105]. Overall, there are two metabolic rewiring types in cancer cells: flexibility, or the ability to use different nutrients for energy production, and plasticity, or the ability to use the same nutrients in different metabolic pathways. Metabolic flexibility is important in the early stages of tumor development, whereas plasticity dominates in metastases [106,107].

9. Metabolic Rewiring and Ferroptosis

Ferroptosis-related metabolic rewiring in cancer cells stems from an elevated cystine and NADPH metabolism. Cystine is imported into the cell via cystine/glutamate antiporter x_C^-. A transport protein of x_C^-, SLC7A11, is overexpressed in many cancers [108]. SLC7A11 exchanges one molecule of glutamate to one molecule of cystine. It is estimated that cells lose thirty to fifty percent of cellular glutamate in exchange for cystine [109]. Inside the cell, cystine is reduced to cysteine by thioredoxin or GSH and incorporated into proteins, new glutathione molecules, or used for the synthesis of taurine and H_2S. Both thioredoxin and GSH utilize NADPH for cystine reduction. An increased glutamate uptake and NADPH catabolism make cancer cells addicted to other nutrients—glutamine and glucose. Glutamine is mainly transported to the cell via ASCT2. Glutaminase catalyzes the conversion of glutamine to glutamate, which is used for the synthesis of GSH or metabolized to α-ketoglutarate that enters the tricarboxylic acid cycle. In cancer cells overexpressing SLC7A11, glutamine import and the activity of glutaminase must be elevated to compensate for glutamate export and glutamine addiction, which is acquired [23,24]. NADPH is synthesized in a pentose phosphate pathway that utilizes glucose. When cells

experience glucose deprivation, NADPH synthesis is halted, and toxic cystine and ROS accumulate inside the cell. This way, SLC7A11 overexpression makes cancer cells addicted to glutamine and glucose [25]. Not surprisingly, cancers with glutamine and glucose addiction are sensitive to class I ferroptosis inducers that inhibit SLC7A11 [110,111]. Vice versa, cells overexpressing SLC7A11 are vulnerable to agents that target glutamine and glucose metabolism, such as inhibitors of glutaminase and glucose transporters [112].

10. Metabolic Rewiring in Endometrial Cancer

Endometrial carcinoma (EC) is a cancer type that is caused by a malignant transformation of the epithelial cells in the lining of the uterus. It is the sixth most common cancer among women worldwide [21]. Common risk factors of EC are aging, obesity, prolonged estrogen exposure, family history, and some inheritable diseases, such as Lynch syndrome [113]. In addition, out of all gynecological cancers, EC is mostly related to metabolic abnormalities. The term "triple syndrome of endometrial cancer" refers to three metabolic disorders that increase the risk of EC: obesity, hyperglycemia, and hypertension [22]. Metabolic changes related to obesity and hyperglycemia connect EC to ferroptosis sensitivity.

In post-menopausal women, adipose tissue mediates the conversion of androgens to estrogens [114]. Estrogen binding to its cytoplasmic receptors initiates signaling cascades that stimulate endometrial cancer cell proliferation, such as ETV4 [115], PI3K/Akt, and Ras–Raf–MEK–ERK (Figure 5) [116]. Estrogen is a double-edged sword in oxidative stress: On one hand, it enhances mitochondrial ROS production and activates redox-active transcription factors. On the other hand, estrogen activates antioxidant Nrf2-Keap1 signaling [117]. Thus, estrogen-sensitive cancers like EC have an upregulated antioxidant defense response and can be targeted by antioxidant inhibitors in combination with ROS inducers. A high-fat diet also causes dyslipidemia—changes in lipid metabolism [118]. As lipogenesis utilizes NADPH, a decreased cellular NADPH/NADP+ ratio causes mitochondrial ROS accumulation and oxidative stress [119]. In addition, it was shown that adipose tissue in obese mice accumulates iron [120]. Thus, metabolic changes during obesity may sensitize EC to ferroptosis inducers.
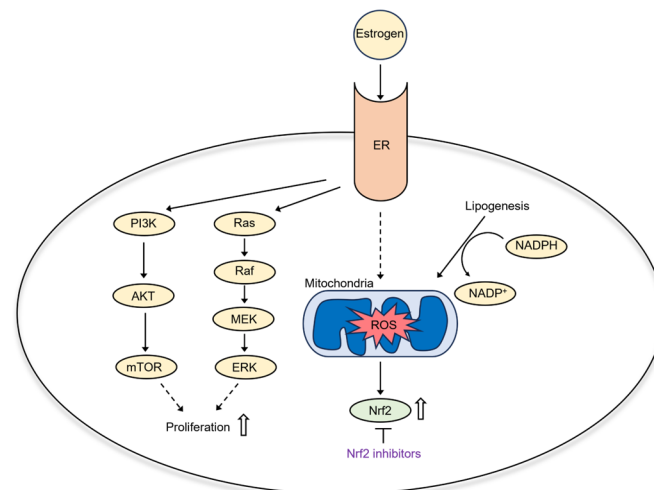

Figure 5. Estrogen signaling in EC.

EC exhibits glucose and glutamine dependency, as well as SLC7A11 overexpression [121–123]. This relates to EC cell metabolic rewiring and sensitivity to ferroptosis (Figure 6). First of all, EC cells rely on a glycolytic–lipogenic metabolism rather than oxidative phosphorylation for energy production [124]. A high rate of glycolysis inhibits the tricarboxylic acid cycle and decreases the levels of NADH and, consequently, ROS. Inhibiting glycolysis promotes the tricarboxylic acid cycle and oxidative phosphorylation and could sensitize cancer cells to ferroptosis induction [125]. Not surprisingly, therapies

targeting glycolysis in EC cells have been investigated. Most of these approaches inhibit glycolytic enzymes [126–128]. Glucose concentration within the tumor can be lowered by glucose oxidase-based therapies. Glucose oxidase catalyzes the conversion of glucose to gluconic acid and hydrogen peroxide. Thus, this reaction not only utilizes glucose but also increases ROS [129]. Glucose oxidase can be immobilized on nanoparticles and then specifically targeted to tumor cells, alone or in combination with ferroptosis-inducing compounds [130–132]. As glutamine addiction is coupled with sensitivity to ferroptosis, therapies targeted to glutamine metabolism could also be exploited in EC. Indeed, glutamine transporter ASCT2 is upregulated in EC. Inhibition of glutamine uptake resulted in a decreased EC cell proliferation [122]. Also, a recent study showed that inhibition of glutaminase, an enzyme that converts glutamate to glutamine, suppresses EC cell growth in vitro and in vivo [133].
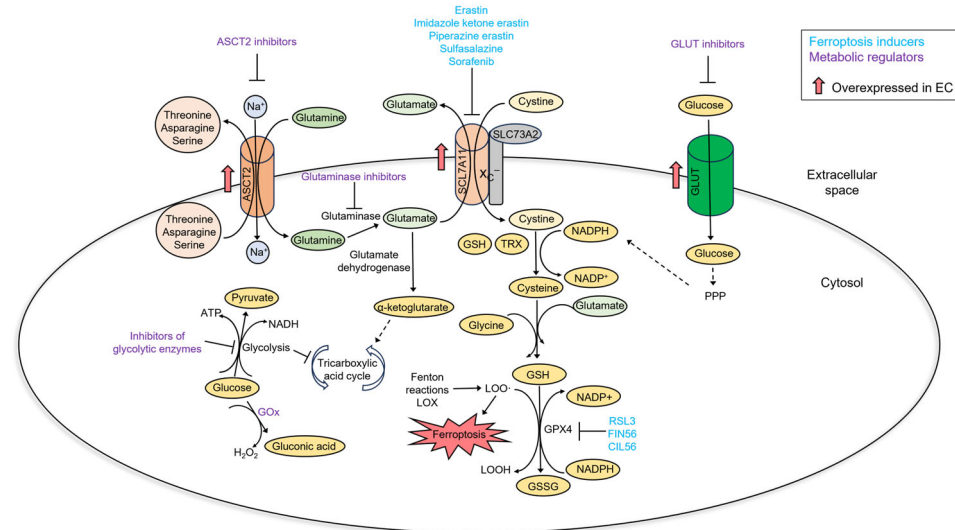

Figure 6. A summary of metabolic changes in EC and their relationship with ferroptosis.

Not surprisingly, other gynecological tumors share similarities with EC. Induction of ferroptosis has been proposed as a possible treatment for ovarian and cervical cancer. For example, ovarian cancer cells tend to accumulate iron due to an increased expression of transferrin receptor I and a decreased expression of ferroportin. Lowering the intracellular iron pool inhibits ovarian cancer cell proliferation in vitro and in vivo and also reduces ovarian cell dissemination [134,135]. Mutations of *TP53* are predominant in ovarian carcinoma [136], and compounds that upregulate p53 increase ovarian cell sensitivity to ferroptosis [137,138]. In addition, erastin was shown to reverse docetaxel resistance in ovarian cancer by reducing the activity of multidrug transporter ABCB1. However, ovarian cancer cells continuously exposed to erastin increase the expression of cysteine biosynthesis and develop resistance [139]. In cervical cancer, ferroptosis can be induced with oleanolic acid, which increases the expression of ACSL4, an enzyme that mediates the synthesis of PUFA-PL [140]. As well as in ovarian cancer, ferroptosis inducers can be exploited to inhibit cervical cancer cell proliferation [141,142]. From a metabolic perspective, as well as EC, ovarian cancer exhibits an increased glucose uptake and a high rate of glycolysis [143,144]. However, not all ovarian cancers are glucose addicted, and the ones dependent on glucose are associated with a better prognosis [145]. Glycolytic enzymes and regulators HK2, PFKFB3, PKM2, and LDH are overexpressed in ovarian cancer and contribute to ovarian carcinogenesis and resistance to chemotherapeutics [146–149]. On the other hand, glucose-independent ovarian tumors rely on OXPHOS [150]. Glutamine addiction mediated by an increased expression of glutamine transporter ASCT2 and glutaminase correlates with poor patient survival and resistance to platinum drugs [151]. In cervical cancer, expression of glucose transporter GLUT1 is upregulated in late stages and positively correlates with HPV infection, lower immune cell scores, and metastasis [152]. The main regulators of

glucose addiction in cervical cancer are glycolytic enzymes PFKFB3 and FBP [153]. What is more, HPV remodels the metabolism of cervical cancer cells via different mechanisms involving glucose uptake, catabolism, glutaminolysis, and the Warburg effect [154].

11. Ferroptosis-Based Prognostic Models of Endometrial Cancer

Wang et al. identified sixty ferroptosis-related genes whose expression was altered in EC versus normal tissues. The authors found out that the upregulated expression of *GPX4*, *SAT1*, and *TP53* correlates with a better prognosis, whereas the upregulated expression of *CBS*, *CHAC1*, and *CISD1* was a prognostic risk factor. Missense mutations were present in the *TP53* gene; *GPX4*, *PGD*, and *CHAC1* bared deletions; in *TFRC*, *KEAP1*, *PHKG2*, and *SQLE*, amplifications were present. The authors divided EC samples into four clusters based on the expression of ferroptosis genes. The clusters exhibited a different tumor-infiltrating cell pattern. A total of 21 types of cells were identified in EC samples, out of which activated CD8 T cells, eosinophils, CD56dim NK cells, and activated B cells correlated with a better EC prognosis. The analysis of differentially expressed ferroptosis genes in four clusters revealed thirteen of them, namely, *TUBB4A*, *TMPRSS2*, *STX18*, *LINC01224*, *SLC25A35*, *CD7*, *COL23A1*, *ZG16B*, *KCNK6*, *NWD1*, *C11orf63*, *GZMM*, and *NMU*, as ferroptosis gene signatures [27]. Although the direct relation of these genes to EC is unclear, some of them are involved in other oncogenic diseases. For example, TMPRSS2 (transmembrane serine protease) is a prognostic biomarker in breast and lung cancer. In addition, its expression positively correlates with immune cell infiltration [155]. STX18 (syntaxin 18) mediates DNA damage response and promotes EMT in lung cancer [156], and LINC01224 (lncRNA 1224) is involved in colorectal cancer progression by sponging of miR-485-5p [157]. The upregulation of ZG16B (Zymogen granule protein 16B) expression correlates to a better prognosis of breast cancer patients [158]; however, ZG16B promotes colorectal cancer progression through the Wnt-β-catenin pathway [159]. KCNK6 (Potassium channel subfamily K member 6) promotes breast cancer cell proliferation and metastasis [160]. NWD1 (NACHT and WD repeat domain-containing 1) modulates androgen receptor signaling in prostate cancer [161]. GZMM (granzyme M) increases chemoresistance and EMT in vitro and metastasis in vivo [162]. NMU (neuromedin U)-expressing macrophages stimulate CRC metastatic potential [163].

Qin et al. analyzed the expression of ferroptosis-related genes in different stages of EC. The authors found out that the expression of *HSPA5*, *HSPB1*, *CS*, *CARS*, *EMC2*, *TFRC*, *NCOA4*, *ACSL4*, *RPL8*, *GPX4*, *CDKN1A*, *LPCAT3*, *NFE2L2*, *CISD1*, *SLC1A5*, *SAT1*, *FDFT1*, and *MT1G* was upregulated, whereas *FANCD2*, *SLC7A11*, *GLS2*, *DPP4*, and *ALOX15* expression were downregulated in grade 1-3 EC. The overexpression of *CDKN1A*, *SLC7A11*, and *SAT1* was a positive prognostic factor of EC. However, overexpression of *ATP5MC3* correlated with a higher EC grade and poor patient survival. SAT1 (spermidine/spermine N1-acetyltransferase 1) is a known regulator of the oxidative stress response; its activation increases ALOX15 expression, promotes lipid peroxidation, and, consequently, ferroptosis [164]. In addition, SAT1 overexpression in tumor tissues correlates with a higher degree of infiltrating macrophages and CD8+ T cells in tumor mass; however, SAT1 prognostic value depends on a tumor type [165].

Another study created a prognostic model for EC that contained six ferroptosis and lipid metabolism-related genes: *CDKN1A*, *ESR1*, *PGR*, *CDKN2A*, *PSAT1*, and *RSAD2*. PSAT1 was confirmed as a modulator of EC cell proliferation and migration. Genes related to lipid metabolism and ferroptosis correlated with a higher EC risk, and the degree of immune cell (B cells, T cells CD8, monocytes) tumor infiltration was higher in a low-risk group. The authors also showed that immune checkpoint proteins CTLA-4 and PD1 are potential targets for low-risk EC patients, while high-risk patients were more likely to benefit from standard chemotherapeutics, such as cisplatin, paclitaxel, a multikinase inhibitor AMG.706 and PARP inhibitor ABT.888. These results highlight the importance of personalized therapy for patients with different EC risk statuses [166].

Recently, several lncRNAs were identified as ferroptosis inhibitors in prostate, lung, and bladder cancer [167–169]. Also, it was shown that ferroptosis-related lncRNAs have a prognostic value in ovarian cancer [170]. Authors identified nine lncRNA that modulate ferroptosis resistance and proposed that it could be an independent prognostic index of EC. The knockdown of CFAP58-DT lncRNA decreased the viability and migratory properties of EC cells Ishikawa and HEC-1A. In accordance with the previous studies, low and high-risk EC groups differed in the degree of immune cell infiltration; for example, the number of dendritic cells and T cells was lower in the tissues of high-risk patient tumors [171].

Liu et al. investigated the mutational status and epigenetic modifications of twenty-four ferroptosis-related genes among different cancer types. Interestingly, the mutation rate of thirteen ferroptosis genes in EC was higher than five percent, although in other cancers, except for *NFE2L2*, it was low. The upregulated ferroptosis genes among all cancers were *SLC7A11*, *FANCD2*, *CARS*, *SLC1A5*, and *RPL8*, while the expression of *NCOA4* was downregulated. In most cases, the expression of ferroptosis genes correlated with copy number variations. In addition, most ferroptosis genes had a distinctive promoter methylation pattern among different cancers, and only *CDKN1A* exhibited consistent hypomethylation. However, as expected, in all cases, DNA methylation correlated with a decreased gene expression. Also, the study showed that the expression of ferroptosis genes *ACSL4*, *NCOA4*, and *CDKN1A* can be altered by miRNAs and is tumor-specific [172].

A study by Zhang et al. identified thirteen genes whose expression differed in type I and type II EC: *MAPK1*, *PHLPP1*, *ESR1*, *MDM2*, *CDKN2A*, *CDKN1A*, *AURKA*, *BCL2L1*, *POLQ*, *PIK3R3*, *RHOQ*, *EIF4E*, and *LATS2*. Most of these genes possessed amplifications and were involved in the regulation of cell death and tumor differentiation [173].

12. Conclusions

Ferroptosis is a newly discovered cell death type that requires iron overload, oxidation-prone polyunsaturated fatty acids in cellular membranes, and inactive GPX4. However, it is still unknown where exactly in the cell ferroptosis is initiated and executed. Possible targets include endoplasmic reticulum, Golgi complex, mitochondria, lysosomes, and peroxisomes. Also, it is still debated what a critical factor causing cell death is—membrane protrusions caused by lipid peroxidation or toxic side products of the oxidation reaction. Although at first glance, ferroptosis seems to be a rather primitive cell death type, its regulation is complex and depends on many factors, including cell metabolism. Metabolic rewiring is an intrinsic trait of cancer cells; however, not all cancers depend equally on metabolic abnormalities. In EC, many ferroptosis-related genes coding proteins and lncRNAs are mutated and differentially expressed in comparison to normal tissue. Overexpression of some, like SLC7A11, makes EC cells addicted to glucose and glutamine. This way, EC cells become vulnerable to agents that target glutamine and glucose metabolism. However, an elevated glucose and glutamine uptake increase EC cell resistance to oxidative stress and, consequently, ferroptosis-inducing agents. Thus, cell sensitivity to ferroptosis and metabolism are interconnected. This can be exploited by therapies that combine ferroptotic stimuli with metabolism-targeting agents. For example, inhibition of glycolysis or glutamine uptake combined with ferroptosis inducers kills two birds with the same stone and significantly improves the therapeutic effect. Thus, deciphering the connection between ferroptosis and cellular metabolism is important for both scientific research and clinical applications.

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