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Review

Ferroptosis in life: To be or not to be

Ling Xu [a,*,1], Yu'e Liu [b,*,1], Xi Chen [c], Hua Zhong [d], Yi Wang [e]

[a] Department of Internal Medicine of Traditional Chinese Medicine, Shanghai East Hospital, School of Medicine, Tongji University, Shanghai 200120, China
[b] Tongji University Cancer Center, Shanghai Tenth People's Hospital of Tongji University, School of Medicine, Tongji University, Shanghai 200092, China
[c] Xi Chen, Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA
[d] Cancer Epidemiology Division, Population Sciences in the Pacific Program, University of Hawaii Cancer Center, University of Hawaii at Manoa, Honolulu, HI, USA 96813
[e] Department of Critical Care Medicine, Sichuan Academy of Medical Science and Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China

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ABSTRACT

Ferroptosis is a novel type of programmed cell death, characterized by a dysregulated iron metabolism and accumulation of lipid peroxides. It features the alteration of mitochondria and aberrant accumulation of excessive iron as well as loss of the cysteine-glutathione-GPX4 axis. Eventually, the accumulated lipid peroxides result in lethal damage to the cells. Ferroptosis is induced by the overloading of iron and the accumulation of ROS and can be inhibited by the activation of the GPX4 pathway, FS1-CoQ10 pathway, GCH1-BH4 pathway, and the DHODH pathway, it is also regulated by the oncogenes and tumor suppressors. Ferroptosis involves various physiological and pathological processes, and increasing evidence indicates that ferroptosis play a critical role in cancers and other diseases. It inhibits the proliferation of malignant cells in various types of cancers and inducing ferroptosis may become a new method of cancer treatment. Many inhibitors targeting the key factors of ferroptosis such as SLC7A11, GPX4, and iron overload have been developed. The application of ferroptosis is mainly divided into two directions, i.e. to avoid ferroptosis in healthy cells and selectively induce ferroptosis in cancers. In this review, we provide a critical analysis of the concept, and regulation pathways of ferroptosis and explored its roles in various diseases, we also summarized the compounds targeting ferroptosis, aiming to promote the speed of clinical use of ferroptosis induction in cancer treatment.

1. Introduction

All living organisms have been refined by natural selection during evolution. A sophisticated and unique reproduction system has evolved in various species to ensure sustained anagenesis. Cell suicide, namely programmed cell death including apoptosis, necrosis, ferroptosis and pyroptosis, is indispensably involved in the evolutionary process and plays a key role in the maturation and well-being of all living organisms [1–4]. Ferroptosis is a novel type of programmed cell death, which is characterized by a dysregulated iron metabolism and accumulation of lipid peroxides [5,6]. Ferroptosis differs from other types of cell death such as apoptosis and necrosis. It features the alteration of mitochondria and aberrant accumulation of excessive iron as well as loss of the cysteine-glutathione-GPx4 axis, a major cellular antioxidant system [7,8]. Eventually, the accumulated lipid peroxides result in lethal damage to the cells.

Catalytic iron is indispensably involved in the cell growth of all organisms. It ensures the essential function of vital enzymes encompassing oxygen transport, ATP generation, and DNA synthesis [9]. However, excessive iron can also impair cells by induction of the Fenton reaction, leading to various DNA damages and even death [10]. Therefore, maintaining an appropriate labile iron is critical for cell viability. Briefly, the intracellular iron acquisition is predominantly mediated by transferrin receptor 1 (TfR1) engages in the uptake of transferrin-bound Fe (III) and cooperates with clathrin-mediated endocytosis [11]. The absorbed iron then is released into acidic endosomes where the Fe (III) is reduced to Fe (II) status by the ferriductase enzyme STEAP3 [12]. Then, Fe (II) is released from the endosome to cytosol by divalent metal transporter 1 (DMT1) which is also involved in Fe (II) and other ions such as cadmium (Cd^{2+}), copper (Cu^{2+}), and zinc (Zn^{2+},) uptake across

* Corresponding authors.
E-mail addresses: xuling2087@126.com (L. Xu), yueliu@tongji.edu.cn (Y. Liu).
[1] These authors contributed equally.

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the plasma membrane [13]. Iron storage is primarily conducted by the ferritin protein complex which comprises heavy chain (FTH) and light chain (FTL) protecting cells against reactive oxygen species (ROS)[14,15]. Ferroportin (FPN-1), the only known iron exporter, enables iron exporting across the plasma membrane[16]. The catalytic iron transiently assembles in the cytosol and constitutes a labile-iron pool (LIP) serving as a crossroad of intracellular iron trafficking[17].

Accumulated evidence has suggested that ferroptosis have roles in dominating both physiological homeostasis and pathogenesis in human beings suggesting it may be utilized as a beneficial strategy to augment the treatments of various human disorders [18–21]. Induction of ferroptosis can be exploited to improve efficacy in cancer treatment [22–24]. While inhibition of ferroptosis may be utilized for the prevention of neurodegenerative disorders such as Alzheimer's and Parkinson's diseases [25,26]. In this article, we summarized the mechanisms and related signaling pathways of ferroptosis and discussed its roles in various cancers and other diseases, we also highlighted targeting ferroptosis in cancer therapy. We are aiming to elucidate the role of ferroptosis in both pathological and physiological processes including cancer and embryogenesis surrounding the viewpoint of iron metabolism.

2. Mechanisms and related signaling pathways of ferroptosis

The initial investigation of ferroptosis as a new concept of cell death derives from the studies aiming to identify small molecules to kill the oncogene RAS[3,27,28], and the first ferroptosis-inducing agent, erastin was discovered in an engineered cell expressing an HRas proto-oncogene (a GTPase, HRAS)[27,29]. The increasing evidence indicates that the major target of erastin is SLC7A11, it exhibits anticancer activity in multiple cancer types [3,30,31].

2.1. Mechanisms of ferroptosis

The induction of ferroptosis comes from iron overload or the inactivation of glutathione peroxidase 4 (GPX4). The cystine transporter SLC7A11(xc-) transports the intracellular Glu to the extracellular space, meanwhile transports the extracellular cystine into the cytosol, the cystine is converted to cysteine (Cys) through an NADPH-consuming reduction reaction for glutathione (GSH) biosynthesis. GPX4 reduces the endogenous neutralization of polyunsaturated fatty acids (PUFAs)-OOH to PUFAs-OH and finally reduces ROS accumulation. The inactivation of GPX4 leads to iron-dependent ROS accumulation and ferroptosis. Excessive irons are the basis for ferroptosis, the circulated iron combined with transferrin in the form of Fe (III) entered the cells by TRF1, and then it is oxidized into iron in Fe (II) by oxide reductase STEAP3, the accumulated Fe (II) is released into a labile iron pool in the cytoplasm from the endosome mediated by DMT1 (Fig. 1).

Ferroptosis inducers can be divided into two main categories: the first type works through the cystine-glutamate transporter (SLC7A11) such as erastin and sulfasalazine which decrease the intracellular GSH; the second type inhibits the glutathione peroxidase (GPX) activity and induces RSL3 and DP17[8,32]. The erastin-induced ferroptosis is widely used as its induction of ferroptosis is efficient, rapid, and lasting [33].

2.2. The regulation of ferroptosis

Ferroptosis is regulated by inducers and suppressors, the overload of iron and the accumulation of ROS induces the ferroptosis, the GPX4 pathway, the FS1-Coenzyme Q10 (CoQ10) pathway and the GTP cyclohydrolase-1 (GCH1)-tetrahydrobiopterin (BH4) pathway, and the dihydroorotate dehydrogenase (DHODH)-CoQH$_2$ pathway suppresses ferroptosis. Moreover, the oncogenes and tumor suppressors also regulate ferroptosis.

2.2.1. Iron metabolism regulates ferroptosis

Iron as an indispensable element plays critical roles in metabolic processes including oxygen transport, electron transport and DNA synthesis. The excessive accumulation of iron causes oxidative damage and death in cells.

2.2.1.1. Iron from extracellular into the cell. The transferrin protein in the serum has two specific Fe (III) binding sites and serves as an iron source for hemoglobin synthesis[34–36]. The uptake of iron by cells through receptor-mediated endocytosis. When TfR1 is located on the cell surface, it binds to the transferrin with high affinity[37–39]. This binding forms a transferrin bond iron which profoundly affects iron release from transferrin, then the transferrin bond iron is engulfed into the cell and forms an endosome.

2.2.1.2. Iron from the endosome to the cytosol. The six-transmembrane epithelial antigen of prostate family member 3 (STEAP3) is essential for transferrin-mediated iron uptake, participating in the regulation of ferroptosis[12]. Iron in Fe (III) form was deoxidized to iron in Fe (II) by iron oxide reductase STEAP3. Iron easily interconverts between the ferrous state Fe (II) and ferric state Fe (III) and may exist in a wider range of oxidation states[10]. After the Fe (III) is converted to Fe (II) in the endosome, it is transported to the cytosol by divalent metal transporter 1

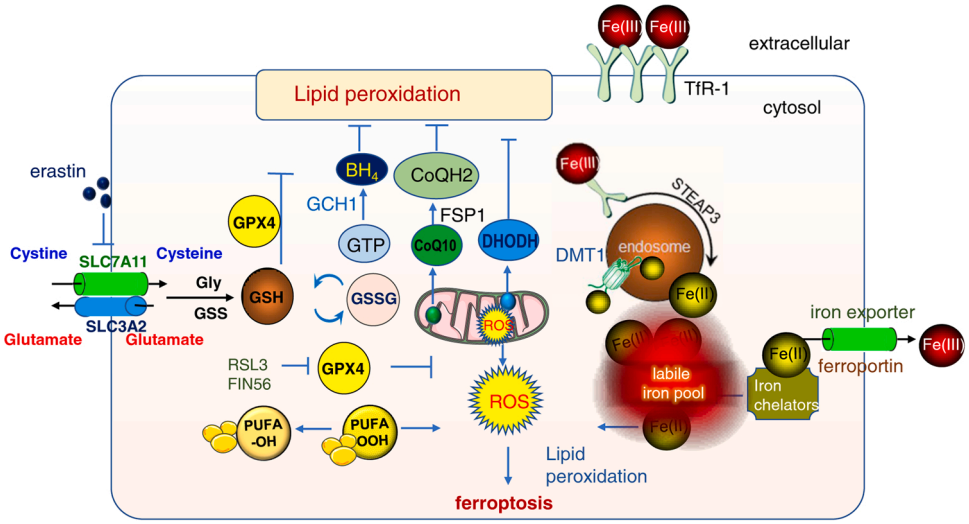


Fig. 1. The mechanism of ferroptosis.

(DMT1)[40] (Fig. 1).

2.2.1.3. Iron from cell to extracellular. Ferroportin (FPN), a transmembrane protein is the sole iron exporter in vertebrate species, responsible for exporting cellular iron to maintain iron homeostasis. Ectopic FPN expression increases the iron efflux to suppress the upregulation of intracellular iron after ferric ammonium citrate treatment [41,42]. Knockdown of FPN accelerates erastin-induced ferroptosis in neuroblastoma and other diseases [43].

In a word, iron homeostasis is regulated very strictly, any of the above transporters' mutation or deficiency interrupts the balance of iron and causes diseases.

2.2.2. ROS accumulation induces ferroptosis

ROS are a group of highly reactive chemicals under the tight control of intracellular antioxidants [44], they are mainly produced by normal physical processes and play important roles in cell signaling, cell death and cell homeostasis [45]. But the excessive ROS may cause metabolic disorders, DNA damage and augment pathogenesis [46]. The iron-dependent accumulation of ROS is one of the typical characteristics of ferroptosis.

TfR1 is required for iron delivery from transferrin to cells, it functions as a gatekeeper for regulating iron uptake by most cells. The conversion process from Fe (III) to Fe (II) produces ROS. Moreover, it has been found that ROS-induced autophagy is a key regulator of ferritin degradation and TfR1 expression during ferroptosis. autophagy leads to iron-dependent ferroptosis by degradation of ferritin and induction of TfR1 expression [47].

Ferroptosis follows the characteristics of decreased or vanished mitochondria cristae, a ruptured outer mitochondria membrane and a condensed mitochondrial membrane [29,48–50]. Mitochondria is the primary site for endogenous ROS production. Most of the oxygen consumed in the process of respiration is reduced to water, but around 1–2% of oxygen is converted into ROS [51]. Mutations of mitochondria genes lead to the over-production of ROS. The voltage-dependent anion channel (VDAC) is an ion channel located in the mitochondria out membrane, it controls the molecular and ion exchange between the mitochondria and the cytoplasm [52,53]. The permeability of VDAC altered by drugs or other interruptions causes metabolic disorders, and increases ROS production and subsequent oxidative death [54]. Under the oxidative stress conditions, the transsulfuration pathway transfers a sulfur atom from methionine to serine and generates cystine, which acts as a substrate for the synthesis of GSH, GSH helps GPXs to main redox homeostasis and prevents oxidative damage.

2.2.3. GPX4 pathway inhibits ferroptosis

Ferroptosis is characterized by the excessive peroxidation of phospholipid membranes which is rich in PUFAs via an iron-dependent mechanism leading to cell death. The GSH-dependent lipid peroxide protects membranes from peroxidation damage and controls intracellular homeostasis. The decrease of cysteine-glutamate metabolism suppresses GPX activity [22]. The peroxidation will be induced if any of the phospholipid metabolisms are impaired, and thus promoting ferroptosis. GPX4 is a member of the GPX family, it catalyzes the conversion of endogenous lipid hydroperoxides into innocuous lipid alcohols by the oxidation of GSH [55,56]. Inhibition of GPX4 pharmacologically by RSL3 and DP17 or genetically leads to a decrease in the cellular antioxidant capacity and ultimately leads to ferroptosis [57–59]. The depletion of GSH also induces the inactivation of GPX4 [3,8]. Besides inducing ferroptosis, the depletion of GPX4 may also sensitize the cell to other regulated cell death such as apoptosis, necroptosis, and pyroptosis [60–62].

2.2.4. FSP1-CoQ10 pathway suppresses ferroptosis

The inactivation of GPX4 doesn't induce ferroptosis in some kinds of cells. The apoptosis-inducing factor mitochondria-associated 2 (AIFM2, also known as FSP1) overexpression largely abrogates GPX4 inhibition-induced ferroptosis [63,64]. FSP1 has been verified as a ferroptosis suppressor [65]. FSP1 is a nicotinamide-adenine dinucleotide phosphate- (NADP-) dependent coenzyme Q (CoQ) oxidoreductase, located in the cell membrane [66]. Coenzyme Q10 (CoQ10) or ubiquinone is endogenously produced in the human body and plays important roles in mitochondrial bioenergetics as an electron and proton carrier, later its antioxidant role was investigated. FSP1 catalyzes the regeneration of CoQ10 using NADPH. Inhibition of FSP1 strongly synergized with GPX4 inhibitors to trigger ferroptosis in various cancers. The FSP1-CoQ10 pathway cooperates with GPX4 and glutathione to suppress phospholipid peroxidation and ferroptosis [63,67].

2.2.5. GCH1-BH4 pathway inhibits ferroptosis

BH4 is an enzymatic redox-active cofactor required in the production of nitric oxide and aromatic amino acids [68,69]. Its de novo synthesis requires three enzymes and the major controlling one is GCH1. GCH1 catalyzes GTP to BH4 and GCH1 is a rate-limiting enzyme in the synthesis of BH4 [70–72]. BH4 play antioxidant roles in vitro, the overexpression of GCH1 abolishes lipid peroxidation and yields almost complete protection against ferroptosis which was induced by RSL3 or the ablation of GPX4 [69]. The supplementation of BH4 rescues cells from ferroptosis [69,72]. Therefore, the GCH1-BH4 pathway serves as an endogenous antioxidant pathway to inhibit ferroptosis via a mechanism independent of the GPX4/glutathione system [69] (Fig. 1).

2.2.6. The DHODH-CoQH2 system inhibits ferroptosis

DHODH is a flavin-dependent mitochondrial enzyme catalyzing the fourth step in the de novo pyrimidine synthesis pathway [73]. Recently, DHODH has been verified as a defense system against ferroptosis in mitochondria [74]. DHODH exists in the inner membrane of mitochondria and covert ubiquinone into dihydropanthenol [75]. DHODH can oxidize dihydrolactic acid (DHO) into orotic acid (OA) through transferring electrons to ubiquinone. DHO protects cells from RSL3-induced ferroptosis, and DHODH inhibitor brequinar (BRQ) promotes ferroptosis in GPX4-deficient cancer cells. The FSP1 activation can't rescue the RSL3-treated cells in DHODH deficient cells, suggesting that the DHODH functioning in FSP1 independent way. A later study indicates that DHODH can work parallel with mitochondrial GPX4 to inhibit ferroptosis [74,76].

2.2.7. P53 regulates ferroptosis

The tumor suppressor gene p53 plays a critical role in the biological processes and oncogene activation [77]. Cell stress induces the activation of p53 to induce cell cycle arrest and DNA repair. P53 also protects oxidative stress-induced DNA damage and death by reducing ROS production in cells. High-level stress induces p53 activation and thus induces the cell to apoptosis. P53 plays pro-death and pro-survival functions under different circumstances in ferroptosis.

The activation of the p53 gene can inhibit cystine uptake by suppressing the expression of SLC7A11 and sensitizing cells to ferroptosis [78,79]. Erastin is able to activate p53 and thus can enhance ferroptosis. The erastin treatment in lung cancer A549 cells indicates that the p53 expression is upregulated and the ROS production is significantly increased but pretreating the ROS scavenger and then treating erastin can't affect p53 activation, suggesting that the p53 activation depends on the ROS induced by erastin treatment. Reversely, the increased ROS exacerbates the cytotoxicity and cause apoptosis [80]. Besides inducing ferroptosis via inhibiting SLC7A11 and reducing GSH, the activation of Spermine N1-acetyltransferase 1 (SAT1) and GLS2 induced by p53 can also lead to the accumulation of lipid hydroperoxides and ultimately lead to ferroptosis. The inhibition of p53 increases the anticancer activity of type I ferroptosis inducers such as erastin and SAS, but not type II ferroptosis inducers such as RSL3 and FIN56 [81].

The pro-survival function of p53 has been found in the inhibition of

ferroptosis via the regulation of dipeptidyl peptidase-4 (DDP4) localization and activity instead of its expression [81]. Inhibition of DDP4 blocks the erastin-induced ferroptosis in p53-deficient colon cancer cells. P53 deficiency prevents nuclear accumulation of DDP4 and triggers lipid peroxidation [81]. The activation of p53 can also suppress ferroptosis through the inhibition of DDP4 and the induction of CDK1A/p21 which is a key mediator of p53-dependent cell cycle arrest after DNA damage [82]. CDKN1A also has pro-survival functions in response to oxidative stress by inhibiting apoptosis [83].

SLC7A11 transports the intracellular glutamine to extracellular space and extracellular cystine into the cell to form glutathione (GSH), GSH is oxidized into glutathione disulfide (GSSG). GPX4 reduces the PUFAs-OOH to PUFAs-OH and reduces ROS. ROS is mainly produced from mitochondria. The accumulated ROS also induces lipid peroxidation and finally leads to ferroptosis. Iron can be taken up from extracellular by the binding between TfR1 and transferrin, their binding forms a transferrin bond iron, which is then engulfed into the cell and forms an endosome. Iron in Fe (III) form was deoxidized to iron in Fe (II) by iron oxide reductase STEAP3, then the Fe (II) is released into a labile iron pool in the cytoplasm from the endosome mediated by DMT1. The iron is exported to extracellular by ferroportin, thus maintaining iron homeostasis. Three pathways inhibit ferroptosis: the GPX4 pathway, the FS1-CoQ10 pathway, the GCH1-BH4 pathway and the DHODH pathway.

3. Ferroptosis in cancers and tumor microenvironment (TME)

3.1. Ferroptosis in TME

TME is created by varieties of complex and dynamic interactions resulted from not only tumor cells but also including fibroblasts, myofibroblasts, neuroendocrine and adipose cells as well as immune and inflammatory cells [84–86] (Fig. 2a). The TME endows manifold merits for tumor growth, such as hypoxia, acidosis, oncogenes activation and evasion of immune surveillance [87–90]. Among them, hypoxia is the hallmark existing in most of the sold malignancies based on an aberrant activation of a heterodimeric transcription factor, hypoxia-inducible factor (HIF) which directly activates multiplicity of downstream signaling pathways and switches the cellular metabolism from oxidative phosphorylation (OXPHOS) to glycolytic mode in tumor cells [91–94]. Commonly, tumor cells display a great level of ROS in contrast to the normal cells due to the ramping up oxidant generation which is resulted from a decrease in O_2 availability (hypoxia) and retarding of the electron transporting across the mitochondrial complexes. Electrons leaking from the electron transport chain (ETC) will react with O_2 which potentially produces substantial ROS [95,96]. However, tumor cells can flourish themselves by increasingly importing cysteine, which is a semi-essential proteinogenic amino acid reduced from cystine after uptake through cystine/glutamate antiporter (xCT) [97,98]. The increased absorption of cysteine in tumor cells is utilized to build up the cysteine-glutathione (GSH)-GPx4 axis which plays a crucial role in detoxifying the cellular oxidants. Of note, disruption of cysteine-GSH-GPx4 remarkably triggers ferroptosis in comparison to the corresponding normal cells [8]. In addition to the disruption of the defense system, iron addiction, which is commonly existed in most malignancies, has been revealed as another risk of ferroptosis [99,100]. The rapid consumption of iron fulfills the needs of aggressive behaviors including higher proliferation, metastasis and invasion in tumors [101]. Furthermore, the high concentration of catalytic iron enriched in tumor cells can be further enhanced by hypoxia. Both increased levels of iron-transporter (TfR1 and DMT1) and iron regulatory protein 2 (IRP2) have been uncovered in response to the activation of HIF-1 accompanied by stabilization of iron-storage proteins (FTL/H) [100, 102–105]. These pieces of evidence suggest that higher iron addiction is favored by cancer cells, however, it also could be a hazard factor contributing to cancer cell ferroptosis.

3.2. Ferroptosis in cancers and other diseases

The role of ferroptosis in cancer has been reviewed [18,106,107]. Here, we talk about ferroptosis in malignant mesothelioma (MM), breast cancer (BC), melanoma and embryogenesis.

3.2.1. Ferroptosis in malignant mesothelioma (MM)

Among the varied types of cancer, MM is a rare, but aggressive tumor predominantly localized at the pleura and peritoneum [108]. Asbestos, which had been most applicable for manufacturing and construction in the last century, has been considered as the most common predisposition

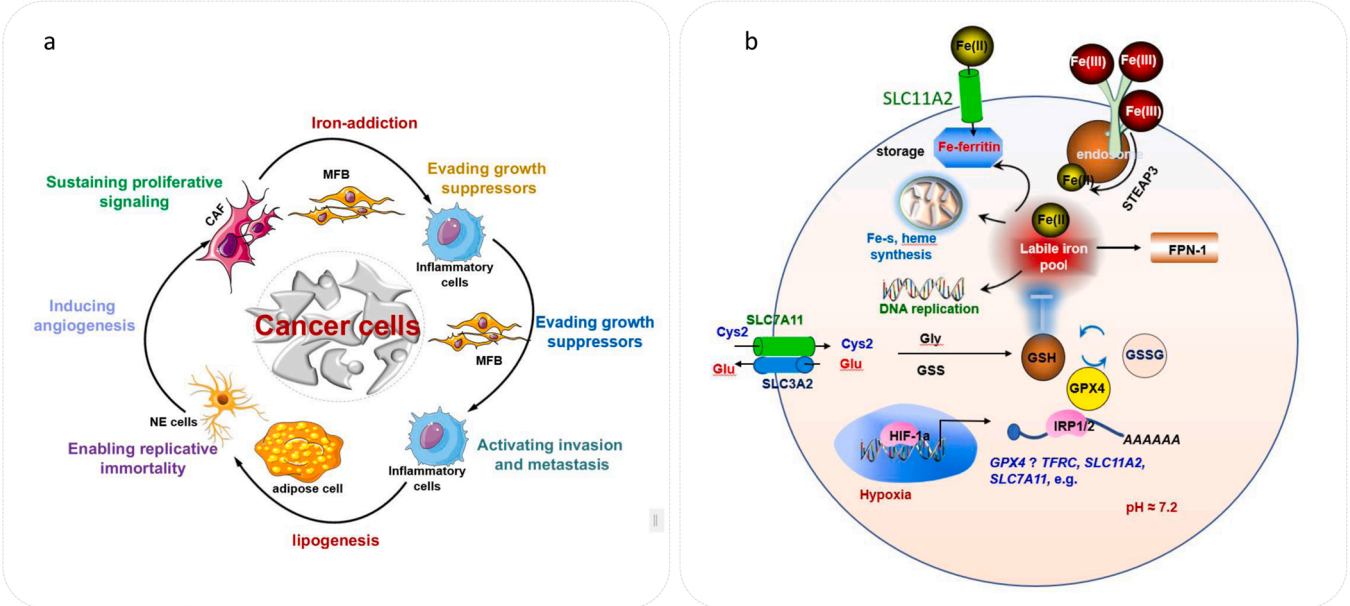


Fig. 2. Ferroptosis in the tumor microenvironment a The TME harbors various cell types consisting of cancer-associated fibroblasts (CAF), myofibroblasts (MFB), inflammatory cells, neuroendocrine cells (NE) and adipose cells, etc. Besides the common hallmarks of cancers, iron addiction and lipogenesis are characterized by multiple types of cancer. b Cancer cells displayed higher iron transporting, storage and bioavailability as well as increased levels of GSH and GPX4 for detoxification in contrast to normal cells.

to malignant mesothelioma[109]. Asbestos fiber has been shown to possess a higher affinity to bind with iron-rich proteins such as hemoglobin and transferrin [99,110,111]. Iron overload due to hemoglobin degradation, as well as hemolysis, will consequently lead to a chronic inflammatory circumstance which drives the formation of TME. In addition to the proteins binding, macrophage, which plays a vital role in clearing digests cellular debris, foreign materials and iron storage, has been recognized as another crucial factor involved in mesothelial carcinogenesis [112,113]. Macrophages are engaged in the formation of asbestos bodies by absorbing asbestos fibers. However, a dysregulated capability of macrophages may occur if the engulfed asbestos fibers are longer than 20 μm which can mechanically penetrate macrophages and interfere with their activities [114]. Consequently, abundantly catalytic iron will be liberated from the dysfunctional macrophages and aggravates mesothelial tumorigenesis associated with increased ROS and secreted cytokine/chemokine [115,116]. On the other hand, iron enriched in the asbestos surface is capable of causing DNA damage and genomic alteration through Fenton reaction [117]. Moreover, the phagocytosed asbestos exhibiting higher affinity to histone proteins has been reported which suggested asbestos may also affect genomic transcription [118].

Despite emerging studies concluded that iron-overload acts as an important factor involved in mesothelial carcinogenesis. The catalytic iron is indispensable to sustain the malignant characteristics of MM cells during the progress which is implied as iron addiction. MM cells appear to be resilient and resourceful as they not only are able to fulfill their own needs of iron to boost cell proliferation, and higher metastasis but also refrain from iron-induced cytotoxicity [119]. Of note, a reduction of systemic iron concentration by oral administration of deferasirox, an iron chelating agent, has been found to dramatically decrease asbestos-induced mesothelial carcinogenesis in the rat which is followed by decreases in oxidative stress and viability of MM cells [120,121]. Remarkably, deferasirox treatment also significantly diminishes asbestos-induced cytotoxicity in non-carcinogenesis rat mesothelial cells. Therefore, this evidence strongly suggested that iron is not only vitally involved in the carcinogenesis initiation of mesothelial cells but also indispensable to tumor progression.

Recently, the emerging evidence of ferroptosis may provide a promising approach for MM treatment since the character of iron addiction in mesothelioma cells may precipitate them into higher vulnerability to ferroptosis. Wu, J et.al have concluded that neurofibromin 2 (NF2) and the Hippo signaling pathway dictate ferroptosis in MM cells. The gene *NF2* that encodes tumor suppressor merlin, is frequently mutated in malignant mesotheliomas. In general, the inactivation form of *NF2* weakens the intercellular contact of mesothelioma cells by diminishing the protein levels of cadherin and de-represses the motility and invasiveness of MM cells. Counterintuitively, it is the genetic mutation of *NF2*, however, rendering mesothelioma cells more susceptible to ferroptosis which is associated with loss of intercellular contact modulated by E- and N-cadherin (E/NCAD) proteins. Subsequently, either loss of ECAD or NF2 knockdown induced overexpression of long-chain-fatty-acid–CoA ligase 4 (*ACSL4*) and *TFRC*, which are two putative targets of yes-associated protein (YAP) and are recognized as surrogate markers of ferroptosis [122,123]. It should be noted that the aberrant activation of YAP, as well as the transforming growth factor β (TGFβ), are able to promote epithelial–mesenchymal transition (EMT) and metastasis by inducing several EMT genes accompanied by elevating ROS and iron level [124–126]. Indeed, iron overload has been shown to promote cancer cells to EMT phenotype exhibiting increases in EMT-related genes such as Zeb1/2, Twist, and Snail, which is partly due to loss of p53 activity [127]. Consistently, iron depletion has been shown to alleviate the degradation of E-cadherin and β-catenin induced by TGFβ. Additionally, TGFβ has also been found to a role in augmenting ferroptosis in mammary tumor cells isolated from MMTV-neu mice even at high cell density which generally shows resistance to ferroptosis [24]. Given this evidence, we suggest that the MM undergoing higher proliferation, metastasis and invasiveness are supposed to be more vulnerable to ferroptosis. Although the loss of adhesive property is critically involved in EMT which endows MM cells with aggressive features and motility, as a result of YAP retention in the nuclear, ferroptosis will be easily triggered due to the unlimited expressions of *TFRC* and *ACSL4*. Since both *NF2* mutation and EMT commonly co-existed in MM cells[128], we tend to believe these characteristics can escalate the risk of ferroptosis in cooperation with iron addiction in MM cells.

Apart from NF2 mutation, tumor hypoxia is another important impediment to effective MM therapy. Recently, Zan Li, et al. have illuminated that disruption of tumor hypoxia by inhibiting carbonic anhydrase IX (CAIX) enables a severe cell lethality consisting of mitochondrion-associated autophagy, ferroptosis and apoptosis[100]. CAIX is inductively expressed in hypoxic tumor cells. The primary function of CAIX is involved in pH-equilibrating by hydrating CO_2 into H^+ and bicarbonate ($HCO3^-$) in tumor cells. As a result, the produced $HCO3^-$ will be utilized to neutralize intracellular pH [129]. Meanwhile, the remained H^+ escalates extracellular acidosis which provides multiple merits for cancer cells such as extracellular matrix remodeling [130], evasion of apoptosis as well as EMT [131]. CAIX up-regulation parallels a significant increase in catalytic iron in response to hypoxia which is mostly sequestrated in lysosomes, mitochondria as well as ferritin without interfering with the MM cells' viability [132–134]. Moreover, cell death resulting from CA IX inhibition not only is slightly rescued by apoptosis inhibitor (Z-VAD-FMK) but also by iron chelator, deferoxamine (DFO) and a ferroptosis inhibitor (Fer-1). Further studies are necessary to illustrate more details about the crosslink between CA IX regulation and ferroptosis since the latent mechanism remains unclear. It should be noted that CAIX has been shown to co-localize with F-actin, cofilin and α2/β1 integrin [135], supporting actin polymerization, invadopodia elongation and resembling lamellipodia which have the suppressive function in endocytosis-mediated Tf/TfR1 internalization [130,136,137]. Indeed, a previous study has revealed treatment of non-thermal plasma to MM cells aberrantly activated endocytosis accompanied by inductions of autophagy and ferroptosis[132].

Furthermore, it has also highlighted the role of iron in promoting mitochondrial fission and mitophagy. Notably, the involvement of mitochondrial fission due to dynamin-related protein 1 (DRP1) activation is essentially required to trigger ferroptosis since either *DRP1* depletion or mitochondrial inactivation has been shown to alleviate ferroptosis [138]. However, the mechanism of mitochondrial fission induction remains undefined. We propose that certain levels of mitochondrial iron may augment ferroptosis by re-routing OXPHOS in mitochondria which are generally malfunctioning due to the Warburg effect [139]. Indeed, we have seen a great elevation of mitochondrial mass in response to CA IX inhibition in MM cells [100]. However, a switch of cell death mode from ferroptosis to apoptosis might take place and become overwhelmed when the concentration of mitochondrial iron reaches a saturated level or exceeds their own tolerance [140]. This hypothesis may explain the phenomenon that apoptosis is the predominant type of cell death resulting from CA IX inhibition which causes mitochondria iron overload in the MM cells. (Figs. 3–5).

a. The epithelial cells and the mesenchymal cells exhibit different sensitivities to ferroptosis.

3.2.2. Ferroptosis in breast cancer (BC)

In addition to MM, a multiplicity of distinguished studies has elucidated the crucial role of ferroptosis in the treatment of BC which is the leading cause of death globally [141]. Similar to MM cells, the inverse correlation between ferroptosis and cell density has been identified in the BC cells [142]. The integrin proteins mediate cell adhesive properties through binding extracellular matrix (ECM) which impedes invasion and metastasis of cancer cells [143]. However, it is also utilized by breast cancer cells to evade cell death. Brown, C. W et al. have reported α6β4 complex of integrin proteins enables the protection of epithelial

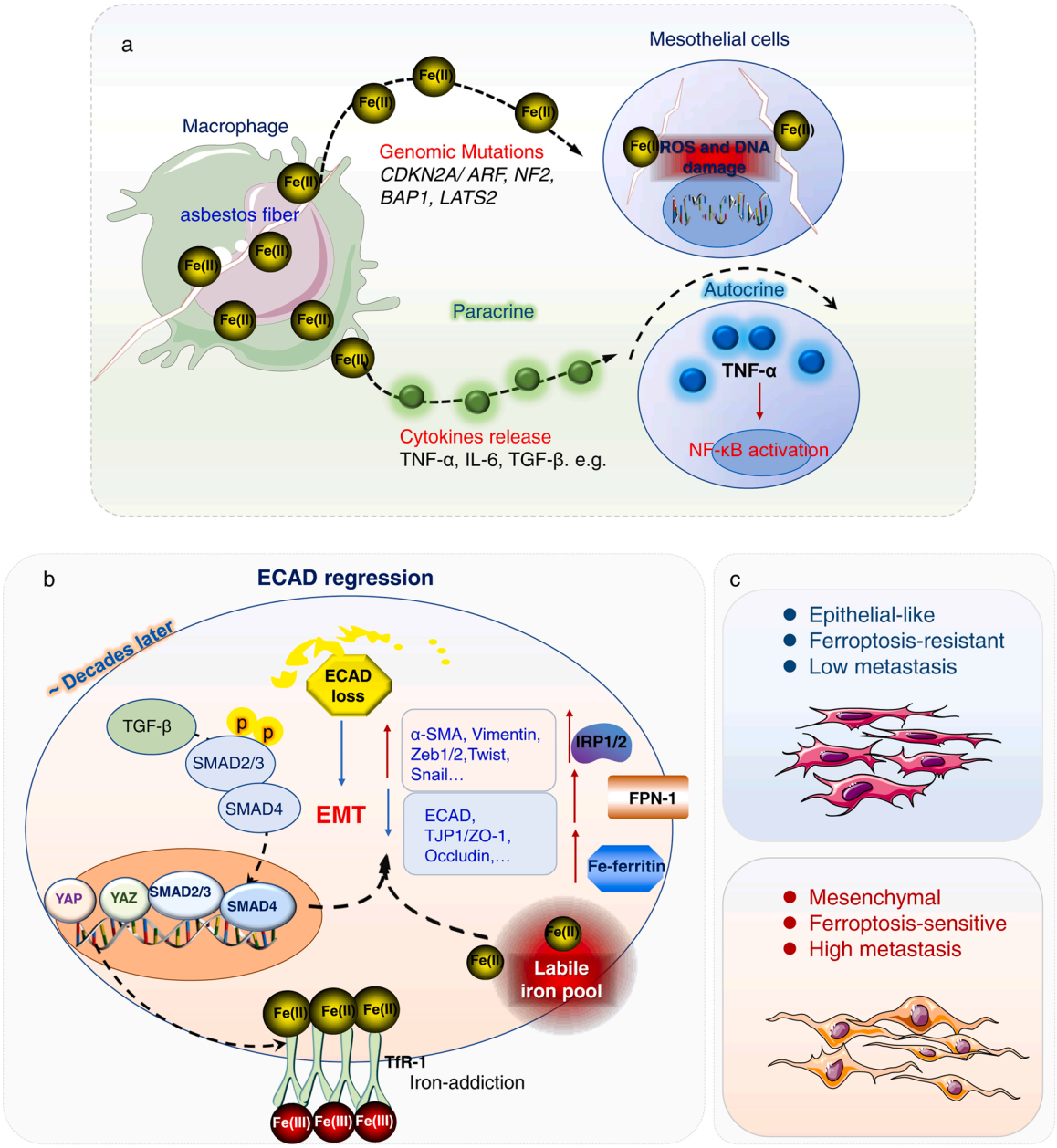


Fig. 3. Reprogramming of iron-metabolism is linked with initiation, progression and ferroptosis vulnerability of mesothelioma cells induced by asbestos exposure. a Mesothelial carcinogenesis exposed to asbestos is associated with the malfunction of macrophages. A large amount of catalytic iron released from dysfunctional macrophages as well as liberated various cytokines not only induce genomic mutations but also transduction of survival signaling by activating NF-κB in mesothelial cells. b During the progress of mesothelial carcinogenesis, iron-metabolism will be re-programmed by exhibiting an iron addiction phenotype that subsequently promotes EMT. Loss of adhesive property during EMT endows MM cells with metastatic capability, but also renders MM cells more vulnerable to ferroptosis.

(MCF-10A) and carcinoma (SUM-159) cells from ferroptosis [144]. The induction of Src/STAT3 signaling inhibits ACSL4 expression and disrupted the enrichment of long polyunsaturated fatty acids in the plasma membranes. Furthermore, lacking α6β4 causes ferroptosis in either MCF-10A or SUM-159 cells is sufficiently rescued by GPX4 expression. However, another study has reported dispersed cell-density sensitized breast cancer cells to ferroptosis in an EMT-independent manner. In this study, low cell density triggers ferroptosis in BC cells associated with the storage of neutral triacylglycerides (TAG) enriched with polyunsaturated fatty acids (PUFA) as well as the increased uptake of fatty acid regardless of oncogenic signaling, cellular phenotype and ACSL4 protein level. In this study, the accumulation of PUFAs in TAGs has been considered a protective response to reduce ROS and lipid peroxidation. However, it renders the metastasizing BC cells more vulnerable to ferroptosis. Future studies are necessary to clarify the bio-meaning of TAG as well as the link between PUFA-TAG enrichment and cell density in the ferroptosis of breast cancers.

Besides the PUFAs, iron accumulation has been realized as another determinant of ferroptosis in BCs[145]. It should be noted that a significant alteration of iron level has been revealed in circuiting serum between pre- and postmenopausal BC patients which may lead to distinctive effects on breast tumorigenesis and prognosis [146,147]. Breast cancers in premenopausal women generally display higher metastasis, recurrence and lethality in contrast to those in postmenopausal patients. However, iron appears to be important but not an indispensable factor since premenopausal patients are more likely to show an iron deficiency in their circuiting serum which in turn aggravates the hypoxia condition and further stimulates tumor cell

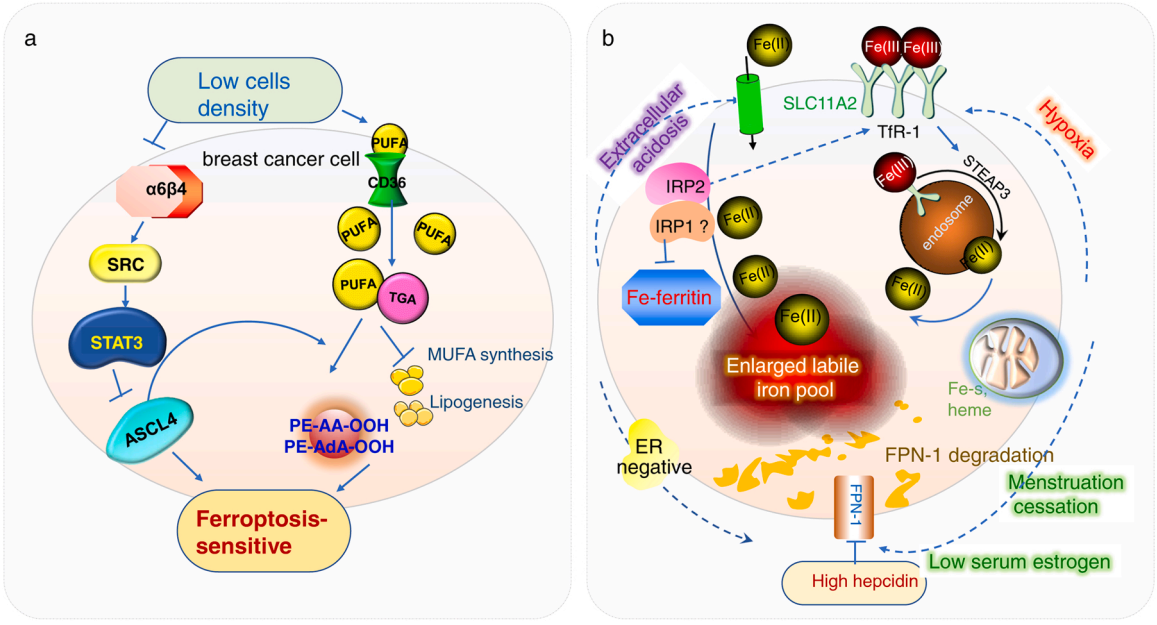


Fig. 4. Significances of lipid and iron-metabolism regulation in ferroptosis of BC cells. a Low cell density sensitizes BC cells to ferroptosis which can be mediated either by EMT-dependent or -independent pathways. Breast carcinomas derived from post-menopausal patients and the TNBC subtype exhibit a higher risk of ferroptosis due to the enrichment of catalytic iron. b Lacking estrogen or cessation of menstruation renders BC cells more susceptible to ferroptosis due to increased hepcidin levels. Breast carcinomas derived from post-menopausal patients and the TNBC subtype exhibit lower levels of FPN-1 and higher sensitivity to ferroptosis due to menstruation cessation and the lack of estrogen.

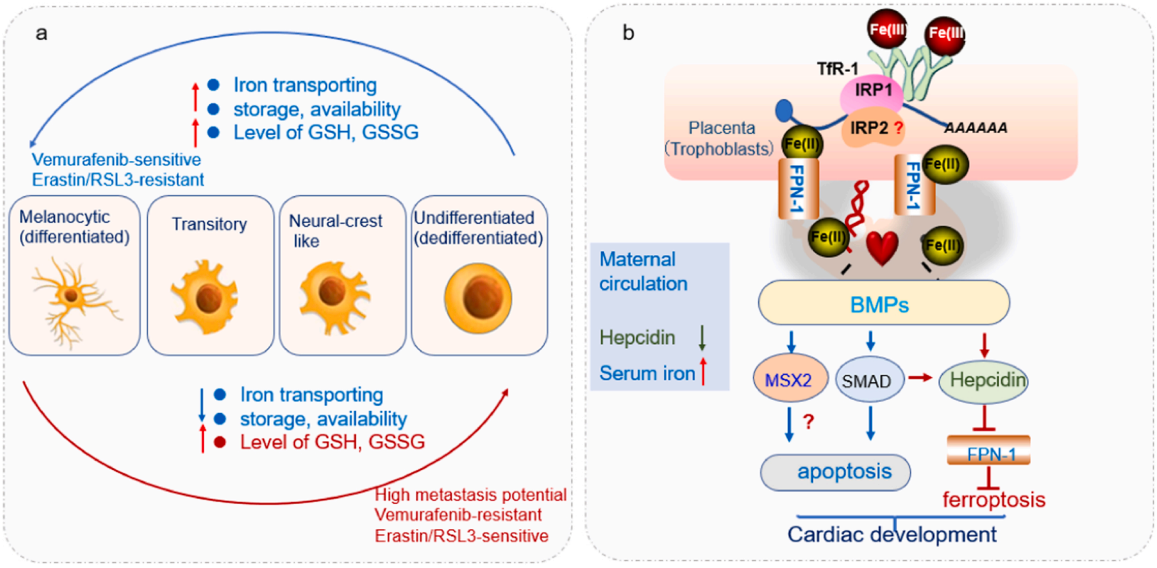


Fig. 5. Ferroptosis in melanoma and in cardiac development a The four stages of melanoma differentiation show distinct patterns of susceptibility to apoptosis and ferroptosis. The process of melanoma differentiation is accompanied by a variation of several transcriptional factors (MITF, SOX10, SMAD3, CTNNB1, etc.) which are related to iron-metabolism regulation. The differentiated (melanocytic subtype) melanoma cells show sensitivity to vemurafenib treatment whereas resistant to erastin and RSL3 induced ferroptosis by displaying higher levels of intracellular iron and GSH/GSSH. While the acquired resistance to vemurafenib always occurs in melanoma cells, which is associated with dedifferentiation induced by cellular stress. The dedifferentiated melanoma cells also enrich the higher concentrations of catalytic iron. However, the basic levels of GSH and GSSH are much lower in such dedifferentiated cells that confers higher vulnerability to ferroptosis. b Potential signaling pathways involved in regulations of iron metabolism and cell death during cardiac development. Down-regulation of maternal hepcidin during pregnancy crucially maintains an appropriate iron bioavailability for the mother and fetus. The hepcidin secreted by the fetal heart as well as the liver also has specific roles in iron homeostasis. BMP family proteins are involved in embryogenesis by induction of MSX2- and SMAD- mediated apoptosis. Simultaneously, BMPs and SMAD can positively regulate hepcidin expression which potentially contributed to cardiac iron retardation. The nature of these proteins' expression during embryonic development suggests that apoptosis, iron overload, and ferroptosis are involved in cardiac morphogenesis. The effect of MSX2 resulting from the transduction of BMPs signaling on apoptosis remains poorly understood.

proliferation and metastasis [148,149]. These characteristics enriched in premenopausal people may partly account for the tumor malignancy and high recurrence rate in the young population of breast cancer patients. In contrast to premenopausal patients, inversion exists in postmenopausal patients that frequently display a higher modality with remarkable oxidative stress. As the cessation of menstrual bleeding, iron

accumulation commonly occurs in older patients of BC. Excess of catalytic iron enables the Fenton reaction induction which subsequently creates substantial hydroxyl radicals to induce various lesions in DNA. As a result of DNA damage, the amplified mutations will give rise to altered proteins to induce carcinogenesis [150]. However, as it has been shown in MM cells, re-programming of iron-metabolism has been also revealed in BC cells during progression which exhibits an iron-addiction phenotype by up-regulating TfR-1 and FTL/H while FPN-1 degradation in MDA-MB-231 as well as MCF-7 cells which are originally derived from a post-menopausal patient [151–153]. These changes propose the importance of iron addiction during the progression of BC. Moreover, breast cancer. MCF-7 cells grown under post-menopausal conditions in vitro showed higher pre-existing levels of lipid peroxidation in contrast to those in pre-menopausal conditions [154]. In addition, the reduction of estrogen levels is also known to aggregate iron accumulation followed by restoring hepcidin levels among post-menopausal patients [155]. The recovered hepcidin has been found closely correlated to bone morphologic proteins (BMPs)[156–160]. This evidence suggests that the gain of iron in post-menopausal patients may increase the susceptibility to ferroptosis. It might be worth addressing the issue of whether a condition of moderate ferroptosis naturally exists among post-menopausal patients since epidemic analysis has reported that older BC patients more than 40 years old are at a lower risk of dying in contrast to their older counterparts [161].

Similarly, the triple-negative breast cancer (TNBC) cells lacking estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) also possess higher availability of catalytic iron displaying higher levels of basic levels of endogenous TfR-1whereas dramatically diseases in FTH and FPN-1 proteins in contrast to the non-TNBC cells [162]. IRP2, which directly regulates the mRNA level of iron-associated proteins, has been suggested with a potential role in promoting ferroptosis [3]. The enlarged labile iron poor driven by IRP2 has been concluded in TNBC, MDA-MB-231 cells[151]. Genomic depletion of IRP2 was shown to significantly cease proliferation in MDA-MB-231 cells relative to the non-TNBC, MCF-7 cells which propose the enlarged labile iron pool modulated by IRP2 are more prerequisite to the TNBC subtype.

Currently, another study has emphasized the impact of ferroptosis on TNBC treatment [162]. A combined synthetic-lethal (SL) treatment using bromodomain (JQ1) and a proteasome inhibitor (BTZ) remarkably reduces viability of TNBC cells compared to either non-TNBC or non-carcinomatous mammary epithelial cells (MCF-10A) cultured in both of 2D condition and 3D spheroids. Unexpectedly, the cell death is effectively rescued by GSH and ferrostatin-1 as well as an iron chelator, 2,2-bipyridyl (2,2-BP) relative to apoptosis and necrosis inhibitors. TNBC cells treated with SL show dramatically increased levels of TfR-1, and ACSL4 proteins while decreased FPN-1 and FTH accompanied by declined levels of GPX4 and GSS in comparison to the non-TNBC cells. However, the details of iron-metabolism regulation have not been illustrated in this study. Other studies have investigated that JQ1 may augment ferroptosis by triggering ferritinophagy [163]. Given the outlined above, we believe ferroptosis can present an orthogonal therapeutic approach to target breast cancers. We emphasize that both of physiological period (menopause status) and cancer subtype (TNBC) should be rigorously considered as vital factors dictating the sensitivity of BC cells to ferroptosis.

3.2.3. Ferroptosis in melanoma

Melanoma is a rare skin cancer which originates from melanocytes [164]. The differentiation status dictates the prognosis of melanoma. Many patients, however, either relapse or cannot benefit from targeted treatments or immunotherapy due to the dedifferentiation [165,166]. Ferroptosis has been heightened to straighten the treatment of melanoma [167]. Of note, the progressive stage of melanoma recently has been classified as undifferentiated, neural crest-like, transitory and melanocytic four subtypes. Treatment with vemurafenib, a potent inhibitor which is commonly utilized for melanoma treatment by targeting *BRAF* mutation [168], induces dedifferentiation (switching to the undifferentiated status) in melanoma cells which showed a signature of vemurafenib resistance. However, the authors have revealed that the fully undifferentiated subtype of melanoma cells with higher malignant proprieties displayed the utmost vulnerability to ferroptosis in contrast to the transitory or neural crest-like subtypes (moderate) as well as the melanocytic cells (insensitive). Furthermore, a combined administration of vemurafenib and erastin not only overcomes the emerging resistance attributed to the treatment of vemurafenib alone but also contributes to a synergistic effect on melanoma viability.

However, iron metabolism regulation remains unclear in this study. It should be noted that analysis of the transcriptome profile has found some specific variations of typical transcriptional factors during multi-status differentiation in melanoma, such as *MITF*, *SOX10*, *SMAD3*, *CTNNB1*, which are potentially associated with iron-metabolism regulation. MITF and SOX10 have been reported to a role in improving melanogenesis that drives the aggressive behaviors of melanoma by stimulating HIF-1 expression [169,170]. SOX10 is involved in melanocyte development and determines the expression level of MITF. Importantly, melanogenesis has been shown an iron-dependent manner following overexpression of *MITF* and *SOX10* as well as increases in both pigmentation and melanosome mass in human fetal retinal pigment epithelial cells [169]. The alteration of *SMAD3* expression is indicative of TGFβ signaling activation which determines the aggressive phenotype of melanomas[171]. As mentioned above, TGFβ has the capability of inducing hepcidin that in turn suppresses FPN-1 protein to limit iron-exporting in tumor cells [172]. The role of TGFβ in hepcidin induction appears to rely on TGFβ1 type I receptor (ALK5) and TGFβ1 type II receptor (TβRII) which are associated with Smad1/5/8 phosphorylation. Additionally, TGFβ1 expression has been found to increase in response to iron overload which suggests TGFβ1 may activate hepcidin synthesis. However, it has been also reported that the simultaneously increased Smad2/3 phosphorylation induced by TGFβ1 is able to negatively regulate hepcidin expression by conquering Smad1/5/8 phosphorylation [173]. This enrichment of complex properties suggests that a multiplicity of hepcidin/FPN-1 regulations may be existed during melanoma differentiation and potentially account for the importance of iron export modulated by a flexible regulation of hepcidin/FPN-1. The observation of *CTNNB1* overexpression during differentiation may further signify the role of iron in melanoma progression as iron is able to enhance the WNT signaling pathway associated with the loss of the *APC* gene in colon cancers [174]. Iron blocking by iron chelators indeed dramatically weakens WNT signaling and reduced the viability of cancer cells. c-Myc, which is localized downstream of WNT, can trigger the TfR-1 expression in colon cancers [174,175]. The above evidence indicates that iron is a prerequisite involved in melanoma differentiation. However, these are still insufficient to explain why dedifferentiated melanoma renders more susceptibility to ferroptosis in contrast to the melanocytic subtype. We reason that there are two main possibilities that might be involved. Firstly, melanoma differentiation is a long-period process and the plasticity of melanoma cells may adopt an alteration of both differentiated and dedifferentiated stages for optimization or survival. During the differentiation trajectory, iron uptake is indispensably required to maintain cell proliferation as well as aggressive phenotypes, irrespective of the multi-stage dedifferentiation. Simultaneously, the level of intracellular iron is supposed to be sufficient and irreversibly altered even though the expression levels of the corresponding gene which may potentially participate in iron regulation would be reversed. Thereby, it may cause dedifferentiated melanomas more susceptible to ferroptosis. Of note, E-cadherin, which provides an inhibitory effect on melanoma growth and invasion, can be remarkably reduced by iron overloading [176,177]. Secondly, despite the switched melanoma towards the dedifferentiated stage showing resistance to vemurafenib-induced apoptosis, intracellular levels of GSH and GSSG are somehow much lower in such dedifferentiated cells. It is unclear the

reason why dedifferentiated melanoma cells possess much lower levels of GSH and GSSG. We propose that one reasonable possibility is due to the rapid exhaustion of GSH and GSSG during melanoma cells metastasizing. A higher level of GSH and GSSG are needed and robustly consumed to counteract the accompanied generation of ROS during metastasis and invasion. It is worth stressing that 35–50% of BRAF-mutant and wild-type cell lines as well as patient samples of melanoma have been characterized as "High-OXPHOS" [178,179]. Therefore, induction of ferroptosis may potentially conquer the dedifferentiated melanoma cells undergoing metastasizing.

In addition, ferroptosis can be also induced by the administration of PD-L1 blockade in melanoma cells [22]. $CD8^+$ T cells are massively activated result of PD-L1 blockade treatment and consequently induce lipid peroxidation in melanoma cells. Mechanistically, interferon-gamma (IFNγ) liberated from $CD8^+$ T cells has been shown to play the central role in ferroptosis by suppressing the expression of *SLC3A2* and *SLC7A11* to impede the cysteine uptake and GSH biosynthesis. A combined treatment of IFNγ and erastin has synergistically reduced the intracellular GSH. Yet, it is unknown whether and how an alteration of iron metabolism plays an important role in PD-L1-blockade induced ferroptosis in both of melanoma cells and T cells. It will be interesting to figure out the reason why a significantly increased lipid ROS specifically occurs in melanoma but not the $CD8^+$ T cells, and whether there is an alteration of iron metabolism in $CD8^+$ T cells in response to PD-L1 blockade treatment. It should be noted that, as the result of enlarged labile iron poor which is characterized by cells undergoing ferroptosis, a culminated amount of catalytic iron might be released from the dying cells and the freedom of catalytic iron has been shown to suppress the function of surrounding T cells in the tumor microenvironment [180–182]. In addition to $CD8^+$ T cells, excessive iron may also abrogate the activity of helper $CD4^+$ T cells [183]. It has been indicated that iron accumulation dictates the pathogenicity of T_{Helper} cells which associates with PCBP11 (an RNA-binding protein) mediated production cytokines. The stabilized PCBP1 resulting from intracellular iron overload will stabilize granulocyte-macrophage colony-stimulating factor (GM-CSF) mRNA to stimulate GM-CSF translation which is indispensable for the pathogenicity of multiple autoimmune disorders.

As emphasized above, although a plethora of studies have emphasized the blueprint of ferroptosis as a novel option for cancer therapy, the concept of ferroptosis side effects thus far has not been evaluated. As iron acts as a "double-edged sword" and even indispensably for ferroptosis, the liberation of catalytic iron has various capabilities of affecting cellular activities. In the near future, it is better to investigate the potential side effects caused by ferroptosis on cancer therapy as well as the impact of cytotoxicity on nearby health tissues prior to the widespread clinical application.

3.2.4. Ferroptosis in embryogenesis

Programmed cell death has been recognized as a key process involved in tissue or organ formation during embryonic development [184,185]. Apart from apoptosis, thus far, it is poorly understood whether other types of cell death are involved in embryogenesis. It is worth mentioning that both ROS and corresponding scavenger levels are elevated to contribute to tissue differentiation and integrity [186–189]. The previous study has discovered an enhancement of lipid peroxidation occurs as development proceeds. Malondialdehyde (MDA), an oxidized form of polyunsaturated fatty acids, is remarkably elevated accompanied by the cumulative amount of oxygen consumption during embryonic development. Moreover, genes encoding the superoxide dismutase and catalase are also increased and detection of either peroxidase expression or activity is restricted in the non-apoptotic tissues such as digits but not the interdigital forms during the developing process in mice [190]. We hypothesize that ferroptosis is highly relevant to both embryonic and fetal status in which a cumulative amount of iron is needed to meet normal development. In human pregnancy, iron transporting is well handled by the maternal-placental-fetal unit [191]. Maternal hepcidin, but not embryo hepcidin, has been uncovered to limit embryo iron endowment and the hepcidin-modulated maternal iron restriction during pregnancy can contribute to embryo anemia and lethality by degrading FPN-1 [192,193]. Therefore, limited maternal hepcidin profoundly pursues iron transfer across the placenta to the embryo/fetus to ensure adequate iron availability for embryogenesis. Intriguingly, hepcidin is refrained by estrogen which is culminated in pregnancy of a woman throughout her entire life [194].

In addition to systemic (liver) hepcidin, some other studies have suggested the importance of cardiac hepcidin in heart morphogenesis and development[158,195,196]. The transformation of the endocardial cushion into valves and septa plays an essential and initiated role in the formatting of a four-chambered heart which requires tight maintenance of iron-homeostasis, precise patterns of programmed cell death as well as expression of key regulators such as bone morphogenetic proteins (BMPs) and MSX2[197,198]. The expression of BMP2, BMP4, and MSX2 has been proposed in tissue transformation and differentiation during earlier embryonic hearts[195]. Both BMP2 and BMP4 as well as BMP9 are able to improve the hepcidin expression which in turn destabilizes the FPN-1 protein[158]. Additionally, BMP6 has also been considered as a key endogenous regulator of hepcidin expression and iron metabolism [156,199]. Moreover, BMP4 proteins enable the induction of cell death via MSX2, which are expressed at sites where the developing limb and the cephalic neural crest[198,200]. Hence, based on the coincided expression of BMP4 and MSX2 in the cell lethal region, and the promotive role of other BMP proteins in facilitating hepcidin expression and increasing the local iron concentration, we suggest ferroptosis might be involved in the embryonic development of the heart.

In addition to hepcidin, the link of IRP1/2 to ferroptosis has been also addressed in embryogenesis. Loss of IRP1/2 shows an iron deficiency, brown discoloration and abnormal morphology during embryonic development in mice [201,202]. The previous study has concluded that homozygous deletion of IRP2 in combination with heterozygous IRP1 develops more severe anemia and neurodegeneration in contrast to deletion of IRP2 alone. However, mice that lack IRP1 displayed no overt abnormalities during embryonic development. Although IRP1 has a minimal role in direct sensing of cellular iron status in comparison with IRP2, IRP1 may be involved in ferroptosis in an alternative way which is associated with its aconitase activity [203,204]. Cytosolic aconitase is able to trigger the biosynthesis of glutamate and the downstream conversion of isocitrate to alpha-ketoglutarate (α-KG) [203,205]. Either glutamate or αKG has the capability of triggering ferroptosis [7]. In the trophoblast cells, which are key components in the placental, IRP1 is predominantly involved in sensing iron status in contrast to IRP2 [192]. The overwhelming function of IRP1 in placental iron transporting compared to IRP2 may account for the importance of aconitase activity in trophoblast cells. Of note, the mitochondrial isoform of aconitase not only drives mitochondrial iron metabolism, but also may compensate for the loss of enzymatic activity of cytosol IRP1 [203]. Similarly, IRP2 loss can also compromise mitochondrial function by reducing frataxin and IscU levels and repressing mitochondrial function in embryonic fibroblasts [206]. More importantly, IRP2 has been uncovered to modulate the switch from aerobic glycolysis to oxidative phosphorylation in mouse embryonic cells [207]. In the coming days, elucidating the role of cytosol IRP1/2 and mitochondrial aconitase in embryogenesis will improve the understanding of ferroptosis [197].

Despite iron deficiency having causal links to developmental anomaly and malformation as well as early embryonic lethality, we should realize that it is unclear whether such embryonic defects are directly contributed by iron deficiency or attributable to lacking ferroptosis. Indeed, the previous study has shown maternal iron deficiency can induce abnormalities in cardiovascular development and early lethality exhibiting a delayed regression of pharyngeal arch artery (PAA2), persistent right dorsal aorta and overlarge outflow tract. These retardations of development suggest ferroptosis may be involved in the

early development of the heart[192].

4. Targeting ferroptosis in diseases

We can utilize the ferroptosis-inducing system to induce cancer cell ferroptosis and the defense systems to inhibit ferroptosis in normal cells. Ferroptosis inhibition can be achieved by the activation of the GPX4-GSH system, FSP1-CoQ10 pathway, GCH1-BH4 pathway and the DHODH-$CoQH_2$ system.

4.1. Ferroptosis- inducing system

Cancer cells exhibit an increased iron demand compared with normal cells, which made them more vulnerable to ferroptosis[208]. Targeting ferroptosis as a vulnerability in cancer would be a potential therapy. Ferroptosis can be induced by various small molecules named ferroptosis inducers (Table 1). They can be divided into the following categories: 1) Type I compounds inhibit SLC7A11-mediated cystine uptake and reduce the GSH level. Erastin is the most widely used inhibitor of this type. Sulfasalazine is an FDA-approved anti-inflammatory drug which can inhibit tumor growth in glioblastoma, the combinational therapy with radiotherapy is on clinical trial now (NCT04205357)[209,210]. In cancer stem cells, transcription factor SOX2 confers ferroptosis resistance in lung cancer via upregulation of SLC7A11 [211], targeting cancer stem cells via ferroptosis induction by inhibiting SLC7A11 will be a potential therapy method in lung cancer. 2) Type II compounds suppress the activity of GPX4, such as RSL3, ML162. 3) Type III compounds inhibit GPX4 and ubiquinone such as FIN56. 4) Type IV is iron-loading related compounds such as $FeCl_2$. 5) Type V compounds oxidize the iron and induce lipid ROS.

4.2. Ferroptosis inhibition system

Ferroptosis inhibition can be achieved by the activation of the GPX4-GSH system, FSP1-CoQ10 pathway, GCH1-BH4 pathway and the DHODH-$CoQH_2$ system. The working mechanisms of these four pathways were discussed in part 2. The activation of GPX4, upregulation of SLC7A11 or increase expression of anti-oxidant proteins can inhibit ferroptosis. Moreover, other methods which can suppress PUFA oxidation or restrict the labile iron pool also inhibit ferroptosis [107]. A recent study indicates that NUPR1, a stress-inducible transcription factor, is a critical repressor of ferroptosis [236].

Besides the above pathways, there are many small molecules inhibiting ferroptosis, the discovered small molecules and their working mechanisms are shown in Table 2. At present, the common ferroptosis inhibitors mainly aim at the two important characteristics of ferroptosis: iron overload and lipid peroxide accumulation, which play an important role by reducing free iron, eliminating free radicals, and inhibiting lipid peroxidation.

4.3. Targeting ferroptosis in clinical trials

The earlier study indicated that ferroptosis played an important role in the suppression of tumor progression. Even ferroptosis inducers and inhibitors were developed a lot, however, targeting ferroptosis going forward to clinical trial still confronts lots of challenges. How to induce cancer cells into ferroptosis safely and with high effectiveness is a difficult question.

Sorafenib is a first-line drug approved by the FDA and widely used in the treatment of advanced liver cancer, usually, it doesn't induce apoptosis, but it can promote cancer cells into ferroptosis. The loss of leukemia inhibitory factor receptor (LIFR) activates the NF-kB pathway and thus upregulates the iron chelator LCN2, which prompts tumor progression and leads to drug resistance of ferroptosis inducers[256]. It is also reported that YAP/TAZ and ATF4 drive resistance to Sorafenib in hepatocellular carcinoma by repressing Sorafenib-induced ferroptosis

Table 1
Ferroptosis inducers.

compound	target	mechanism	reference
erastin	SLC7A11, GPX4 inactivation due to GSH depletion (class I FINs)	lipid ROS	[3,27]
piperazine erastin	SLC7A11	increases in PTGS2 mRNA regression HT1080 xenografts	[8]
imidazole ketone erastin	SLC7A11	Inhibits lipid ROS	[212,213]
sulfasalazine	SLC7A11	death inhibited by DFO, Fer1, and Trolox	[3,214]
sorafenib	SLC7A11	lipid ROS death inhibited by DFO and Fer1	[215]
glutamate	SLC7A11	inhibited by CPX and Fer1	[3]
buthionine sulfoximine (BSO)	glutamate-cysteine ligase	lipid ROS	[8,216]
artesunate	glutathione S-transferase	lipid ROS death inhibited by DFO, Fer1, and Trolox	[217,218]
DPI2	unknown	death inhibited by DFO and α-Toc	[8]
[Cys] depletion	cyst(e)inase	reduces GSH levels regression of MDA-MB-361, DU145 and PC3 xenografts	[219]
BAY 87–2243	ND dehydrogenase	lipid ROS death inhibited by Fer1 and α-Toc	[138,220]
1 *S*,3*R*-RSL3	GPX4 inactivation/ depletion (class II, III FINs)	lipid ROS death inhibited by DFO and Fer1 increase in PTGS2 mRNA HT1080 tumor regression	[3,8,58]
DPI7	GPX4	lipid ROS	[8,221]
ML210/JKE1674	GPX4	Inhibiting GPX4 using masked nitrile-oxide electrophiles	[222]
altretamine	GPX4	lipid ROS	[59]
FIN56	GPX4 and ubiquinone	lipid ROS death inhibited by DFO and α-Toc	[223,224]
withaferin A	GPX4	lipid ROS in neuroblastoma cells death inhibited by DFO, Fer1 and α-Toc	[225]
FIN56	Squalene synthase	increase lipid ROS death inhibited by DFO and α-Toc	[223,224]
fluvastatin, lovastatin acid, simvastatin	HMG-CoA reductase	lipid ROS	[224,226]
hemoglobin	Iron loading (class IV FINs)	lipid ROS death inhibited by Fer1 in organotypic hippocampal slice cultures	[227]
$FeCl_2$	Iron loading	death inhibited by Fer1 in organotypic hippocampal slice cultures	[227]
hemin	Iron loading	death inhibited by DFO and Fer1	[225,228,229]
$(NH_4)_2Fe(SO_4)_2$	Iron loading	death inhibited by Fer1	[225]
non-thermal plasma	Iron loading	lipid ROS death inhibited by DFO	[132,230]
salinomycin	Iron loading		[231]

(*continued on next page*)

Table 1 (*continued*)

compound	target	mechanism	reference
		lipid ROS death inhibited by Fer1	
amino acid depletion + Cornell dots	Iron loading	lipid ROS death inhibited by Fer1 and Trolox	[232]
lapatinib + siramesine	transferrin ↑ ferroportin-1 ↓	death inhibited by DFO and Fer1	[145]
$FINO_2$	Iron oxidation	lipid ROS death inhibited by Fer1	[223]
withaferin A	Increase in LIP by HMOX1 KEAP1 inactivation KEAP1 inactivation	lipid ROS n neuroblastoma death inhibited by DFO, Fer1 and α-Toc	[225]
lanperisone	unknown	death inhibited by DFO and Trolox	[233]
artemisinin derivatives	unknown	death inhibited by DFO and Fer1	[234, 235]
CIL41, CIL56, CIL69, CIL70, CIL75, and CIL79	unknown	lipid ROS for CIL56 death inhibited by DFO and α-Toc	[224]

Table 2
Ferroptosis inhibitors.

compound	Inhibition target	mechanism	reference
BRD4770	Protect cystine deprivation	inhibiting the inflammatory response, lipid peroxidation and ferroptosis	[237]
ferrostatin-1	antioxidant	inhibition of ferrous iron and lipid hydroperoxide dependent peroxidation	[238]
liproxstatin-1	restore the redox equilibrium	protecting mitochondrial functions and ameliorating lipid peroxidation	[239]
Deferoxamine mesylate	Iron chelator	reducing the iron	[240]
UAMC-3203	antioxidant	capture antioxidant	[241]
Liproxstain-1	antioxidant	scavenging ROS, activating Nrf2 pathway and rescue the GPX4 level	[242]
Trolox	antioxidant	inhibiting lipid oxidation	[243]
XJB-5–131	antioxidant	scavenging ROS in mitochondria	[244]
Deferasirox	Iron chelator	reducing the free iron ion, inhibiting Fenton reaction	[245]
Zileuton	LOX inhibitor	inhibiting 5-LOX	[246]
AA861	LOX inhibitor	inhibiting 5-LOX	[247]
PD146176	LOX inhibitor	inhibiting 15-LOX	[248]
Baicalein	LOX inhibitor	inhibiting 12/15-LOX and up-regulating GPX4	[249]
Troglitazone	ACSL4 inhibitor	inhibiting ACSL4 function,	[250]
Rosiglitazone	ACSL4 inhibitor	inhibiting the activation of	[251]
Piogliatazone	ACSL4 inhibitor	PUFA and phosphitylation, reducing the production of lipid peroxide	[252]
TEMPO	Nitrogenoxides	inhibiting Fenton reaction, suppressing the generation of hydroxyl radicals	[253]
selenium	Selenium supplementation	supplementing GPX4	[254]
Vitamin E	Anti-oxidant	rescues the Gpx4-deficient HSPCs from ferroptosis	[255]

[257].

Compared to the ferroptosis-inducers used in cancer treatment, the clinical trials of ferroptosis-inhibitors' application in clinal trials are more promising. Inhibitors regulation iron metabolism or function as antioxidants in targeting neurodegeneration has been widely applied in clinical trials. For example, DFP reduced SN iron deposition and progression of motor handicap in Parkinson's Disease and it is in Phase II clinical trials now (NCT00943748, NCT01539837)[258,259]. Moreover, the antioxidants including N-acetylcysteine (NAC) (NCT02212678)[260], GSH (NCT02424708)[261], Vitamin E (IRCT201604035623N73)[262] and CoQ10 (NCT01892176)[263] have shown beneficial effects in PD patients.

5. Conclusion and perspectives

In this article, we have retrospected, refined and extended the role of ferroptosis in both cancers and embryogenesis surrounding the viewpoint of iron metabolism. We believe that ferroptosis can enable a great improvement in the therapeutic modality for cancers. The malignant neoplasms are characterized by higher proliferation, invasiveness and metastasis, in a large part, attributed to dysregulated levels of lipid and catalytic iron which are fundamental components involved in all cell maturation. Although the increased iron supply and accelerated lipid production satisfy the demand of cancer cells to boost cancer cell division and spreading, excessive iron will greatly accelerate lipid peroxidation which consequently gives rise to higher vulnerability to ferroptosis. Future studies are needed to elucidate the details of crosstalk between iron- and lipid metabolisms in ferroptosis which are remained poorly known thus far. Moreover, it is still obscure whether lipid peroxidation plays the role of an executioner in killing cells. Since many intensive studies have also indicated that products of lipid peroxidation are involved in maintaining proper signaling transduction under physiological conditions [264]. We should realize that ferroptosis features iron addiction and tightly correlates to mitochondrial activity. Unlike apoptosis, which is remarkably dictated by the collapse of mitochondrial activity [265]. Ferroptosis, however, favors a transient activation of mitochondria and reduced activity of mitochondria preserves cells against ferroptosis suggesting an effect of reciprocal inhibitory may exist between apoptosis and ferroptosis. Besides, we should remind that although the Warburg effect dominates the energy acquisition in most solid malignancies, it is not as universal as assumed previously, since the OXPHOS is also required by many types of cancers to meet their energy demand [94,266,267]. It is better to evaluate the distinctive vulnerabilities to ferroptosis by comparison between glycolysis and OXPHOS stages in various types of cancers. We believe re-routing cancer cells from glycolysis to OXPHOS may potentially enhance the susceptibility to drug-induced ferroptosis. Moreover, considering the important role of iron in mitochondrial activity and iron overload in mitochondria may be involved in initiating the ferritonophagy process. Therefore, mitochondrial iron might be a potential target of ferroptosis induction.

In another part of this review, we have underlined the role of ferroptosis in embryogenesis which is still unclarified thus far. However, given the importance of iron accessibility from the mother to the developing embryo and the dramatic discovery of lipid ROS products during embryonic formation, we speculate ferroptosis is supposed to play an indispensable role in morphogenesis which accurately processes the spatial distribution of cells throughout embryonic development. Maternal hepcidin has been found to maintain an adequate level of iron transporting from mother to fetus, while the function of hepcidin in an embryo or fetus is still unclear thus far. Future studies are necessary to not only illuminate the role of ferroptosis, but also distinguish the types of cell death during embryogenesis. Investigation of the role of embryonic hepcidin in development as well as ferroptosis might be valued.

As summarized above, targeting ferroptosis has emerged as a beneficial strategy to promote clinical efficacy against cancers. It may be also utilized to improve the understanding of congenital disorders such as congenital heart disease. As the fundamental element, iron distribution is dynamically and strictly regulated throughout all human organisms. However, regulation of iron metabolism including transporting and storage verifies in differential types of cancers and other diseases. This character may in part explains the reason why there is a wide range of difference in ferroptosis sensitivity among various types of cancer cells.

A better understanding of iron metabolism will provide valuable insights into the underlying mechanisms of ferroptosis.

Declarations ethics approval and consent to participate

Not applicable.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

References

[1] R.C. Taylor, S.P. Cullen, S.J. Martin, Apoptosis: controlled demolition at the cellular level, Nat. Rev. Mol. Cell Bio 9 (3) (2008) 231–241.
[2] W.X. Zong, C.B. Thompson, Necrotic death as a cell fate, Gene Dev. 20 (1) (2006) 1–15.
[3] S.J. Dixon, K.M. Lemberg, M.R. Lamprecht, R. Skouta, E.M. Zaitsev, C.E. Gleason, D.N. Patel, A.J. Bauer, A.M. Cantley, W.S. Yang, 3rd Morrison B, B.R. Stockwell, Ferroptosis: an iron-dependent form of nonapoptotic cell death, Cell 149 (5) (2012) 1060–1072.
[4] T. Bergsbaken, S.L. Fink, B.T. Cookson, Pyroptosis: host cell death and inflammation, Nat. Rev. Microbiol 7 (2) (2009) 99–109.
[5] M. Conrad, V.E. Kagan, H. Bayir, G.C. Pagnussat, B. Head, M.G. Traber, B. R. Stockwell, Regulation of lipid peroxidation and ferroptosis in diverse species, Genes Dev. 32 (9–10) (2018) 602–619.
[6] A.R. Bogdan, M. Miyazawa, K. Hashimoto, Y. Tsuji, Regulators of iron homeostasis: new players in metabolism, cell death, and disease, Trends Biochem Sci. 41 (3) (2016) 274–286.
[7] M. Gao, J. Yi, J. Zhu, A.M. Minikes, P. Monian, C.B. Thompson, X. Jiang, Role of mitochondria in ferroptosis, Mol. Cell 73 (2) (2019) 354–363, e3.
[8] W.S. Yang, R. SriRamaratnam, M.E. Welsch, K. Shimada, R. Skouta, V. S. Viswanathan, J.H. Cheah, P.A. Clemons, A.F. Shamji, C.B. Clish, L.M. Brown, A. W. Girotti, V.W. Cornish, S.L. Schreiber, B.R. Stockwell, Regulation of ferroptotic cancer cell death by GPX4, Cell 156 (1–2) (2014) 317–331.
[9] B. Silva, P. Faustino, An overview of molecular basis of iron metabolism regulation and the associated pathologies, Biochim Biophys. Acta 1852 (7) (2015) 1347–1359.
[10] R. Eid, N.T. Arab, M.T. Greenwood, Iron mediated toxicity and programmed cell death: A review and a re-examination of existing paradigms, Biochim Biophys. Acta Mol. Cell Res. 1864 (2) (2017) 399–430.
[11] H. Kawabata, Transferrin and transferrin receptors update, Free Radic. Biol. Med. 133 (2019) 46–54.
[12] R.S. Ohgami, D.R. Campagna, E.L. Greer, B. Antiochos, A. McDonald, J. Chen, J. J. Sharp, Y. Fujiwara, J.E. Barker, M.D. Fleming, Identification of a ferrireductase required for efficient transferrin-dependent iron uptake in erythroid cells, Nat. Genet 37 (11) (2005) 1264–1269.
[13] A.C. Illing, A. Shawki, C.L. Cunningham, B. Mackenzie, Substrate profile and metal-ion selectivity of human divalent metal-ion transporter-1, J. Biol. Chem. 287 (36) (2012) 30485–30496.
[14] K.H. Zhang, H.Y. Tian, X. Gao, W.W. Lei, Y. Hu, D.M. Wang, X.C. Pan, M.L. Yu, G. J. Xu, F.K. Zhao, J.G. Song, Ferritin heavy chain-mediated iron homeostasis and subsequent increased reactive oxygen species production are essential for epithelial-mesenchymal transition, Cancer Res 69 (13) (2009) 5340–5348.
[15] R. Vidal, L. Miravalle, X. Gao, A.G. Barbeito, M.A. Baraibar, S.K. Hekmatyar, M. Widel, N. Bansal, M.B. Delisle, B. Ghetti, Expression of a mutant form of the ferritin light chain gene induces neurodegeneration and iron overload in transgenic mice, J. Neurosci. 28 (1) (2008) 60–67.
[16] D.M. Ward, J. Kaplan, Ferroportin-mediated iron transport: expression and regulation, Biochim. Biophys. Acta 1823 (9) (2012) 1426–1433.
[17] O. Kakhlon, Z.I. Cabantchik, The labile iron pool: characterization, measurement, and participation in cellular processes(1), Free Radic. Biol. Med. 33 (8) (2002) 1037–1046.
[18] Y. Mou, J. Wang, J. Wu, D. He, C. Zhang, C. Duan, B. Li, Ferroptosis, a new form of cell death: opportunities and challenges in cancer, J. Hematol. Oncol. 12 (1) (2019) 34.
[19] Y. Yu, L. Jiang, H. Wang, Z. Shen, Q. Cheng, P. Zhang, J. Wang, Q. Wu, X. Fang, L. Duan, S. Wang, K. Wang, P. An, T. Shao, R.T. Chung, S. Zheng, J. Min, F. Wang, Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis, Blood 136 (6) (2020) 726–739.
[20] X. Fang, Z. Cai, H. Wang, D. Han, Q. Cheng, P. Zhang, F. Gao, Y. Yu, Z. Song, Q. Wu, P. An, S. Huang, J. Pan, H.Z. Chen, J. Chen, A. Linkermann, J. Min, F. Wang, Loss of cardiac ferritin H facilitates cardiomyopathy via Slc7a11-mediated ferroptosis, Circ. Res. 127 (4) (2020) 486–501.
[21] J.P.F. Angeli, D.V. Krysko, M. Conrad, Ferroptosis at the crossroads of cancer-acquired drug resistance and immune evasion, Nat. Rev. Cancer 19 (7) (2019) 405–414.
[22] W. Wang, M. Green, J.E. Choi, M. Gijon, P.D. Kennedy, J.K. Johnson, P. Liao, X. Lang, I. Kryczek, A. Sell, H. Xia, J. Zhou, G. Li, J. Li, W. Li, S. Wei, L. Vatan, H. Zhang, W. Szeliga, W. Gu, R. Liu, T.S. Lawrence, C. Lamb, Y. Tanno, M. Cieslik, E. Stone, G. Georgiou, T.A. Chan, A. Chinnaiyan, W. Zou, CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy, Nature 569 (7755) (2019) 270–274.
[23] E. Lachaier, C. Louandre, C. Godin, Z. Saidak, M. Baert, M. Diouf, B. Chauffert, A. Galmiche, Sorafenib induces ferroptosis in human cancer cell lines originating from different solid tumors, Anticancer Res. 34 (11) (2014) 6417–6422.
[24] J. Wu, A.M. Minikes, M. Gao, H. Bian, Y. Li, B.R. Stockwell, Z.N. Chen, X. Jiang, Intercellular interaction dictates cancer cell ferroptosis via NF2-YAP signalling, Nature 572 (7769) (2019) 402–406.
[25] N. Yan, J. Zhang, Iron metabolism, ferroptosis, and the links with Alzheimer's disease, Front. Neurosci. 13 (2019) 1443.
[26] A. Weiland, Y. Wang, W. Wu, X. Lan, X. Han, Q. Li, J. Wang, Ferroptosis and its role in diverse brain diseases, Mol. Neurobiol. 56 (7) (2019) 4880–4893.
[27] S. Dolma, S.L. Lessnick, W.C. Hahn, B.R. Stockwell, Identification of genotype-selective antitumor agents using synthetic lethal chemical screening in engineered human tumor cells, Cancer Cell 3 (3) (2003) 285–296.
[28] D. Vigil, J. Cherfils, K.L. Rossman, C.J. Der, Ras superfamily GEFs and GAPs: validated and tractable targets for cancer therapy? Nat. Rev. Cancer 10 (12) (2010) 842–857.
[29] N. Yagoda, M. von Rechenberg, E. Zaganjor, A.J. Bauer, W.S. Yang, D.J. Fridman, A.J. Wolpaw, I. Smukste, J.M. Peltier, J.J. Boniface, R. Smith, S.L. Lessnick, S. Sahasrabudhe, B.R. Stockwell, RAS-RAF-MEK-dependent oxidative cell death involving voltage-dependent anion channels, Nature 447 (7146) (2007) 864–868.
[30] X. Sun, Z. Ou, M. Xie, R. Kang, Y. Fan, X. Niu, H. Wang, L. Cao, D. Tang, HSPB1 as a novel regulator of ferroptotic cancer cell death, Oncogene 34 (45) (2015) 5617–5625.
[31] H. Huo, Z. Zhou, J. Qin, W. Liu, B. Wang, Y. Gu, Erastin disrupts mitochondrial permeability transition pore (mPTP) and induces apoptotic death of colorectal cancer cells, PLoS One 11 (5) (2016), e0154605.
[32] C. Liang, X. Zhang, M. Yang, X. Dong, Recent progress in ferroptosis inducers for cancer therapy, Adv. Mater. 31 (51) (2019), e1904197.
[33] M. Sato, R. Kusumi, S. Hamashima, S. Kobayashi, S. Sasaki, Y. Komiyama, T. Izumikawa, M. Conrad, S. Bannai, H. Sato, The ferroptosis inducer erastin irreversibly inhibits system xc- and synergizes with cisplatin to increase cisplatin's cytotoxicity in cancer cells, Sci. Rep. 8 (1) (2018) 968.
[34] C.G. Holmberg, C.B. Laurell, Investigations in serum copper; nature of serum copper and its relation to the iron-binding protein in human serum, Acta Chem. Scand. 1 (10) (1947) 944–950.
[35] Nutrition classics. Acta Chemica Scandinavica, Volume 1, 1947: The iron-binding protein of swine serum. By C. B. Laurell and B. Ingelman, Nutr Rev.43(7) (1985) 209–11.
[36] J.H. Jandl, J.K. Inman, R.L. Simmons, D.W. Allen, Transfer of iron from serum iron-binding protein to human reticulocytes, J. Clin. Invest. 38(1, Part 1 (1959) 161–185.
[37] P. Aisen, Transferrin receptor 1, Int J. Biochem Cell Biol. 36 (11) (2004) 2137–2143.
[38] P. Ponka, C.N. Lok, The transferrin receptor: role in health and disease, Int. J. Biochem Cell Biol. 31 (10) (1999) 1111–1137.
[39] S.P. Young, A. Bomford, R. Williams, The effect of the iron saturation of transferrin on its binding and uptake by rabbit reticulocytes, Biochem J. 219 (2) (1984) 505–510.
[40] I. Yanatori, F. Kishi, DMT1 and iron transport, Free Radic. Biol. Med 133 (2019) 55–63.
[41] E. Nemeth, M.S. Tuttle, J. Powelson, M.B. Vaughn, A. Donovan, D.M. Ward, T. Ganz, J. Kaplan, Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization, Science 306 (5704) (2004) 2090–2093.

[42] N. Song, J. Wang, H. Jiang, J. Xie, Ferroportin1 and hephaestin overexpression attenuate iron-induced oxidative stress in MES23.5 dopaminergic cells, J. Cell Biochem 110 (5) (2010) 1063–1072.
[43] N. Geng, B.J. Shi, S.L. Li, Z.Y. Zhong, Y.C. Li, W.L. Xua, H. Zhou, J.H. Cai, Knockdown of ferroportin accelerates erastin-induced ferroptosis in neuroblastoma cells, Eur. Rev. Med Pharm. Sci. 22 (12) (2018) 3826–3836.
[44] K.K. Singh, V. Ayyasamy, K.M. Owens, M.S. Koul, M. Vujcic, Mutations in mitochondrial DNA polymerase-gamma promote breast tumorigenesis, J. Hum. Genet. 54 (9) (2009) 516–524.
[45] C.A. Ferreira, D. Ni, Z.T. Rosenkrans, W. Cai, Scavenging of reactive oxygen and nitrogen species with nanomaterials, Nano Res 11 (10) (2018) 4955–4984.
[46] C.A.K. Lundgren, D. Sjostrand, O. Biner, M. Bennett, A. Rudling, A.L. Johansson, P. Brzezinski, J. Carlsson, C. von Ballmoos, M. Hogbom, Scavenging of superoxide by a membrane-bound superoxide oxidase, Nat. Chem. Biol. 14 (8) (2018) 788–793.
[47] E. Park, S.W. Chung, ROS-mediated autophagy increases intracellular iron levels and ferroptosis by ferritin and transferrin receptor regulation, Cell Death Dis. 10 (11) (2019) 822.
[48] H. Yu, P. Guo, X. Xie, Y. Wang, G. Chen, Ferroptosis, a new form of cell death, and its relationships with tumourous diseases, J. Cell Mol. Med 21 (4) (2017) 648–657.
[49] G.O. Latunde-Dada, Ferroptosis: Role of lipid peroxidation, iron and ferritinophagy, Biochim Biophys. Acta Gen. Subj. 1861 (8) (2017) 1893–1900.
[50] J.Y. Cao, S.J. Dixon, Mechanisms of ferroptosis, Cell Mol. Life Sci. 73 (11–12) (2016) 2195–2209.
[51] M.P. Murphy, How mitochondria produce reactive oxygen species, Biochem J. 417 (2009) 1–13.
[52] N.M. Mazure, VDAC in cancer, Biochim. Biophys. Acta Bioenerg. 1858 (8) (2017) 665–673.
[53] T. Becker, R. Wagner, Mitochondrial outer membrane channels: emerging diversity in transport processes, Bioessays 40 (7) (2018), e1800013.
[54] E.N. Maldonado, VDAC-tubulin, an anti-warburg pro-oxidant switch, Front Oncol. 7 (2017) 4.
[55] F. Ursini, M. Maiorino, M. Valente, L. Ferri, C. Gregolin, Purification from pig-liver of a protein which protects liposomes and biomembranes from peroxidative degradation and exhibits glutathione-peroxidase activity on phosphatidylcholine hydroperoxides, Biochim. Et. Biophys. Acta 710 (2) (1982) 197–211.
[56] M. Deponte, Glutathione catalysis and the reaction mechanisms of glutathione-dependent enzymes, Biochim Biophys. Acta 1830 (5) (2013) 3217–3266.
[57] F. Ursini, M. Maiorino, C. Gregolin, The selenoenzyme phospholipid hydroperoxide glutathione peroxidase, Biochim Biophys. Acta 839 (1) (1985) 62–70.
[58] W.S. Yang, B.R. Stockwell, Synthetic lethal screening identifies compounds activating iron-dependent, nonapoptotic cell death in oncogenic-RAS-harboring cancer cells, Chem. Biol. 15 (3) (2008) 234–245.
[59] J.H. Woo, Y. Shimoni, W.S. Yang, P. Subramaniam, A. Iyer, P. Nicoletti, M. Rodriguez Martinez, G. Lopez, M. Mattioli, R. Realubit, C. Karan, B. R. Stockwell, M. Bansal, A. Califano, Elucidating compound mechanism of action by network perturbation analysis, Cell 162 (2) (2015) 441–451.
[60] A. Seiler, M. Schneider, H. Forster, S. Roth, E.K. Wirth, C. Culmsee, N. Plesnila, E. Kremmer, O. Radmark, W. Wurst, G.W. Bornkamm, U. Schweizer, M. Conrad, Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lip-oxygenase dependent- and AIF-mediated cell death, Cell Metab. 8 (3) (2008) 237–248.
[61] O. Canli, Y.B. Alankus, S. Grootjans, N. Vegi, L. Hultner, P.S. Hoppe, T. Schroeder, P. Vandenabeele, G.W. Bornkamm, F.R. Greten, Glutathione peroxidase 4 prevents necroptosis in mouse erythroid precursors, Blood 127 (1) (2016) 139–148.
[62] R. Kang, L. Zeng, S. Zhu, Y. Xie, J. Liu, Q. Wen, L. Cao, M. Xie, Q. Ran, G. Kroemer, H. Wang, T.R. Billiar, J. Jiang, D. Tang, Lipid peroxidation drives gasdermin D-mediated pyroptosis in lethal polymicrobial sepsis, Cell Host Microbe 24 (1) (2018) 97–108, e4.
[63] S. Doll, F.P. Freitas, R. Shah, M. Aldrovandi, M.C. da Silva, I. Ingold, A.G. Grocin, T.N.X. da Silva, E. Panzilius, C.H. Scheel, A. Mourao, K. Buday, M. Sato, J. Wanninger, T. Vignane, V. Mohana, M. Rehberg, A. Flatley, A. Schepers, A. Kurz, D. White, M. Sauer, M. Sattler, E.W. Tate, W. Schmitz, A. Schulze, V. O'Donnell, B. Proneth, G.M. Popowicz, D.A. Pratt, J.P.F. Angeli, M. Conrad, FSP1 is a glutathione-independent ferroptosis suppressor, Nature 575 (7784) (2019), 693-+.
[64] Y. Ohiro, I. Garkavtsev, S. Kobayashi, K.R. Sreekumar, R. Nantz, B. T. Higashikubo, S.L. Duffy, R. Higashikubo, A. Usheva, D. Gius, N. Kley, N. Horikoshi, A novel p53-inducible apoptogenic gene, PRG3, encodes a homologue of the apoptosis-inducing factor (AIF), FEBS Lett. 524 (1–3) (2002) 163–171.
[65] K. Bersuker, J.M. Hendricks, Z. Li, L. Magtanong, B. Ford, P.H. Tang, M. A. Roberts, B. Tong, T.J. Maimone, R. Zoncu, M.C. Bassik, D.K. Nomura, S. J. Dixon, J.A. Olzmann, The CoQ oxidoreductase FSP1 acts parallel to GPX4 to inhibit ferroptosis, Nature 575 (7784) (2019) 688–692.
[66] K.R. Marshall, M. Gong, L. Wodke, J.H. Lamb, D.J.L. Jones, P.B. Farmer, N. S. Scrutton, A.W. Munro, The human apoptosis-inducing protein AMID is an oxidoreductase with a modified flavin cofactor and DNA binding activity, J. Biol. Chem. 280 (35) (2005) 30735–30740.
[67] X. Wei, X. Yi, X.H. Zhu, D.S. Jiang, Posttranslational modifications in ferroptosis, Oxid. Med Cell Longev. 2020 (2020) 8832043.
[68] S.J.F. Cronin, C. Seehus, A. Weidinger, S. Talbot, S. Reissig, M. Seifert, Y. Pierson, E. McNeill, M.S. Longhi, B.L. Turnes, T. Kreslavsky, M. Kogler, D. Hoffmann, M. Ticevic, D. da Luz Scheffer, L. Tortola, D. Cikes, A. Jais, M. Rangachari, S. Rao, M. Paolino, M. Novatchkova, M. Aichinger, L. Barrett, A. Latremoliere, G. Wirnsberger, G. Lametschwandtner, M. Busslinger, S. Zicha, A. Latini, S. C. Robson, A. Waisman, N. Andrews, M. Costigan, K.M. Channon, G. Weiss, A. V. Kozlov, M. Tebbe, K. Johnsson, C.J. Woolf, J.M. Penninger, The metabolite BH4 controls T cell proliferation in autoimmunity and cancer, Nature 563 (7732) (2018) 564–568.
[69] V.A.N. Kraft, C.T. Bezjian, S. Pfeiffer, L. Ringelstetter, C. Muller, F. Zandkarimi, J. Merl-Pham, X.W. Bao, N. Anastasov, J. Kossl, S. Brandner, J.D. Daniels, P. Schmitt-Kopplin, S.M. Hauck, B.R. Stockwell, K. Hadian, J.A. Schick, GTP cyclohydrolase 1/tetrahydrobiopterin counteract ferroptosis through lipid remodeling, ACS Central Sci 6 (1) (2020) 41–53.
[70] J. Xu, Y. Wu, P. Song, M. Zhang, S.X. Wang, M.H. Zou, Proteasome-dependent degradation of guanosine 5 '-triphosphate cyclohydrolase I causes tetrahydrobiopterin deficiency in diabetes mellitus, Circulation 116 (8) (2007) 944–953.
[71] S. Kojima, S. Ona, I. Iizuka, T. Arai, H. Mori, K. Kubota, Antioxidative activity of 5,6,7,8-tetrahydrobiopterin and its inhibitory effect on paraquat-induced cell toxicity in cultured rat hepatocytes, Free Radic. Res 23 (5) (1995) 419–430.
[72] M. Soula, R.A. Weber, O. Zilka, H. Alwaseem, K. La, F. Yen, H. Molina, J. Garcia-Bermudez, D.A. Pratt, K. Birsoy, Metabolic determinants of cancer cell sensitivity to canonical ferroptosis inducers, Nat. Chem. Biol. 16 (12) (2020) 1351–1360.
[73] Y. Zhou, L. Tao, X. Zhou, Z.P. Zuo, J. Gong, X.C. Liu, Y. Zhou, C.Q. Liu, N. Sang, H. Liu, J. Zou, K. Gou, X.W. Yang, Y.L. Zhao, DHODH and cancer: promising prospects to be explored, Cancer Metab. 9 (1) (2021).
[74] L. Mao, T. Zhao, Y. Song, L. Lin, X. Fan, B. Cui, H. Feng, X. Wang, Q. Yu, J. Zhang, K. Jiang, B. Wang, C. Sun, The emerging role of ferroptosis in non-cancer liver diseases: hype or increasing hope? Cell Death Dis. 11 (7) (2020) 518.
[75] K. Vasan, M. Werner, N.S. Chandel, Mitochondrial metabolism as a target for cancer therapy, Cell Metab. 32 (3) (2020) 341–352.
[76] J. Wu, Y. Wang, R.T. Jiang, R. Xue, X.H. Yin, M.C. Wu, Q.H. Meng, Ferroptosis in liver disease: new insights into disease mechanisms, Cell Death Discov. 7 (1) (2021).
[77] J.A. Kassis, J.A. Kennison, Recruitment of polycomb complexes: a role for SCM, Mol. Cell Biol. 30 (11) (2010) 2581–2583.
[78] K. Gnanapradeepan, S. Basu, T. Barnoud, A. Budina-Kolomets, C.P. Kung, M. E. Murphy, The p53 tumor suppressor in the control of metabolism and ferroptosis, Front. Endocrinol. 9 (2018).
[79] L. Jiang, N. Kon, T.Y. Li, S.J. Wang, T. Su, H. Hibshoosh, R. Baer, W. Gu, Ferroptosis as a p53-mediated activity during tumour suppression, Nature 520 (7545) (2015) 57.
[80] C. Huang, M. Yang, J. Deng, P. Li, W. Su, R. Jiang, Upregulation and activation of p53 by erastininduced reactive oxygen species contribute to cytotoxic and cytostatic effects in A549 lung cancer cells, Oncol. Rep. 40 (4) (2018) 2363–2370.
[81] Y. Xie, S. Zhu, X. Song, X. Sun, Y. Fan, J. Liu, M. Zhong, H. Yuan, L. Zhang, T. R. Billiar, M.T. Lotze, H.J. Zeh 3rd, R. Kang, G. Kroemer, D. Tang, The tumor suppressor p53 limits ferroptosis by blocking DPP4 activity, Cell Rep. 20 (7) (2017) 1692–1704.
[82] T. Abbas, A. Dutta, p21 in cancer: intricate networks and multiple activities, Nat. Rev. Cancer 9 (6) (2009) 400–414.
[83] A. Tarangelo, L. Magtanong, K.T. Bieging-Rolett, Y. Li, J. Ye, L.D. Attardi, S. J. Dixon, p53 Suppresses Metabolic Stress-Induced Ferroptosis in Cancer Cells, Cell Rep. 22 (3) (2018) 569–575.
[84] M. Wang, J. Zhao, L. Zhang, F. Wei, Y. Lian, Y. Wu, Z. Gong, S. Zhang, J. Zhou, K. Cao, X. Li, W. Xiong, G. Li, Z. Zeng, C. Guo, Role of tumor microenvironment in tumorigenesis, J. Cancer 8 (5) (2017) 761–773.
[85] T. Marsh, K. Pietras, S.S. McAllister, Fibroblasts as architects of cancer pathogenesis, Bba-Mol. Basis Dis. 1832 (7) (2013) 1070–1078.
[86] K.M. Bussard, L. Mutkus, K. Stumpf, C. Gomez-Manzano, F.C. Marini, Tumor-associated stromal cells as key contributors to the tumor microenvironment, Breast Cancer Res. 18 (2016).
[87] V. Petrova, M. Annicchiarico-Petruzzelli, G. Melino, I. Amelio, The hypoxic tumour microenvironment, Oncogenesis 7 (1) (2018) 10.
[88] V. Estrella, T. Chen, M. Lloyd, J. Wojtkowiak, H.H. Cornnell, A. Ibrahim-Hashim, K. Bailey, Y. Balagurunathan, J.M. Rothberg, B.F. Sloane, J. Johnson, R. A. Gatenby, R.J. Gillies, Acidity generated by the tumor microenvironment drives local invasion, Cancer Res 73 (5) (2013) 1524–1535.
[89] T.L. Whiteside, The tumor microenvironment and its role in promoting tumor growth, Oncogene 27 (45) (2008) 5904–5912.
[90] D.S. Vinay, E.P. Ryan, G. Pawelec, W.H. Talib, J. Stagg, E. Elkord, T. Lichtor, W. K. Decker, R.L. Whelan, H. Kumara, E. Signori, K. Honoki, A.G. Georgakilas, A. Amin, W.G. Helferich, C.S. Boosani, G. Guha, M.R. Ciriolo, S. Chen, S. I. Mohammed, A.S. Azmi, W.N. Keith, A. Bilsland, D. Bhakta, D. Halicka, H. Fujii, K. Aquilano, S.S. Ashraf, S. Nowsheen, X. Yang, B.K. Choi, B.S. Kwon, Immune evasion in cancer: Mechanistic basis and therapeutic strategies, Semin. Cancer Biol. 35 (Suppl) (2015) S185–S198.
[91] J. Zheng, Energy metabolism of cancer: glycolysis versus oxidative phosphorylation (Review), Oncol. Lett. 4 (6) (2012) 1151–1157.
[92] G.L. Semenza, Targeting HIF-1 for cancer therapy, Nat. Rev. Cancer 3 (10) (2003) 721–732.
[93] R.A. Gatenby, R.J. Gillies, Glycolysis in cancer: a potential target for therapy, Int J. Biochem Cell Biol. 39((7–8) (2007) 1358–1366.
[94] Y.E. Liu, Y.F. Shi, Mitochondria as a target in cancer treatment, Medcomm 1 (2) (2020) 129–139.
[95] L.B. Sullivan, N.S. Chandel, Mitochondrial reactive oxygen species and cancer, Cancer Metab. 2 (2014) 17.

[96] S.S. Sabharwal, P.T. Schumacker, Mitochondrial ROS in cancer: initiators, amplifiers or an Achilles' heel? Nat. Rev. Cancer 14 (11) (2014) 709–721.
[97] X. Ji, J. Qian, S.M.J. Rahman, P.J. Siska, Y. Zou, B.K. Harris, M.D. Hoeksema, I. A. Trenary, C. Heidi, R. Eisenberg, J.C. Rathmell, J.D. Young, P.P. Massion, xCT (SLC7A11)-mediated metabolic reprogramming promotes non-small cell lung cancer progression, Oncogene 37 (36) (2018) 5007–5019.
[98] J.K.M. Lim, A. Delaidelli, S.W. Minaker, H.F. Zhang, M. Colovic, H. Yang, G. L. Negri, S. von Karstedt, W.W. Lockwood, P. Schaffer, G. Leprivier, P. H. Sorensen, Cystine/glutamate antiporter xCT (SLC7A11) facilitates oncogenic RAS transformation by preserving intracellular redox balance, Proc. Natl. Acad. Sci. USA 116 (19) (2019) 9433–9442.
[99] D. Basuli, L. Tesfay, Z. Deng, B. Paul, Y. Yamamoto, G. Ning, W. Xian, F. McKeon, M. Lynch, C.P. Crum, P. Hegde, M. Brewer, X. Wang, L.D. Miller, N. Dyment, F. M. Torti, S.V. Torti, Iron addiction: a novel therapeutic target in ovarian cancer, Oncogene 36 (29) (2017) 4089–4099.
[100] Z. Li, L. Jiang, S.H. Chew, T. Hirayama, Y. Sekido, S. Toyokuni, Carbonic anhydrase 9 confers resistance to ferroptosis/apoptosis in malignant mesothelioma under hypoxia, Redox Biol. 26 (2019), 101297.
[101] H.W. Hann, M.W. Stahlhut, B.S. Blumberg, Iron nutrition and tumor growth: decreased tumor growth in iron-deficient mice, Cancer Res. 48 (15) (1988) 4168–4170.
[102] L. Tacchini, L. Bianchi, A. Bernelli-Zazzera, G. Cairo, Transferrin receptor induction by hypoxia. HIF-1-mediated transcriptional activation and cell-specific post-transcriptional regulation, J. Biol. Chem. 274 (34) (1999) 24142–24146.
[103] Z.M. Qian, X.M. Wu, M. Fan, L. Yang, F. Du, W.H. Yung, Y. Ke, Divalent metal transporter 1 is a hypoxia-inducible gene, J. Cell. Physiol. 226 (6) (2011) 1596–1603.
[104] E.S. Hanson, L.M. Foot, E.A. Leibold, Hypoxia post-translationally activates iron-regulatory protein 2, J. Biol. Chem. 274 (8) (1999) 5047–5052.
[105] B.W. Huang, M. Miyazawa, Y. Tsuji, Distinct regulatory mechanisms of the human ferritin gene by hypoxia and hypoxia mimetic cobalt chloride at the transcriptional and post-transcriptional levels, Cell Signal 26 (12) (2014) 2702–2709.
[106] D.S. Li, Y.S. Li, The interaction between ferroptosis and lipid metabolism in cancer, Signal Transduct. Target. Ther. 5 (1) (2020).
[107] G. Lei, L. Zhuang, B.Y. Gan, Targeting ferroptosis as a vulnerability in cancer, Nat. Rev. Cancer 22 (7) (2022) 381–396.
[108] P. Boffetta, Epidemiology of peritoneal mesothelioma: a review, Ann. Oncol. 18 (6) (2007) 985–990.
[109] Y. Sekido, Molecular pathogenesis of malignant mesothelioma, Carcinogenesis 34 (7) (2013) 1413–1419.
[110] H. Nagai, T. Ishihara, W.H. Lee, H. Ohara, Y. Okazaki, K. Okawa, S. Toyokuni, Asbestos surface provides a niche for oxidative modification, Cancer Sci. 102 (12) (2011) 2118–2125.
[111] A.J. Ghio, J. Stonehuerner, J. Richards, R.B. Devlin, Iron homeostasis in the lung following asbestos exposure, Antioxid. Redox Signal 10 (2) (2008) 371–377.
[112] N.R. Miselis, Z.J. Wu, N. Van Rooijen, A.B. Kane, Targeting tumor-associated macrophages in an orthotopic murine model of diffuse malignant mesothelioma, Mol. Cancer Ther. 7 (4) (2008) 788–799.
[113] R. Noy, J.W. Pollard, Tumor-associated macrophages: from mechanisms to therapy, Immunity 41 (1) (2014) 49–61.
[114] C.A. Barlow, M. Grespin, E.A. Best, Asbestos fiber length and its relation to disease risk, Inhal. Toxicol. 29 (12–14) (2017) 541–554.
[115] F. Ito, I. Yanatori, Y. Maeda, K. Nimura, S. Ito, T. Hirayama, H. Nagasawa, N. Kohyama, Y. Okazaki, S. Akatsuka, S. Toyokuni, Asbestos conceives Fe(II)-dependent mutagenic stromal milieu through ceaseless macrophage ferroptosis and beta-catenin induction in mesothelium, Redox Biol. 36 (2020).
[116] J.P. Hegmans, A. Hemmes, H. Hammad, L. Boon, H.C. Hoogsteden, B. N. Lambrecht, Mesothelioma environment comprises cytokines and T-regulatory cells that suppress immune responses, Eur. Respir. J. 27 (6) (2006) 1086–1095.
[117] R. Okayasu, S. Takahashi, S. Yamada, T.K. Hei, R.L. Ullrich, Asbestos and DNA double strand breaks, Cancer Res. 59 (2) (1999) 298–300.
[118] S. Toyokuni, Iron overload as a major targetable pathogenesis of asbestos-induced mesothelial carcinogenesis, Redox Rep. 19 (1) (2014) 1–7.
[119] S. Toyokuni, Iron addiction with ferroptosis-resistance in asbestos-induced mesothelial carcinogenesis: toward the era of mesothelioma prevention, Free Radic. Biol. Med 133 (2019) 206–215.
[120] H. Nagai, Y. Okazaki, S.H. Chew, N. Misawa, H. Yasui, S. Toyokuni, Deferasirox induces mesenchymal-epithelial transition in crocidolite-induced mesothelial carcinogenesis in rats, Cancer Prev. Res (Philos.) 6 (11) (2013) 1222–1230.
[121] L. Jiang, S.H. Chew, K. Nakamura, Y. Ohara, S. Akatsuka, S. Toyokuni, Dual preventive benefits of iron elimination by desferal in asbestos-induced mesothelial carcinogenesis, Cancer Sci. 107 (7) (2016) 908–915.
[122] H. Feng, K. Schorpp, J. Jin, C.E. Yozwiak, B.G. Hoffstrom, A.M. Decker, P. Rajbhandari, M.E. Stokes, H.G. Bender, J.M. Csuka, P.S. Upadhyayula, P. Canoll, K. Uchida, R.K. Soni, K. Hadian, B.R. Stockwell, Transferrin receptor is a specific ferroptosis marker, Cell Rep. 30 (10) (2020) 3411.
[123] S. Doll, B. Proneth, Y.Y. Tyurina, E. Panzilius, S. Kobayashi, I. Ingold, M. Irmler, J. Beckers, M. Aichler, A. Walch, H. Prokisch, D. Trumbach, G. Mao, F. Qu, H. Bayir, J. Fullekrug, C.H. Scheel, W. Wurst, J.A. Schick, V.E. Kagan, J.P. Angeli, M. Conrad, ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition, Nat. Chem. Biol. 13 (1) (2017) 91–98.
[124] K. Miyazono, Transforming growth factor-beta signaling in epithelial-mesenchymal transition and progression of cancer, Proc. Jpn Acad. Ser. B Phys. Biol. Sci. 85 (8) (2009) 314–323.
[125] M. Risolino, N. Mandia, F. Iavarone, L. Dardaei, E. Longobardi, S. Fernandez, F. Talotta, F. Bianchi, F. Pisati, L. Spaggiari, P.N. Harter, M. Mittelbronn, D. Schulte, M. Incoronato, P.P. Di Fiore, F. Blasi, P. Verde, Transcription factor PREP1 induces EMT and metastasis by controlling the TGF-beta-SMAD3 pathway in non-small cell lung adenocarcinoma, Proc. Natl. Acad. Sci. USA 111 (36) (2014). E3775-84.
[126] R.M. Liu, L.P. Desai, Reciprocal regulation of TGF-beta and reactive oxygen species: a perverse cycle for fibrosis, Redox Biol. 6 (2015) 565–577.
[127] Y.D. Bhutia, J. Ogura, P.J. Grippo, C. Torres, T. Sato, M. Wachtel, S. Ramachandran, E. Babu, S. Sivaprakasam, D. Rajasekaran, B. Schniers, N. On, L. Smoot, M. Thangaraju, J.P. Gnana-Prakasam, V. Ganapathy, Chronic exposure to excess iron promotes EMT and cancer via p53 loss in pancreatic cancer, Asian J. Pharm. Sci. 15 (2) (2020) 237–251.
[128] J. Hmeljak, F. Sanchez-Vega, K.A. Hoadley, J. Shih, C. Stewart, D. Heiman, P. Tarpey, L. Danilova, E. Drill, E.A. Gibb, R. Bowlby, R. Kanchi, H. U. Osmanbeyoglu, Y. Sekido, J. Takeshita, Y. Newton, K. Graim, M. Gupta, C. M. Gay, L. Diao, D.L. Gibbs, V. Thorsson, L. Iype, H. Kantheti, D.T. Severson, G. Ravegnini, P. Desmeules, A.A. Jungbluth, W.D. Travis, S. Dacic, L.R. Chirieac, F. Galateau-Salle, J. Fujimoto, A.N. Husain, H.C. Silveira, V.W. Rusch, R. C. Rintoul, H. Pass, H. Kindler, M.G. Zauderer, D.J. Kwiatkowski, R. Bueno, A. S. Tsao, J. Creaney, T. Lichtenberg, K. Leraas, J. Bowen, T.R. Network, I. Felau, J. C. Zenklusen, R. Akbani, A.D. Cherniack, L.A. Byers, M.S. Noble, J.A. Fletcher, A. G. Robertson, R. Shen, H. Aburatani, B.W. Robinson, P. Campbell, M. Ladanyi, Integrative molecular characterization of malignant pleural mesothelioma, Cancer Disco 8 (12) (2018) 1548–1565.
[129] N. Robertson, C. Potter, A.L. Harris, Role of carbonic anhydrase IX in human tumor cell growth, survival, and invasion, Cancer Res 64 (17) (2004) 6160–6165.
[130] M. Debreova, L. Csaderova, M. Burikova, L. Lukacikova, I. Kajanova, O. Sedlakova, M. Kery, J. Kopacek, M. Zatovicova, J. Bizik, S. Pastorekova, E. Svastova, CAIX regulates invadopodia formation through both a pH-dependent mechanism and interplay with actin regulatory proteins, Int. J. Mol. Sci. 20 (11) (2019).
[131] C. Ryder, K. McColl, F. Zhong, C.W. Distelhorst, Acidosis promotes Bcl-2 family-mediated evasion of apoptosis: involvement of acid-sensing G protein-coupled receptor Gpr65 signaling to Mek/Erk, J. Biol. Chem. 287 (33) (2012) 27863–27875.
[132] L. Shi, F. Ito, Y. Wang, Y. Okazaki, H. Tanaka, M. Mizuno, M. Hori, T. Hirayama, H. Nagasawa, D.R. Richardson, S. Toyokuni, Non-thermal plasma induces a stress response in mesothelioma cells resulting in increased endocytosis, lysosome biogenesis and autophagy, Free Radic. Biol. Med 108 (2017) 904–917.
[133] D.R. Richardson, D.J. Lane, E.M. Becker, M.L. Huang, M. Whitnall, Y. Suryo Rahmanto, A.D. Sheftel, P. Ponka, Mitochondrial iron trafficking and the integration of iron metabolism between the mitochondrion and cytosol, Proc. Natl. Acad. Sci. USA 107 (24) (2010) 10775–10782.
[134] T. Kurz, J.W. Eaton, U.T. Brunk, The role of lysosomes in iron metabolism and recycling, Int J. Biochem Cell Biol. 43 (12) (2011) 1686–1697.
[135] M. Swayampakula, P.C. McDonald, M. Vallejo, E. Coyaud, S.C. Chafe, A. Westerback, G. Venkateswaran, J. Shankar, G. Gao, E.M.N. Laurent, Y. Lou, K. L. Bennewith, C.T. Supuran, I.R. Nabi, B. Raught, S. Dedhar, The interactome of metabolic enzyme carbonic anhydrase IX reveals novel roles in tumor cell migration and invadopodia/MMP14-mediated invasion, Oncogene 36 (45) (2017) 6244–6261.
[136] Z. Li, L. Jiang, S. Toyokuni, Role of carbonic anhydrases in ferroptosis-resistance, Arch. Biochem. Biophys. 689 (2020), 108440.
[137] B. Qualmann, M.M. Kessels, R.B. Kelly, Molecular links between endocytosis and the actin cytoskeleton, J. Cell Biol. 150 (5) (2000) F111–F116.
[138] F. Basit, L.M. van Oppen, L. Schockel, H.M. Bossenbroek, S.E. van Emst-de Vries, J.C. Hermeling, S. Grefte, C. Kopitz, M. Heroult, P. Hgm Willems, W.J. Koopman, Mitochondrial complex I inhibition triggers a mitophagy-dependent ROS increase leading to necroptosis and ferroptosis in melanoma cells, Cell Death Dis. 8 (3) (2017), e2716.
[139] P.P. Hsu, D.M. Sabatini, Cancer cell metabolism: warburg and beyond, Cell 134 (5) (2008) 703–707.
[140] B.T. Paul, D.H. Manz, F.M. Torti, S.V. Torti, Mitochondria and Iron: current questions, Expert Rev. Hematol. 10 (1) (2017) 65–79.
[141] F. Bray, J. Ferlay, I. Soerjomataram, R.L. Siegel, L.A. Torre, A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 68 (6) (2018) 394–424.
[142] Z.Q. Li, L.N. Chen, C. Chen, Y.L. Zhou, D.D. Hu, J.J. Yang, Y.X. Chen, W.Y. Zhuo, M.S. Mao, X. Zhang, L. Xu, L.B. Wang, J.C. Zhou, Targeting ferroptosis in breast cancer, Biomark. Res. 8 (1) (2020).
[143] M. Canel, A. Serrels, M.C. Frame, V.G. Brunton, E-cadherin-integrin crosstalk in cancer invasion and metastasis, J. Cell Sci. 126 (Pt 2) (2013) 393–401.
[144] C.W. Brown, J.J. Amante, H.L. Goel, A.M. Mercurio, The alpha6beta4 integrin promotes resistance to ferroptosis, J. Cell Biol. 216 (12) (2017) 4287–4297.
[145] S. Ma, E.E. Henson, Y. Chen, S.B. Gibson, Ferroptosis is induced following siramesine and lapatinib treatment of breast cancer cells, Cell Death Dis. 7 (2016).
[146] J.L. Jian, Q. Yang, Y.Z. Shao, D. Axelrod, J. Smith, B. Singh, S. Krauter, L. Chiriboga, Z.X. Yang, J.Q. Li, X. Huang, A link between premenopausal iron deficiency and breast cancer malignancy, Bmc Cancer 13 (2013).
[147] S. Sui, S. Xu, D. Pang, Emerging role of ferroptosis in breast cancer: new dawn for overcoming tumor progression, Pharm. Ther. 232 (2022), 107992.

[148] D. Fuckar, A. Dekanic, S. Stifter, E. Mustac, M. Krstulja, F. Dobrila, N. Jonjic, VEGF expression is associated with negative estrogen receptor status in patients with breast cancer, Int J. Surg. Pathol. 14 (1) (2006) 49–55.
[149] C. Dabrosin, Positive correlation between estradiol and vascular endothelial growth factor but not fibroblast growth factor-2 in normal human breast tissue in vivo, Clin. Cancer Res. 11 (22) (2005) 8036–8041.
[150] X. Huang, Iron overload and its association with cancer risk in humans: evidence for iron as a carcinogenic metal, Mutat. Res 533 (1–2) (2003) 153–171.
[151] W. Wang, Z. Deng, H. Hatcher, L.D. Miller, X. Di, L. Tesfay, G. Sui, R. B. D'Agostino Jr., F.M. Torti, S.V. Torti, IRP2 regulates breast tumor growth, Cancer Res 74 (2) (2014) 497–507.
[152] Z.K. Pinnix, L.D. Miller, W. Wang, R. D'Agostino Jr., T. Kute, M.C. Willingham, H. Hatcher, L. Tesfay, G. Sui, X. Di, S.V. Torti, F.M. Torti, Ferroportin and iron regulation in breast cancer progression and prognosis, Sci. Transl. Med 2 (43) (2010) 43ra56.
[153] A.V. Lee, S. Oesterreich, N.E. Davidson, MCF-7 cells–changing the course of breast cancer research and care for 45 years, J. Natl. Cancer Inst. 107 (7) (2015).
[154] J.J. Yang, Y.L. Zhou, S.D. Xie, J. Wang, Z.Q. Li, L.N. Chen, M.S. Mao, C. Chen, A. H. Huang, Y.X. Chen, X. Zhang, N.U. Khan, L.B. Wang, J.C. Zhou, Metformin induces Ferroptosis by inhibiting UFMylation of SLC7A11 in breast cancer, J. Exp. Clin. Canc Res 40 (1) (2021).
[155] Q. Yang, J.L. Jian, S. Katz, S.B. Abramson, X. Huang, 17 beta-estradiol inhibits iron hormone hepcidin through an estrogen responsive element half-site, Endocrinology 153 (7) (2012) 3170–3178.
[156] B. Andriopoulos, E. Corradini, Y. Xia, S.A. Faasse, S.Z. Chen, L. Grgurevic, M. D. Knutson, A. Pietrangelo, S. Vukicevic, H.Y. Lin, J.L. Babitt, BMP6 is a key endogenous regulator of hepcidin expression and iron metabolism, Nat. Genet. 41 (4) (2009) 482–487.
[157] V. Sangkhae, E. Nemeth, Regulation of the iron homeostatic hormone hepcidin, Adv. Nutr. 8 (1) (2017) 126–136.
[158] J. Truksa, H. Peng, P. Lee, E. Beutler, Bone morphogenetic proteins 2, 4, and 9 stimulate murine hepcidin 1 expression independently of Hfe, transferrin receptor 2 (Tfr2), and IL-6, Proc. Natl. Acad. Sci. USA 103 (27) (2006) 10289–10293.
[159] Y. Ikeda, S. Tajima, Y. Izawa-Ishizawa, Y. Kihira, K. Ishizawa, S. Tomita, K. Tsuchiya, T. Tamaki, Estrogen regulates hepcidin expression via GPR30-BMP6-dependent signaling in hepatocytes, PLoS One 7 (7) (2012), e40465.
[160] Y.L. Hou, S.P. Zhang, L. Wang, J.P. Li, G.B. Qu, J.Y. He, H.Q. Rong, H. Ji, S.J. Liu, Estrogen regulates iron homeostasis through governing hepatic hepcidin expression via an estrogen response element, Gene 511 (2) (2012) 398–403.
[161] C.K. Anders, R. Johnson, J. Litton, M. Phillips, A. Bleyer, Breast cancer before age 40 years, Semin. Oncol. 36 (3) (2009) 237–249.
[162] N. Verma, Y. Vinik, A. Saroha, N.U. Nair, E. Ruppin, G. Mills, T. Karn, V. Dubey, L. Khera, H. Raj, F. Maina, S. Lev, Synthetic lethal combination targeting BET uncovered intrinsic susceptibility of TNBC to ferroptosis, Sci. Adv. 6 (34) (2020).
[163] S.Y. Sui, J. Zhang, S.P. Xu, Q. Wang, P.Y. Wang, D. Pang, Ferritinophagy is required for the induction of ferroptosis by the bromodomain protein BRD4 inhibitor (+)-JQ1 in cancer cells, Cell Death Dis. 10 (2019).
[164] A.H. Shain, B.C. Bastian, From melanocytes to melanomas, Nat. Rev. Cancer 16 (6) (2016) 345–358.
[165] B. Domingues, J.M. Lopes, P. Soares, H. Populo, Melanoma treatment in review, Immunotargets Ther. 7 (2018) 35–49.
[166] J. Landsberg, J. Kohlmeyer, M. Renn, T. Bald, M. Rogava, M. Cron, M. Fatho, V. Lennerz, T. Wolfel, M. Holzel, T. Tuting, Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation, Nature 490 (7420) (2012) 412.
[167] J. Tsoi, L. Robert, K. Paraiso, C. Galvan, K.M. Sheu, J. Lay, D.J.L. Wong, M. Atefi, R. Shirazi, X.Y. Wang, D. Braas, C.S. Grasso, N. Palaskas, A. Ribas, T.G. Graeber, Multi-stage differentiation defines melanoma subtypes with differential vulnerability to drug-induced iron-dependent oxidative stress, Cancer Cell 33 (5) (2018) 890.
[168] J.A. Sosman, K.B. Kim, L. Schuchter, R. Gonzalez, A.C. Pavlick, J.S. Weber, G. A. McArthur, T.E. Hutson, S.J. Moschos, K.T. Flaherty, P. Hersey, R. Kefford, D. Lawrence, I. Puzanov, K.D. Lewis, R.K. Amaravadi, B. Chmielowski, H. J. Lawrence, Y. Shyr, F. Ye, J. Li, K.B. Nolop, R.J. Lee, A.K. Joe, A. Ribas, Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib, N. Engl. J. Med 366 (8) (2012) 707–714.
[169] N. Wolkow, Y. Li, A. Maminishkis, Y. Song, O. Alekseev, J. Iacovelli, D. Song, J. C. Lee, J.L. Dunaief, Iron upregulates melanogenesis in cultured retinal pigment epithelial cells, Exp. Eye Res 128 (2014) 92–101.
[170] R. Busca, E. Berra, C. Gaggioli, M. Khaled, K. Bille, B. Marchetti, R. Thyss, G. Fitsialos, L. Larribere, C. Bertolotto, T. Virolle, P. Barbry, J. Pouyssegur, G. Ponzio, R. Ballotti, Hypoxia-inducible factor 1 alpha is a new target of microphthalmia-associated transcription factor (MITF) in melanoma cells, J. Cell Biol. 170 (1) (2005) 49–59.
[171] K.S. Hoek, N.C. Schlegel, P. Brafford, A. Sucker, S. Ugurel, R. Kumar, B.L. Weber, K.L. Nathanson, D.J. Phillips, M. Herlyn, D. Schadendorf, R. Dummer, Metastatic potential of melanomas defined by specific gene expression profiles with no BRAF signature, Pigment Cell Res. 19 (4) (2006) 290–302.
[172] R.H. Wang, C.L. Li, X.L. Xu, Y. Zheng, C.Y. Xiao, P. Zerfas, S. Cooperman, M. Eckhaus, T. Rouault, L. Mishra, C.X. Deng, A role of SMAD4 in iron metabolism through the positive regulation of hepicidin expression, Cell Metab. 2 (6) (2005) 399–409.
[173] S. Chen, T. Feng, M. Vujic Spasic, S. Altamura, K. Breitkopf-Heinlein, J. Altenoder, T.S. Weiss, S. Dooley, M.U. Muckenthaler, Transforming growth factor beta1 (TGF-beta1) activates hepcidin mRNA expression in hepatocytes, J. Biol. Chem. 291 (25) (2016) 13160–13174.
[174] M.J. Brookes, J. Boult, K. Roberts, B.T. Cooper, N.A. Hotchin, G. Matthews, T. Iqbal, C. Tselepis, A role for iron in Wnt signalling, Oncogene 27 (7) (2008) 966–975.
[175] F. Okazaki, N. Matsunaga, H. Okazaki, N. Utoguchi, R. Suzuki, K. Maruyama, S. Koyanagi, S. Ohdo, Circadian rhythm of transferrin receptor 1 gene expression controlled by c-Myc in colon cancer-bearing mice, Cancer Res 70 (15) (2010) 6238–6246.
[176] M.Y. Hsu, F.E. Meier, M. Nesbit, J.Y. Hsu, P. Van Belle, D.E. Elder, M. Herlyn, E-cadherin expression in melanoma cells restores keratinocyte-mediated growth control and down-regulates expression of invasion-related adhesion receptors, Am. J. Pathol. 156 (5) (2000) 1515–1525.
[177] M.J. Brookes, S. Hughes, F.E. Turner, G. Reynolds, N. Sharma, T. Ismail, G. Berx, A.T. McKie, N. Hotchin, G.J. Anderson, T. Iqbal, C. Tselepis, Modulation of iron transport proteins in human colorectal carcinogenesis, Gut 55 (10) (2006) 1449–1460.
[178] Y.N. Gopal, H. Rizos, G. Chen, W. Deng, D.T. Frederick, Z.A. Cooper, R.A. Scolyer, G. Pupo, K. Komurov, V. Sehgal, J. Zhang, L. Patel, C.G. Pereira, B.M. Broom, G. B. Mills, P. Ram, P.D. Smith, J.A. Wargo, G.V. Long, M.A. Davies, Inhibition of mTORC1/2 overcomes resistance to MAPK pathway inhibitors mediated by PGC1alpha and oxidative phosphorylation in melanoma, Cancer Res 74 (23) (2014) 7037–7047.
[179] G.M. Fischer, Y.N. Vashisht Gopal, J.L. McQuade, W. Peng, R.J. DeBerardinis, M. A. Davies, Metabolic strategies of melanoma cells: Mechanisms, interactions with the tumor microenvironment, and therapeutic implications, Pigment Cell Melanoma Res. 31 (1) (2018) 11–30.
[180] C. Pfeifhofer-Obermair, P. Tymoszuk, V. Petzer, G. Weiss, M. Nairz, Iron in the tumor microenvironment-connecting the dots, Front. Oncol. 8 (2018) 549.
[181] G. Porto, C. Vicente, M.A. Teixeira, O. Martins, J.M. Cabeda, R. Lacerda, C. Goncalves, J. Fraga, G. Macedo, B.M. Silva, H. Alves, B. Justica, M. de Sousa, Relative impact of HLA phenotype and CD4-CD8 ratios on the clinical expression of hemochromatosis, Hepatology 25 (2) (1997) 397–402.
[182] R. Reimao, G. Porto, M. de Sousa, Stability of CD4/CD8 ratios in man: new correlation between CD4/CD8 profiles and iron overload in idiopathic haemochromatosis patients, C. R. Acad. Sci. III 313 (11) (1991) 481–487.
[183] Z. Wang, W. Yin, L. Zhu, J. Li, Y. Yao, F. Chen, M. Sun, J. Zhang, N. Shen, Y. Song, X. Chang, T. Iron Drives, Helper cell pathogenicity by promoting RNA-binding protein PCBP1-mediated proinflammatory cytokine production, Immunity 49 (1) (2018) 80–92, e7.
[184] C. Penaloza, L. Lin, R.A. Lockshin, Z. Zakeri, Cell death in development: shaping the embryo, Histochem Cell Biol. 126 (2) (2006) 149–158.
[185] M. Suzanne, H. Steller, Shaping organisms with apoptosis, Cell Death Differ. 20 (5) (2013) 669–675.
[186] F. Esposito, R. Ammendola, R. Faraonio, T. Russo, F. Cimino, Redox control of signal transduction, gene expression and cellular senescence, Neurochem Res. 29 (3) (2004) 617–628.
[187] T. Jabs, Reactive oxygen intermediates as mediators of programmed cell death in plants and animals, Biochem. Pharmacol. 57 (3) (1999) 231–245.
[188] C. Ufer, C.C. Wang, The roles of glutathione peroxidases during embryo development, Front Mol. Neurosci. 4 (2011) 12.
[189] J.E. Dvorska, P.F. Surai, B.K. Speake, N.H. Sparks, Antioxidant systems of the developing quail embryo are compromised by mycotoxin aurofusarin, Comp. Biochem Physiol. C Toxicol. Pharm. 131 (2) (2002) 197–205.
[190] D. Schnabel, E. Salas-Vidal, V. Narvaez, R. Sanchez-Carbente Mdel, D. Hernandez-Garcia, R. Cuervo, L. Covarrubias, Expression and regulation of antioxidant enzymes in the developing limb support a function of ROS in interdigital cell death, Dev. Biol. 291 (2) (2006) 291–299.
[191] V. Sangkhae, E. Nemeth, Placental iron transport: the mechanism and regulatory circuits, Free Radic. Biol. Med. 133 (2019) 254–261.
[192] V. Sangkhae, A.L. Fisher, S. Wong, M.D. Koenig, L. Tussing-Humphreys, A. Chu, M. Lelic, T. Ganz, E. Nemeth, Effects of maternal iron status on placental and fetal iron homeostasis, J. Clin. Invest 130 (2) (2020) 625–640.
[193] V. Sangkhae, A.L. Fisher, K.J. Chua, P. Ruchala, T. Ganz, E. Nemeth, Maternal hepcidin determines embryo iron homeostasis in mice, Blood 136 (19) (2020) 2206–2216.
[194] L. Yang, H. Wang, X. Yang, Q. Wu, P. An, X. Jin, W. Liu, X. Huang, Y. Li, S. Yan, S. Shen, T. Liang, J. Min, F. Wang, Auranofin mitigates systemic iron overload and induces ferroptosis via distinct mechanisms, Signal Transduct. Target Ther. 5 (1) (2020) 138.
[195] T. Uchimura, Y. Komatsu, M. Tanaka, K.L. McCann, Y. Mishina, Bmp2 and Bmp4 genetically interact to support multiple aspects of mouse development including functional heart development, Genesis 47 (6) (2009) 374–384.
[196] D. Vela, Balance of cardiac and systemic hepcidin and its role in heart physiology and pathology, Lab Invest. 98 (3) (2018) 315–326.
[197] H.S. Andersen, L. Gambling, G. Holtrop, H.J. McArdle, Maternal iron deficiency identifies critical windows for growth and cardiovascular development in the rat postimplantation embryo, J. Nutr. 136 (5) (2006) 1171–1177.
[198] G. Marazzi, Y.Q. Wang, D. Sassoon, Msx2 is a transcriptional regulator in the BMP4-mediated programmed cell death pathway, Dev. Biol. 186 (2) (1997) 127–138.
[199] C. Camaschella, BMP6 orchestrates iron metabolism, Nat. Genet. 41 (4) (2009) 386–388.
[200] S. Babajko, M. de La Dure-Molla, K. Jedeon, A. Berdal, MSX2 in ameloblast cell fate and activity, Front. Physiol. 5 (2014) 510.
[201] N. Wilkinson, K. Pantopoulos, The IRP/IRE system in vivo: insights from mouse models, Front. Pharm. 5 (2014) 176.

[202] S.R. Smith, M.C. Ghosh, H. Ollivierre-Wilson, W. Hang Tong, T.A. Rouault, Complete loss of iron regulatory proteins 1 and 2 prevents viability of murine zygotes beyond the blastocyst stage of embryonic development, Blood Cells Mol. Dis. 36 (2) (2006) 283–287.
[203] E.G. Meyron-Holtz, M.C. Ghosh, K. Iwai, T. LaVaute, X. Brazzolotto, U.V. Berger, W. Land, H. Ollivierre-Wilson, A. Grinberg, P. Love, T.A. Rouault, Genetic ablations of iron regulatory proteins 1 and 2 reveal why iron regulatory protein 2 dominates iron homeostasis, EMBO J. 23 (2) (2004) 386–395.
[204] O.V. Lushchak, M. Piroddi, F. Galli, V.I. Lushchak, Aconitase post-translational modification as a key in linkage between Krebs cycle, iron homeostasis, redox signaling, and metabolism of reactive oxygen species, Redox Rep. 19 (1) (2014) 8–15.
[205] A. Nekrutenko, D.M. Hillis, J.C. Patton, R.D. Bradley, R.J. Baker, Cytosolic isocitrate dehydrogenase in humans, mice, and voles and phylogenetic analysis of the enzyme family, Mol. Biol. Evol. 15 (12) (1998) 1674–1684.
[206] H. Li, H. Zhao, S. Hao, L. Shang, J. Wu, C. Song, E.G. Meyron-Holtz, T. Qiao, K. Li, Iron regulatory protein deficiency compromises mitochondrial function in murine embryonic fibroblasts, Sci. Rep. 8 (1) (2018) 5118.
[207] H. Li, Y. Liu, L. Shang, J. Cai, J. Wu, W. Zhang, X. Pu, W. Dong, T. Qiao, K. Li, Iron regulatory protein 2 modulates the switch from aerobic glycolysis to oxidative phosphorylation in mouse embryonic fibroblasts, Proc. Natl. Acad. Sci. USA 116 (20) (2019) 9871–9876.
[208] B. Hassannia, P. Vandenabeele, T. Vanden Berghe, Targeting ferroptosis to iron out cancer, Cancer Cell 35 (6) (2019) 830–849.
[209] G.L. Plosker, K.F. Croom, Sulfasalazine: a review of its use in the management of rheumatoid arthritis, Drugs 65 (13) (2005) 1825–1849.
[210] S.M. Robert, S.C. Buckingham, S.L. Campbell, S. Robel, K.T. Holt, T. Ogunrinu-Babarinde, P.P. Warren, D.M. White, M.A. Reid, J.M. Eschbacher, M.E. Berens, A. C. Lahti, L.B. Nabors, H. Sontheimer, SLC7A11 expression is associated with seizures and predicts poor survival in patients with malignant glioma, Sci. Transl. Med. 7 (289) (2015).
[211] X. Wang, Y. Chen, X. Wang, H. Tian, Y. Wang, J. Jin, Z. Shan, Y. Liu, Z. Cai, X. Tong, Y. Luan, X. Tan, B. Luan, X. Ge, H. Ji, X. Jiang, P. Wang, Stem cell factor SOX2 confers ferroptosis resistance in lung cancer via upregulation of SLC7A11, Cancer Res. 81 (20) (2021) 5217–5229.
[212] M.H. Larraufie, W.S. Yang, E. Jiang, A.G. Thomas, B.S. Slusher, B.R. Stockwell, Incorporation of metabolically stable ketones into a small molecule probe to increase potency and water solubility, Bioorg. Med Chem. Lett. 25 (21) (2015) 4787–4792.
[213] W.S. Yang, K.J. Kim, M.M. Gaschler, M. Patel, M.S. Shchepinov, B.R. Stockwell, Peroxidation of polyunsaturated fatty acids by lipoxygenases drives ferroptosis, Proc. Natl. Acad. Sci. USA 113 (34) (2016) E4966–E4975.
[214] P.W. Gout, A.R. Buckley, C.R. Simms, N. Bruchovsky, Sulfasalazine, a potent suppressor of lymphoma growth by inhibition of the x(c)- cystine transporter: a new action for an old drug, Leukemia 15 (10) (2001) 1633–1640.
[215] C. Louandre, Z. Ezzoukhry, C. Godin, J.C. Barbare, J.C. Maziere, B. Chauffert, A. Galmiche, Iron-dependent cell death of hepatocellular carcinoma cells exposed to sorafenib, Int J. Cancer 133 (7) (2013) 1732–1742.
[216] O.W. Griffith, Mechanism of action, metabolism, and toxicity of buthionine sulfoximine and its higher homologs, potent inhibitors of glutathione synthesis, J. Biol. Chem. 257 (22) (1982) 13704–13712.
[217] A. Hamacher-Brady, H.A. Stein, S. Turschner, I. Toegel, R. Mora, N. Jennewein, T. Efferth, R. Eils, N.R. Brady, Artesunate activates mitochondrial apoptosis in breast cancer cells via iron-catalyzed lysosomal reactive oxygen species production, J. Biol. Chem. 286 (8) (2011) 6587–6601.
[218] A.M. Lisewski, J.P. Quiros, C.L. Ng, A.K. Adikesavan, K. Miura, N. Putluri, R. T. Eastman, D. Scanfeld, S.J. Regenbogen, L. Altenhofen, M. Llinas, A. Sreekumar, C. Long, D.A. Fidock, O. Lichtarge, Supergenomic network compression and the discovery of EXP1 as a glutathione transferase inhibited by artesunate, Cell 158 (4) (2014) 916–928.
[219] S.L. Cramer, A. Saha, J. Liu, S. Tadi, S. Tiziani, W. Yan, K. Triplett, C. Lamb, S. E. Alters, S. Rowlinson, Y.J. Zhang, M.J. Keating, P. Huang, J. DiGiovanni, G. Georgiou, E. Stone, Systemic depletion of L-cyst(e)ine with cyst(e)inase increases reactive oxygen species and suppresses tumor growth, Nat. Med. 23 (1) (2017) 120–127.
[220] <targeting mitochondrial complex I using BAY 87–2243.pdf>.
[221] M. Weiwer, J.A. Bittker, T.A. Lewis, K. Shimada, W.S. Yang, L. MacPherson, S. Dandapani, M. Palmer, B.R. Stockwell, S.L. Schreiber, B. Munoz, Development of small-molecule probes that selectively kill cells induced to express mutant RAS, Bioorg. Med. Chem. Lett. 22 (4) (2012) 1822–1826.
[222] J.K. Eaton, L. Furst, R.A. Ruberto, D. Moosmayer, A. Hilpmann, M.J. Ryan, K. Zimmermann, L.K.L. Cai, M. Niehues, V. Badock, A. Kramm, S.X. Chen, R. C. Hillig, P.A. Clemons, S. Gradl, C. Montagnon, K.E. Lazarski, S. Christian, B. Bajrami, R. Neuhaus, A.L. Eheim, V.S. Viswanathan, S.L. Schreiber, Selective covalent targeting of GPX4 using masked nitrile-oxide electrophiles, Nat. Chem. Biol. 16 (5) (2020) 497.
[223] M.M. Gaschler, A.A. Andia, H.R. Liu, J.M. Csuka, B. Hurlocker, C.A. Vaiana, D. W. Heindel, D.S. Zuckerman, P.H. Bos, E. Reznik, L.F. Ye, Y.Y. Tyurina, A.J. Lin, M.S. Shchepinov, A.Y. Chan, E. Peguero-Pereira, M.A. Fomich, J.D. Daniels, A. V. Bekish, V.V. Shmanai, V.E. Kagan, L.K. Mahal, K.A. Woerpel, B.R. Stockwell, FINO2 initiates ferroptosis through GPX4 inactivation and iron oxidation, Nat. Chem. Biol. 14 (5) (2018) 507.
[224] K. Shimada, R. Skouta, A. Kaplan, W.S. Yang, M. Hayano, S.J. Dixon, L.M. Brown, C.A. Valenzuela, A.J. Wolpaw, B.R. Stockwell, Global survey of cell death mechanisms reveals metabolic regulation of ferroptosis, Nat. Chem. Biol. 12 (7) (2016) 497–503.
[225] B. Hassannia, B. Wiernicki, I. Ingold, F. Qu, S. Van Herck, Y.Y. Tyurina, H. Bayir, B.A. Abhari, J.P.F. Angeli, S.M. Choi, E. Meul, K. Heyninck, K. Declerck, C. S. Chirumamilla, M. Lahtela-Kakkonen, G. Van Camp, D.V. Krysko, P.G. Ekert, S. Fulda, B.G. De Geest, M. Conrad, V.E. Kagan, W. Vanden Berghe, P. Vandenabeele, T. Vanden Berghe, Nano-targeted induction of dual ferroptotic mechanisms eradicates high-risk neuroblastoma, J. Clin. Invest 128 (8) (2018) 3341–3355.
[226] V.S. Viswanathan, M.J. Ryan, H.D. Dhruv, S. Gill, O.M. Eichhoff, B. Seashore-Ludlow, S.D. Kaffenberger, J.K. Eaton, K. Shimada, A.J. Aguirre, S. R. Viswanathan, S. Chattopadhyay, P. Tamayo, W.S. Yang, M.G. Rees, S. Chen, Z. V. Boskovic, S. Javaid, C. Huang, X. Wu, Y.Y. Tseng, E.M. Roider, D. Gao, J. M. Cleary, B.M. Wolpin, J.P. Mesirov, D.A. Haber, J.A. Engelman, J.S. Boehm, J. D. Kotz, C.S. Hon, Y. Chen, W.C. Hahn, M.P. Levesque, J.G. Doench, M.E. Berens, A.F. Shamji, P.A. Clemons, B.R. Stockwell, S.L. Schreiber, Dependency of a therapy-resistant state of cancer cells on a lipid peroxidase pathway, Nature 547 (7664) (2017) 453–457.
[227] Q. Li, X. Han, X. Lan, Y. Gao, J. Wan, F. Durham, T. Cheng, J. Yang, Z. Wang, C. Jiang, M. Ying, R.C. Koehler, B.R. Stockwell, J. Wang, Inhibition of neuronal ferroptosis protects hemorrhagic brain, JCI Insight 2 (7) (2017), e90777.
[228] S. Imoto, M. Kono, T. Suzuki, Y. Shibuya, T. Sawamura, Y. Mizokoshi, H. Sawada, A. Ohbuchi, K. Saigo, Haemin-induced cell death in human monocytic cells is consistent with ferroptosis, Transfus. Apher. Sci. 57 (4) (2018) 524–531.
[229] S.K. NaveenKumar, B.N. SharathBabu, M. Hemshekhar, K. Kemparaju, K.S. Girish, G. Mugesh, The role of reactive oxygen species and ferroptosis in heme-mediated activation of human platelets, ACS Chem. Biol. 13 (8) (2018) 1996–2002.
[230] T. Furuta, L. Shi, S. Toyokuni, Non-thermal plasma as a simple ferroptosis inducer in cancer cells: a possible role of ferritin, Pathol. Int 68 (7) (2018) 442–443.
[231] T.T. Mai, A. Hamai, A. Hienzsch, T. Caneque, S. Muller, J. Wicinski, O. Cabaud, C. Leroy, A. David, V. Acevedo, A. Ryo, C. Ginestier, D. Birnbaum, E. Charafe-Jauffret, P. Codogno, M. Mehrpour, R. Rodriguez, Salinomycin kills cancer stem cells by sequestering iron in lysosomes, Nat. Chem. 9 (10) (2017) 1025–1033.
[232] S.E. Kim, L. Zhang, K. Ma, M. Riegman, F. Chen, I. Ingold, M. Conrad, M. Z. Turker, M. Gao, X. Jiang, S. Monette, M. Pauliah, M. Gonen, P. Zanzonico, T. Quinn, U. Wiesner, M.S. Bradbury, M. Overholtzer, Ultrasmall nanoparticles induce ferroptosis in nutrient-deprived cancer cells and suppress tumour growth, Nat. Nanotechnol. 11 (11) (2016) 977–985.
[233] A.T. Shaw, M.M. Winslow, M. Magendantz, C. Ouyang, J. Dowdle, A. Subramanian, T.A. Lewis, R.L. Maglathin, N. Tolliday, T. Jacks, Selective killing of K-ras mutant cancer cells by small molecule inducers of oxidative stress, Proc. Natl. Acad. Sci. USA 108 (21) (2011) 8773–8778.
[234] R. Lin, Z. Zhang, L. Chen, Y. Zhou, P. Zou, C. Feng, L. Wang, G. Liang, Dihydroartemisinin (DHA) induces ferroptosis and causes cell cycle arrest in head and neck carcinoma cells, Cancer Lett. 381 (1) (2016) 165–175.
[235] E. Ooko, M.E.M. Saeed, O. Kadioglu, S. Sarvi, M. Colak, K. Elmasaoudi, R. Janah, H.J. Greten, T. Efferth, Artemisinin derivatives induce iron-dependent cell death (ferroptosis) in tumor cells, Phytomedicine 22 (11) (2015) 1045–1054.
[236] J. Liu, X. Song, F. Kuang, Q. Zhang, Y. Xie, R. Kang, G. Kroemer, D. Tang, NUPR1 is a critical repressor of ferroptosis, Nat. Commun. 12 (1) (2021) 647.
[237] Y. Chen, X. Yi, B. Huo, Y. He, X. Guo, Z. Zhang, X. Zhong, X. Feng, Z.M. Fang, X. H. Zhu, X. Wei, D.S. Jiang, BRD4770 functions as a novel ferroptosis inhibitor to protect against aortic dissection, Pharm. Res. 177 (2022), 106122.
[238] G. Miotto, M. Rossetto, M.L. Di Paolo, L. Orian, R. Venerando, A. Roveri, A. M. Vuckovic, V. Bosello Travain, M. Zaccarin, L. Zennaro, M. Maiorino, S. Toppo, F. Ursini, G. Cozza, Insight into the mechanism of ferroptosis inhibition by ferrostatin-1, Redox Biol. 28 (2020), 101328.
[239] Y. Cao, Y. Li, C. He, F. Yan, J.R. Li, H.Z. Xu, J.F. Zhuang, H. Zhou, Y.C. Peng, X. J. Fu, X.Y. Lu, Y. Yao, Y.Y. Wei, Y. Tong, Y.F. Zhou, L. Wang, Selective ferroptosis inhibitor liproxstatin-1 attenuates neurological deficits and neuroinflammation after subarachnoid hemorrhage, Neurosci. Bull. 37 (4) (2021) 535–549.
[240] P. Li, M. Jiang, K. Li, H. Li, Y. Zhou, X. Xiao, Y. Xu, S. Krishfield, P.E. Lipsky, G. C. Tsokos, X. Zhang, Glutathione peroxidase 4-regulated neutrophil ferroptosis induces systemic autoimmunity, Nat. Immunol. 22 (9) (2021) 1107–1117.
[241] N. Wang, H. Ma, J. Li, C.Y. Meng, J. Zou, H. Wang, K. Liu, M.D. Liu, X.Z. Xiao, H. L. Zhang, K.K. Wang, HSF1 functions as a key defender against palmitic acid-induced ferroptosis in cardiomyocytes, J. Mol. Cell Cardiol. 150 (2021) 65–76.
[242] J.L. Brown, F.F. Peelor 3rd, C. Georgescu, J.D. Wren, M. Kinter, V.J. Tyrrell, V. B. O'Donnell, B.F. Miller, H. Van Remmen, Lipid hydroperoxides and oxylipins are mediators of denervation induced muscle atrophy, Redox Biol. 57 (2022), 102518.
[243] J.L. Roh, E.H. Kim, H. Jang, D. Shin, Nrf2 inhibition reverses the resistance of cisplatin-resistant head and neck cancer cells to artesunate-induced ferroptosis, Redox Biol. 11 (2017) 254–262.
[244] Z. Zhao, J. Wu, H. Xu, C. Zhou, B. Han, H. Zhu, Z. Hu, Z. Ma, Z. Ming, Y. Yao, R. Zeng, G. Xu, XJB-5-131 inhibited ferroptosis in tubular epithelial cells after ischemia-reperfusion injury, Cell Death Dis. 11 (8) (2020) 629.
[245] Y. Wu, L. Ran, Y. Yang, X. Gao, M. Peng, S. Liu, L. Sun, J. Wan, Y. Wang, K. Yang, M. Yin, W. Chunyu, Deferasirox alleviates DSS-induced ulcerative colitis in mice by inhibiting ferroptosis and improving intestinal microbiota, Life Sci. 314 (2022), 121312.
[246] Y. Liu, W. Wang, Y. Li, Y. Xiao, J. Cheng, J. Jia, The 5-lipoxygenase inhibitor zileuton confers neuroprotection against glutamate oxidative damage by inhibiting ferroptosis, Biol. Pharm. Bull. 38 (8) (2015) 1234–1239.
[247] Y. Huang, J. Wang, S. Huang, X. Zhang, J. Hu, 5-lipoxygenase contributes to benzo[a]pyrene-induced cytotoxicity and DNA damage in human bronchial epithelial cells, Int. J. Toxicol. (2022), 10915818221146286.

[248] O. Zilka, R. Shah, B. Li, J.P. Friedmann Angeli, M. Griesser, M. Conrad, D.A. Pratt, On the mechanism of cytoprotection by ferrostatin-1 and liproxstatin-1 and the role of lipid peroxidation in ferroptotic cell death, ACS Cent. Sci. 3 (3) (2017) 232–243.
[249] M. Yang, X. Li, H. Li, X. Zhang, X. Liu, Y. Song, Baicalein inhibits RLS3-induced ferroptosis in melanocytes, Biochem Biophys. Res Commun. 561 (2021) 65–72.
[250] M.R. Reynolds, B.F. Clem, Troglitazone suppresses glutamine metabolism through a PPAR-independent mechanism, Biol. Chem. 396 (8) (2015) 937–947.
[251] Y. Wang, M. Zhang, R. Bi, Y. Su, F. Quan, Y. Lin, C. Yue, X. Cui, Q. Zhao, S. Liu, Y. Yang, D. Zhang, Q. Cao, X. Gao, ACSL4 deficiency confers protection against ferroptosis-mediated acute kidney injury, Redox Biol. 51 (2022), 102262.
[252] Y.A. Kung, H.J. Chiang, M.L. Li, Y.N. Gong, H.P. Chiu, C.T. Hung, P.N. Huang, S. Y. Huang, P.Y. Wang, T.A. Hsu, G. Brewer, S.R. Shih, Acyl-coenzyme A synthetase long-chain family member 4 is involved in viral replication organelle formation and facilitates virus replication via ferroptosis, mBio 13 (1) (2022), e0271721.
[253] H. Mizuno, C. Kubota, Y. Takigawa, R. Shintoku, N. Kannari, T. Muraoka, H. Obinata, Y. Yoshimoto, M. Kanazawa, I. Koshiishi, S. Torii, 2,2,6,6-Tetramethylpiperidine-1-oxyl acts as a volatile inhibitor of ferroptosis and neurological injury, J. Biochem 172 (2) (2022) 71–78.
[254] Y. Yao, Z. Chen, H. Zhang, C. Chen, M. Zeng, J. Yunis, Y. Wei, Y. Wan, N. Wang, M. Zhou, C. Qiu, Q. Zeng, H.S. Ong, H. Wang, F.V. Makota, Y. Yang, Z. Yang, N. Wang, J. Deng, C. Shen, Y. Xia, L. Yuan, Z. Lian, Y. Deng, C. Guo, A. Huang, P. Zhou, H. Shi, W. Zhang, H. Yi, D. Li, M. Xia, J. Fu, N. Wu, J.B. de Haan, N. Shen, W. Zhang, Z. Liu, D. Yu, Selenium-GPX4 axis protects follicular helper T cells from ferroptosis, Nat. Immunol. 22 (9) (2021) 1127–1139.
[255] Q. Hu, Y. Zhang, H. Lou, Z. Ou, J. Liu, W. Duan, H. Wang, Y. Ge, J. Min, F. Wang, Z. Ju, GPX4 and vitamin E cooperatively protect hematopoietic stem and progenitor cells from lipid peroxidation and ferroptosis, Cell Death Dis. 12 (7) (2021) 706.
[256] F. Yao, Y. Deng, Y. Zhao, Y. Mei, Y. Zhang, X. Liu, C. Martinez, X. Su, R.R. Rosato, H. Teng, Q. Hang, S. Yap, D. Chen, Y. Wang, M.M. Chen, M. Zhang, H. Liang, D. Xie, X. Chen, H. Zhu, J.C. Chang, M.J. You, Y. Sun, B. Gan, L. Ma, A targetable LIFR-NF-kappaB-LCN2 axis controls liver tumorigenesis and vulnerability to ferroptosis, Nat. Commun. 12 (1) (2021) 7333.
[257] R. Gao, R.K.R. Kalathur, M. Coto-Llerena, C. Ercan, D. Buechel, S. Shuang, S. Piscuoglio, M.T. Dill, F.D. Camargo, G. Christofori, F. Tang, YAP/TAZ and ATF4 drive resistance to Sorafenib in hepatocellular carcinoma by preventing ferroptosis, EMBO Mol. Med. 13 (12) (2021), e14351.
[258] D. Devos, C. Moreau, J.C. Devedjian, J. Kluza, M. Petrault, C. Laloux, A. Jonneaux, G. Ryckewaert, G. Garcon, N. Rouaix, A. Duhamel, P. Jissendi, K. Dujardin, F. Auger, L. Ravasi, L. Hopes, G. Grolez, W. Firdaus, B. Sablonniere, I. Strubi-Vuillaume, N. Zahr, A. Destee, J.C. Corvol, D. Poltl, M. Leist, C. Rose, L. Defebvre, P. Marchetti, Z.I. Cabantchik, R. Bordet, Targeting chelatable iron as a therapeutic modality in Parkinson's disease, antioxid redox, Sign 21 (2) (2014) 195–210.
[259] A. Martin-Bastida, R.J. Ward, R. Newbould, P. Piccini, D. Sharp, C. Kabba, M. C. Patel, M. Spino, J. Connelly, F. Tricta, R.R. Crichton, D.T. Dexter, Brain iron chelation by deferiprone in a phase 2 randomised double-blinded placebo controlled clinical trial in Parkinson's disease, Sci. Rep. 7 (1) (2017) 1398.
[260] L.D. Coles, P.J. Tuite, G. Oz, U.R. Mishra, R.V. Kartha, K.M. Sullivan, J.C. Cloyd, M. Terpstra, Repeated-dose oral N-acetylcysteine in Parkinson's disease: pharmacokinetics and effect on brain glutathione and oxidative stress, J. Clin. Pharm. 58 (2) (2018) 158–167.
[261] L.K. Mischley, R.C. Lau, E.G. Shankland, T.K. Wilbur, J.M. Padowski, Phase IIb study of intranasal glutathione in Parkinson's disease, J. Park. Dis. 7 (2) (2017) 289–299.
[262] M. Taghizadeh, O.R. Tamtaji, E. Dadgostar, R. Daneshvar Kakhaki, F. Bahmani, J. Abolhassani, M.H. Aarabi, E. Kouchaki, M.R. Memarzadeh, Z. Asemi, The effects of omega-3 fatty acids and vitamin E co-supplementation on clinical and metabolic status in patients with Parkinson's disease: a randomized, double-blind, placebo-controlled trial, Neurochem Int. 108 (2017) 183–189.
[263] R.C. Seet, E.C. Lim, J.J. Tan, A.M. Quek, A.W. Chow, W.L. Chong, M.P. Ng, C. N. Ong, B. Halliwell, Does high-dose coenzyme Q10 improve oxidative damage and clinical outcomes in Parkinson's disease? Antioxid. Redox Signal 21 (2) (2014) 211–217.
[264] A. Catala, M. Diaz, Editorial: impact of lipid peroxidation on the physiology and pathophysiology of cell membranes, Front Physiol. 7 (2016) 423.
[265] M.O. Hengartner, The biochemistry of apoptosis, Nature 407 (6805) (2000) 770–776.
[266] Y. Liu, C. Chen, X. Wang, Y. Sun, J. Zhang, J. Chen, Y. Shi, An epigenetic role of mitochondria in cancer, Cells 11 (16) (2022).
[267] S. Huang, Y. Liu, Y. Zhang, R. Zhang, C. Zhu, L. Fan, G. Pei, B. Zhang, Y. Shi, Baicalein inhibits SARS-CoV-2/VSV replication with interfering mitochondrial oxidative phosphorylation in a mPTP dependent manner, Signal Transduct. Target Ther. 5 (1) (2020) 266.