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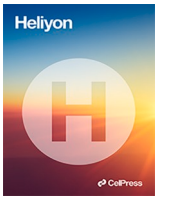

Review article

Ferroptosis, autophagy, tumor and immunity

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ABSTRACT

Ferroptosis was first proposed in 2012, a new form of cell death. Autophagy plays a crucial role in cell clearance and maintaining homeostasis. Autophagy is involved in the initial step of ferroptosis under the action of histone elements such as NCOA4, RAB7A, and BECN1. Ferroptosis and autophagy are involved in tumor progression, treatment, and drug resistance in the tumor microenvironment. In this review, we described the mechanisms of ferroptosis, autophagy, and tumor and immunotherapy, respectively, and emphasized the relationship between autophagy-related ferroptosis and tumor.

1. Introduction

Cell homeostasis is a state of dynamic equilibrium, which is composed of biosynthesis and catabolism. Autophagy is a degradation process that can be divided into three categories: macroautophagy, microautophagy, and chaperone-mediated autophagy [1]. Autophagy, commonly referred to as autophagy (hereinafter referred to as autophagy), is the most studied form of autophagy, which regulates homeostasis by promoting cell death or survival [2–4]. In 2012, the concept of ferroptosis was put forward for the first time. Ferroptosis is different from necrosis, apoptosis, necroptosis, and autophagy [5]. Morphologically, ferroptosis is mainly manifested as mitochondrial atrophy, increased membrane density, and reduced or disappeared cristae. In particular, NCOA4 promotes ferritin phagocytosis, RAB7A-dependent lipophagy, BECN1-mediated system Xc-inhibition, STAT3-induced lysosomal membrane permeability change, and HSP90-related partner-mediated autophagy can all promote ferroptosis. Autophagy-dependent ferroptosis may contribute to the treatment of tumors, inflammatory reactions, and tissue fibrosis [6,7].

Immunity plays a vital role in tumor monitoring, clearance, and prevention. In recent years, Immune checkpoint blockers (ICBs) have played an essential role in tumor treatment. ICBs is a kind of humanized immunoglobulin which targets and inhibits the molecules responsible for the physiological “off-switch” of immune cells to prevent an excessive and uncontrolled immune response [8]. However, tumor cells evade the monitoring of the immune system by reducing immunogenicity, which leads to the imbalance of the immune system in tumor patients. In addition, the immune suppression network of tumor genetic and epigenetic modifiers in the tumor microenvironment helps tumors to develop resistance to immune checkpoint blockers [9].

In recent years, ferroptosis and autophagy have played an essential regulatory role in diseases and tumors, which has been called the focus of treatment and prognosis research of related diseases. Therefore, we reviewed the basic molecular mechanisms of ferroptosis and autophagy. In addition, we also discussed the relationship between ferroptosis, autophagy, tumor, and immunity and the role of autophagy-dependent ferroptosis in tumors.

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2. Ferroptosis mechanism

Ferroptosis is a newly discovered cell death type dependent on lipid peroxidation, which is different from classical Programmed cell death (PCD) in morphology, physiology, and biochemistry [10,11]. Ferroptosis can be induced by external/internal pathways, such as cystine/glutamate transporter (System Xc-) or activation of iron transporter serum transferring and whey ferritin to start external pathways. The intrinsic pathway activates 12 by blocking intracellular antioxidant enzymes (such as GPX4) [12]. Iron accumulation, lipid peroxidation, and membrane damage are the critical signals that ferroptosis initiates membrane oxidative damage (Fig. 1) [12]. The core molecular mechanism of ferroptosis involves regulating the balance between oxidative damage and antioxidant defense [13,14].

2.1. Iron toxicity

The classic ferroptosis inducer erastin or RSL3 can inhibit the antioxidant system and increase cell iron accumulation [15]. Iron produces ROS by Fenton reaction with different types of phosphor lipid and fatty hydrogen peroxide in an oxygen-enriched

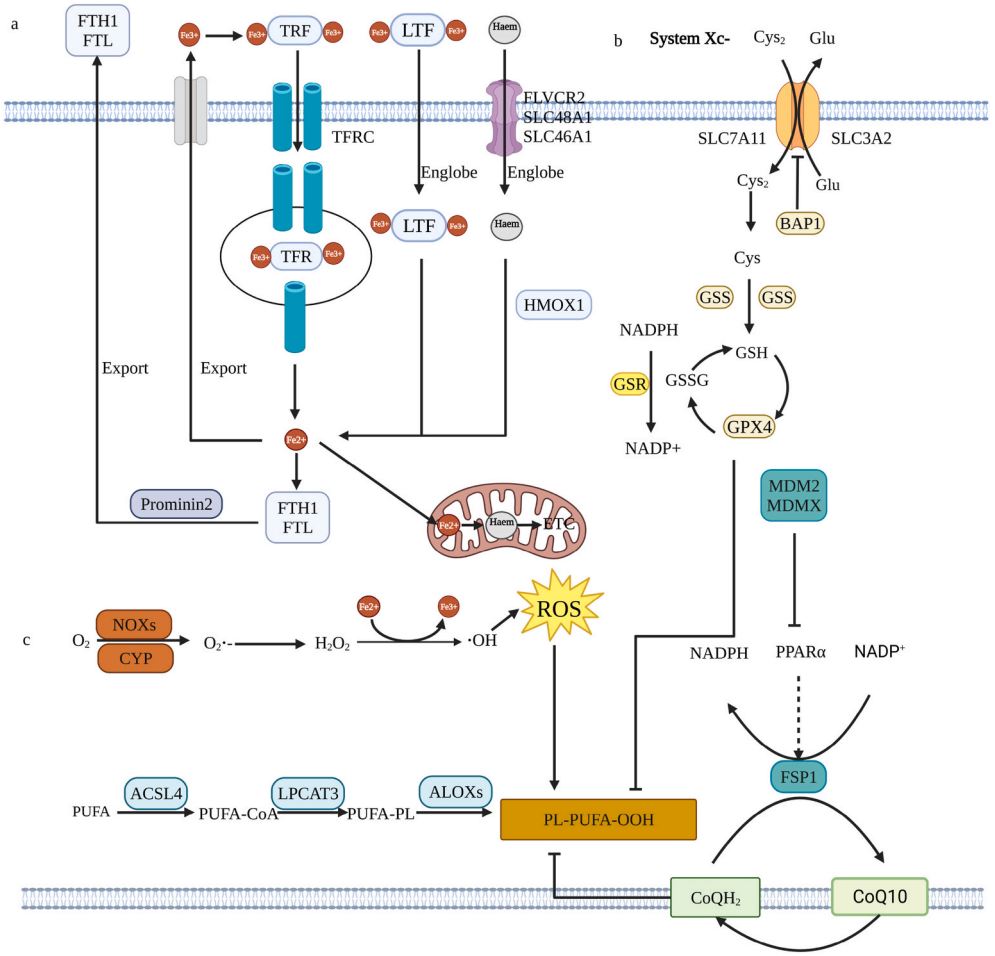

Fig. 1. Mechanism of ferroptosis. a. Extracellular Fe^{3+} enters the nucleosomes in cells via transferrin receptor 1 (TFR1), and Fe^{3+} is reduced to Fe^{2+}, increasing the intracellular level of iron ions and inducing ferroptosis. Excess Fe^{2+} is stored in ferritin to form an unstable iron pool. Ferritin light polypeptide 1 (FTL1) and ferritin heavy polypeptide 1 (FTH1) increase iron levels through autophagic degradation. b. System Xc-transports amino acids in a 1:1 ratio, pumping extracellular cystine and intracellular glutamate. Cystine undergoes a series of enzymatic reactions to form cysteine (Cys), which is synthesized into glutathione (GSH) by the action of cysteine-glutamate ligase and glutathione synthase. GSH is a critical factor in regulating ferroptosis and an essential antioxidant in the body. Glutathione peroxidase 4 (GPX4) precisely resists the peroxidation of cellular membrane lipids by ferroptosis; therefore, inhibition of GPX4 promotes the accumulation of lipid peroxidation and induces ferroptosis. c. Promotion of the long-chain lipid acyl coenzyme 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and arachidonic acid (ALOX15) lipid metabolism pathways induce ferroptosis. ACSL4 catalyzes free polyunsaturated fatty acids (PUFAs) and enters membrane phospholipids with the assistance of LPCAT3 to form polyunsaturated fatty acid phospholipids (PUFA-PLs). Subsequently, ALOX15 is involved in the peroxidation process of membrane phospholipids.

environment, which increases oxidative damage [16]. Fe3+ binds to transferrin (Tf) in serum, and TFRC on the cell membrane recognizes that Fe3+ is transported into the cell through endocytosis. After Fe3+ enters the cell, it is reduced to Fe2+ under the action of the iron body by metal reductase 6- transmembrane prostate epithelial antigen 3(STEAP3). Then Fe2+ is released from the endosome into the cytoplasm through member 2 of solute carrier family 11 (SLC11A2/DMT1) (Fig. 1) [17].

Most iron is stored in ferritin or heme. Ferritin consists of two subunits, ferritin light chain (FTL) and ferritin heavy chain 1(FTH1). Lysosomes can degrade FTL and FTH1 and increase free iron levels [18]. NCOA4 directly participates in the binding of FTH1, forms the ferritin complex, targets lysosomes for "ferritin phagocytosis," promotes ferritin degradation, and increases intracellular free iron [19 20] when an iron deficiency occurs. Finally, iron efflux protein solute carrier family 1(SLC40A1/FPN1) excretes iron, and Fe2+ is reoxidized to Fe3+21 by ferroxin (Fig. 1) [19]. However, most cells have no effective mechanism to export iron, which leads to the increase of unstable iron pool (LIP) and the occurrence of ferroptosis induced by LIP when the iron content exceeds the storage capacity [20].

2.2. Lipid peroxidation

Lipid production is the basis of survival, and lipid peroxidation is a vital sign of ferroptosis [21]. Lipid peroxidation during ferroptosis requires the synthesis of acyl-CoA, including long-chain family member 4 (ACSL4), lysophosphatidylcholine acyltransferase 3 (LPCAT3), and arachidonic acid 15- lipoxygenase (ALOX15) [22]. Glutathione peroxidase 4 (GPX4) is a nuclear enzyme that regulates lipid peroxidation. As a phospholipid peroxidase, it reduces lipid peroxides to fatty alcohols. Therefore, GPX4 plays an essential role in the process of lipid peroxidation [15].

2.2.1. Oxidation mechanism

Polyunsaturated fatty acids are essential to lipid metabolism, information transmission, and cell membrane [23]. AMP-activated protein kinase (AMPK) is a sensor of information transmission, which can regulate ferroptosis through AMPK-mediated phosphorylation of acetyl-CoA carboxylase (ACC) and biosynthesis of polyunsaturated fatty acids [24]. Long-chain fatty acids are mainly obtained in food, and when they include two double bonds, they are called polyunsaturated fatty acids (PUFAs) [25]. The more PUFA double bonds, the easier it is to be oxidized [26]. In addition, sterol lipids, including cholesterol, can be oxidized in membranes or low-density lipoprotein particles [27]. Oxidized cholesterol is also the active substrate of GPx4 [28]. However, exogenous cholesterol cannot regulate the death of human cancer cell ARL3, which proves that PUFAs play a crucial role in ferroptosis [29].

Lipid Peroxidation In the process of ferroptosis, PUFS, especially arachidonic acid and epinephrine, are most easily oxidized, which leads to the destruction of a lipid bilayer and affects membrane function [12]. Biosynthesis and remodeling of PUFAs in cell membranes need ACSL4 to catalyze the combination of free arachidonic acid or epinephrine with CoA to derive AA-CoA or AdA-CoA, respectively. Then LPCAT3 promotes their ethanolization with membrane phosphatidyl to form AA-PE or AdA-PE (Fig. 1) [22,30, 31]. ACSL3 converts monounsaturated fatty acids (MUFAs) into acyl-CoA esters, which can be incorporated into membrane phospholipids, thus protecting cancer cells from ferroptosis [32]. Peroxidase-mediated acetal phospholipids provide another source of PUFA fatty acids. Finally, different lipoxidases play a dependent role in mediating lipid peroxidation to produce hydroperoxide AA-PE-OOH or AdA-PE-OOH, which promotes ferroptosis [29].

Some membrane electron transfer proteins, especially POR46 and NADPH peroxidase (NOXs) [15,33,34], contribute to the production of lipid peroxide ROS in ferroptosis. In other cases, the mitochondrial electron transport chain and tricarboxylic acid cycle in mammals, coupled with glutamine decomposition and lipid synthesis signals, are involved in inducing ferroptosis [35]. However, the role of mitochondria in ferroptosis is still controversial [15,36]. Further evaluation of the expression of lipid peroxidation regulatory factors in different types of tumors plays a vital role in guiding patients when there are new treatment methods.

2.2.2. Antioxidant mechanisms

System Xc-system Xc-is an anti-amino acid transporter composed mainly of members 3 of the Solute Carrier Family (SLC3A2) and 11 of the Solute Carrier Family 7 (SLC7A11). It is widely distributed in the phospholipid bilayer, taking cysteine as 1: 1 and expelling intracellular glutamic acid [15,37,38]. To promote the synthesis of GSH in cells and prevent cells from being affected by oxidative stress (Fig. 1) [39]. GSH reduces ROS and active nitrogen under the action of GPXs. Inhibition of the activity of system Xc-affects the synthesis of GSH by inhibiting the absorption of cystine, which leads to the decrease of the activity of GPX, the accumulation of ROS, and finally, ferroptosis [40].

P53 inhibits the occurrence of tumors by inhibiting system Xc-mediated ferroptosis P53 inhibits the expression of SLC7A11 and the cysteine uptake, thus increasing cells' sensitivity to ferroptosis and inducing ferroptosis [41]. Huang et al. found that erastin can up-regulate the expression of P53 and down-regulate the expression of SLC7A11, thus inhibiting ferroptosis caused by system Xc- [42].

Nrf2-Keap1 induces ferroptosis through system Xc- Under normal circumstances, nuclear factor erythroid 2-related factor (NRF2) binds to Kelch-like ECH-associated protein 1 (Keap1). Under the condition of oxidative stress, Nrf2 is separated from Keap1 and translocated to the nucleus, which starts the transcription of antioxidant reaction elements and produces multiple antioxidant reaction elements and multiple antioxidant genes, including SLC7A11, which promotes the antioxidant effect of system Xc- [43].

GPX4 plays a vital role in limiting lipid peroxidation GPX4 is a multifunctional protein that can reduce free form or contact with lipids, protein, or lipid peroxide in the membrane. Its characteristics of reducing lipid peroxidation in membrane lipids determine its essential role in preventing ferroptosis (Fig. 1). Unlike SLC7A11 knockout mice, GPX4 mice showed early embryo death of [44,45]. It is suggested that SLC7A11 and GPX4 may have different functions in ferroptosis. Mice with a targeted mutation of selenocysteine, the active site of GPX4, into serine (U46S) or alanine (U46A) also showed embryo lethality of [46,47], indicating that the catalytic activity

of GPX4 is significant for normal embryo development. In addition to ferroptosis, GPX4 plays a role in limiting apoptosis [48], necrosis [49], and heat death [50], indicating that lipid peroxidation may be a standard signal to induce various types of RCD.

The SLC7A11-GSH-GPX4 axis is vital for GPX4 catalytic reaction As an electron donor, GSH reduces toxic phospholipid hydroperoxide to nontoxic phospholipid alcohol, and GSSG is produced as a by-product. GSH can be regenerated by reducing GSSG with glutathione reductase (GR) [51]. Therefore, erastin [15] and sorafenib [15,52,53] can inhibit SLC7A11, leading to GSH depletion and subsequent GPX4 inactivation, thus leading to lipid peroxidation-mediated ferroptosis cell apoptosis.

NADPH/FSP1/CoQ10 is another antioxidant pathway parallel to GPX4 Ferroptosis inhibitory protein 1(FSP1) is a crucial protein [54] for resisting ferroptosis. In the plasma membrane, FSP1, as an oxidoreductase, can reduce ubiquinone (CoQ10) to dihydro ubiquinone (CoQH2), which is an antioxidant that captures lipophilic free radicals and can prevent the accumulation of lipid peroxidation (Fig. 1) [55].

Inhibition of the dihydroorotate dehydrogenase (DHODH) pathway can induce ferroptosis, which differs from NADPH-GSH-GPX4 and NADPH-FSP1-CoQ10. Other critical antioxidant pathways include DHODH, a flavin-dependent enzyme located in the inner membrane of mitochondria. DHODH can oxidize dihydroorotate acid into orotic acid while providing electrons to CoQ to reduce it to CoQH2, thus inhibiting the progress of ferroptosis. It has been found that DHODH inactivation can induce extensive mitochondrial

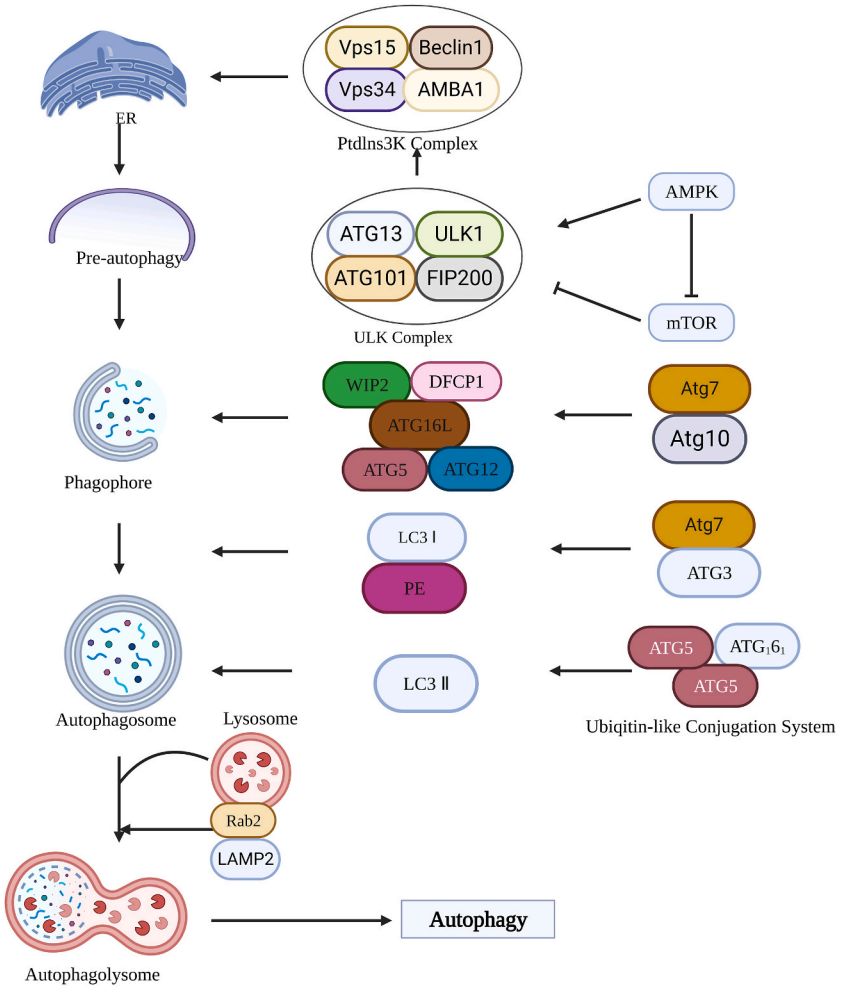

Fig. 2. Autophagic pathway. The molecular mechanism of autophagy is divided into four stages: initiation/extension, closure, fusion with lysosomes, and degradation. Nutrient deficiency is the main factor for autophagy activation by mTOR and AMPK. In addition, the hypo-energetic state activates the ULK complex through AMP-activated AMPK. To nucleate autophagosomes membranes, ULK phosphorylates components of the PI3K complex (composed of Vps15, Beclin1, Vps34, AMBRA1), and Vps34 produces PI3P at the autophagic precursor membrane. During the extension phase, the ATG2A-WIPI4 complex is required to mediate ER-phage binding and to establish lipid membrane transfer from the ER and vesicles to the phagosome. WIPI2 recruits a complex consisting of ATG12-ATG5 and ATG16L, which facilitates the binding of ATG8 family proteins to phosphatidylethanolamine (PE). ATG7 and ATG3T undergo a series of protein-lipid interactions to convert to LC3-I, followed by a ubiquitination-like ligand system that links LC to PE, which generates LC3-II. LC3-II is associated with autophagic vesicles, and once formed, autophagic vesicles fuse with lysosomes, triggering the formation of autophagic lysosomes. In the presence of lysosomal hydrolase, it is recycled into the cytosol and can be used in various metabolic pathways.

lipid peroxidation and ferroptosis in cancer cells with low expression of GPX4, and adding DHODH inhibitor to cancer cells with high expression of GPX4 will increase the sensitivity of cells to ferroptosis inducer [56].

3. Mechanisms of autophagy

Autophagy is a highly conservative catabolic process necessary for cell balance and lipid metabolism and changes the membrane structure to form autophagy [57]. Autophagy involves changes in membrane structure, mainly the changes in phagocytes [4]. Autophagy mainly consists of several key steps: autophagy induction, autophagosomes assembly and formation, autophagosomes and lysosomal membrane docking and fusion, and finally, autophagy content degradation and recycling in autophagy [58,59]. A specific set of ATG and accessory proteins strictly regulates each stage [60]. The critical enzyme of autophagy is autophagy-related (ATG) family protein [61]. 15 ATG family proteins are core ATG genes (ATG1-ATG10, ATG12, ATG13, ATG14, ATG16, and ATG18) because they are necessary for nonselective autophagy and selective autophagy, and they are evolutionarily conservative.

The autophagy initiation step is mediated by inhibition of mTOR (mechanistic target of rapamycin complex 1) or activation of AMPK, the ULK complex (including unc-51-like autophagy kinase 1/2 (ULK1/2, ATG13, ATG101, and RB1-inducible coiled-coil 1) (Fig. 2), and the inositol 3-kinase complex (PIK3C3, direct lineage of VPS34 homolog), act as scaffolds to recruit PI3P molecules [62–66], forming isolated autophagic precursor structures called phagosomes. Mechanisms that stimulate autophagy independent of mTOR, such as those involving LKB1-AMPK (AMP-activated protein kinase), protein kinase C θ, and hypoxia-inducible factor 1 (HIF1), are also known to the general public [67–70]. Hormonal changes and amino acids activate mTOR and inhibit ULK1/2. In circumstances of starvation, the release of inhibited ULK1/2 stimulates the translocation of the complex to the site of autophagosome formation, i.e. the endoplasmic reticulum or associated membrane. ULK1/2 translocates Ptdlns3K complex-mediated phosphatidylinositol 3-phosphate (PI3P) production to induce autophagosome membrane nucleation, likely to result in the recruitment of PI3P-bound ATG proteins, WD repeat structural domain phosphatidylinositol interaction (WIPI) proteins, and ATG9 vesicles to support phagosome nucleation [71]. Two ubiquitin-like binding pathways mediate the binding of microtubule-associated protein 1 light chain 3 (MAP1LC3, the closest homolog of yeast ATG) and phosphatidylethanolamine (PE), a practice called as MAP1LC3 esterification [4], to promote phagosome membrane expansion and closure. During LC3 esterification, LC3 inter-cut into soluble LC3I (Fig. 2), which is a precursor of LC3II, a cargo receptor tightly attached to the phagosomal membrane at the docking sites [72]. LC3II enables the docking of specific carriers and adaptor proteins, such as P62, that recognize the autophagic degradation of carriers, on the phagosomal membrane. The receptor binds to the specific cargo via ubiquitin labeling, followed by the extension of the phagosome to form separate autophagosome.

The autophagosome acquires SNAP receptor proteins, such as sytaxin17 (STX17) and YKT6, which interact with SNAP29 and lysosomal SNARE proteins, such as VAMP7, VAMP8, and STX17, to facilitate fusion with the lysosome. Furthermore, tethering mechanisms regulate the fusion step (e.g., HOPS complex, EPG5, and PLEKHM1) [4,73,74]. On the inner membrane of autophagosomes, ATG8 family proteins recognize specific cargoes, including mitochondria, ER fragments, lysosomes, protein aggregates, and ferritin ATG8 proteins either directly or indirectly recognize substrate proteins with LIRs (LC3 interaction regions) via recognition proteins containing LIRs. These adaptor proteins can carry both specific and non-specific cargoes, such as mitotic and ER-phagocytic adaptors and soluble adaptors, etc. To form autolysosomes, autophagosomes are transported to the perinuclear zone and merge with proximal lysosomes [75]. Autophagosomes can arise randomly throughout the cytoplasm, but lysosomes are predominantly located in the nucleus [76]. In the presence of lysosomal hydrolases, the inner membrane of autophagosomes and cytoplasm-derived macromolecules, such as proteins and organelles, can be degraded into amino acids or peptides for re-absorption and utilization by the cell [77]. Overall, autophagy is usually an exceptionally preserved modification of membrane dynamics.

The final step of autophagy is the degradation of autophagosomes. Syntaxin-17 (STX17) on autophagosomes controls autophagosome-lysosome fusion, and STX17 binds to Vesicle-Associated Membrane Protein 8 (VAMP8) on lysosomes via incorporating Qbc-SNARE Synaptosome-Associated Protein 29 (Synaptosome-Associated Protein 29) into the lysosomal membrane [78]. ATG14 and the homotypic fusion protein sorting (HOPS) tethering complex are crucial accessory proteins for this process [79,80]. Several investigations have demonstrated that the protein kinase ULK1 regulates STX17 during the maturation of autophagic vesicles. Unphosphorylated ULK1 recruits STX17 and enhances SNAP29 affinity. PKC-mediated phosphorylation of ULK1 has little effect on its function, but it suppresses autophagosome-lysosome fusion [81,82].

4. Ferroptosis associated with autophagy

Iron-dependent RCD, discovered in 2012, is considered a form of autophagy-dependent cell death in various cells (including cancer cells) [7]. Ferroptosis can be triggered by the activation of iron accumulation or the inhibition of a specific antioxidant system, which leads to the metabolism of lipid oxidative degradation during lipid peroxidation. Oxidative stress and peroxide products (such as malondialdehyde and 4-hydroxynonenal) are involved in the formation of autophagosomes [83]. Overactivation of autophagy is an essential driver of ferroptosis [84]. The increase of autophagy flux was observed in various cells to cope with the classical ferroptosis inducers, such as erastin and RSL3. Although proper autophagy may be a favorable survival mode [85], excessive autophagy, especially selective autophagy, and impaired lysosomal activity may promote ferroptosis [86]. Here, the critical mechanism of autophagy driving ferroptosis is expounded.

4.1. Nuclear Receptor Cofactor 4

Nuclear Receptor Cofactor 4 (NCOA4) is a selective cargo and receptor which is used for the autophagic turnover of ferritin by lysosomes (i.e., ferritin phagocytosis) (Fig. 3) [87]. Knocking out NCOA4 or ATG (such as ATG3, ATG5, ATG7, ATG13) can inhibit ferritin degradation, iron accumulation, and lipid peroxidation induced by erastin, and the subsequent ferritin transformation [78,88]. When the iron content in cells is high, HECT and RLD domains contain E3 ubiquitin ligase 2 to ubiquitinate NCOA4 and then degrade [89] through the ubiquitin-proteasome pathway, which indicates that HERC2 is negatively correlated with iron phagocytosis induction. In addition, insufficient ferritin phagocytosis may increase the activity of iron reactive element binding protein 2 (IRB2/IRP2) and then up-regulate TF [15] as feedback. There is evidence that ferritin phagocytosis is a necessary condition for iron phagocytosis-mediated inhibition of liver fibrosis [90,91]. Bisartemisinin-induced ferritin phagocytosis can promote ferritin phagocytosis and tumor cell death [91,92]. To further understand the different pathways leading to ferritin degradation, including autophagy and independent lysosomal degradation of ferritin, and their contribution to intracellular and systemic iron balance. These findings provide new insight into the interaction between autophagy and the regulation of cell death.

4.2. BECN1

It has been reported that BECN1 is a homolog of yeast ATG6, which is involved in autophagy induction and tumor inhibition [93]. As a SLC7A11/system Xc-binding protein, BECN1 can inhibit the transport activity of tumor cells to type 1 ferroptosis inducer but has no response to type 2 ferroptosis inducer [94,95]. BECN1 is phosphorylated by AMPK at Ser90 and Ser93, which restrict SLC7A11/system Xc-complex and inhibit cell ferroptosis [95]. On the contrary, Tatbecilin, as BECN1 activating peptide, enhanced the anti-cancer activity of ferroptosis inducer erastin [95]. In addition, it was found that BECN1 regulates ferritin phagocytosis by mediating autophagy-dependent and autophagy-independent regulatory proteins. For example, BECN1 mediated by ELAVL1 can increase the phagocytosis of hepatic stellate cells [91]. Therefore, revealing the complex role of BECN1 in autophagy-dependent

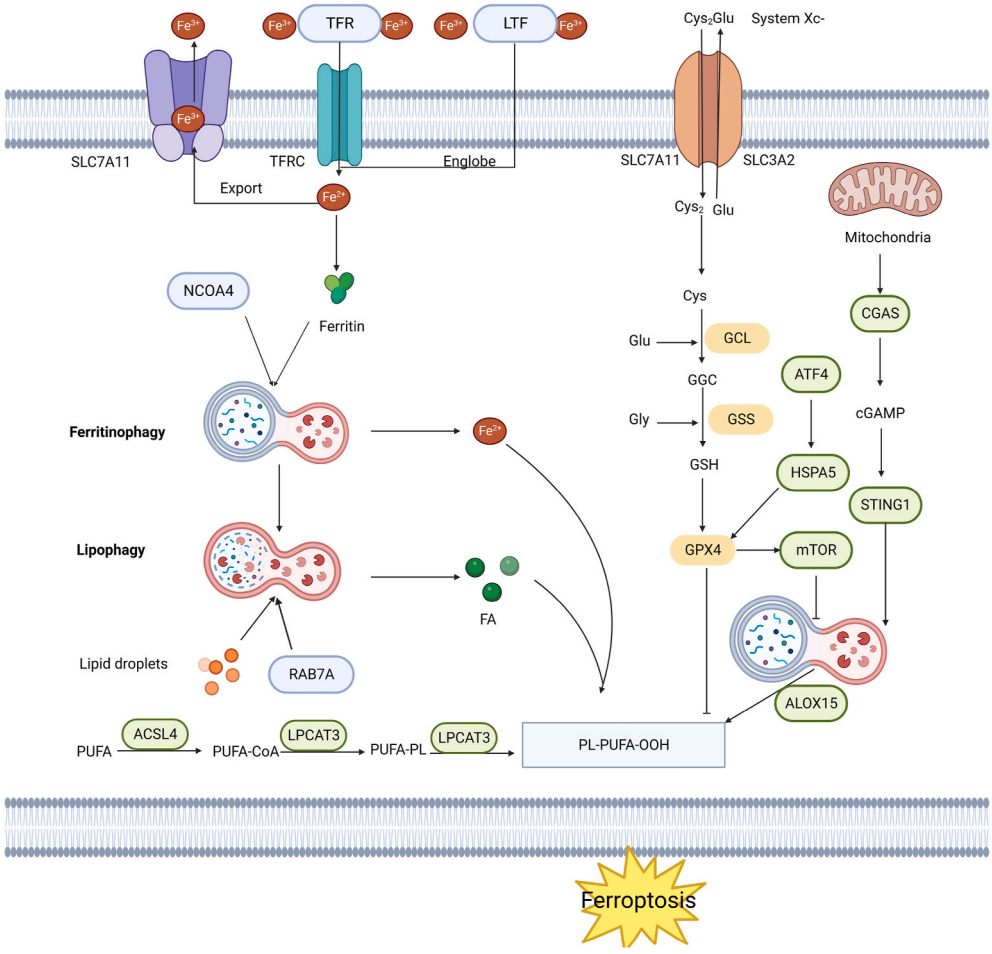

Fig. 3. The role of autophagy in ferroptosis. Ferritin phagocytosis mediated by a. NCOA4; B. RAB7A gene family (Rab7a)-dependent lipophagy; C. mTOR causes autophagy-related ferroptosis through the formation of autophagy bodies and subsequent lipid peroxidation.

ferroptosis may depend on BECN1 recognizing more related proteins [96,97].

4.3. Heat shock protein 90

Heat shock protein 90(HSP90) inhibitor can induce apoptosis [98] through the activation-dependent mitochondrial pathway. In addition, HSP90 plays a vital role in necrosis by binding and regulating the activity of RIPK1, RIPK3, or MLKL in a context-dependent manner [99–101]. Recently it has been found that the ferritin pathway is regulated by HSP90 [102]. In addition, knocking out HSP90 by siRNA can partially reverse the ferroptosis induced by erastin/glutamate [102]. In mechanism, HSP90 promotes ferroptosis by regulating the stability of LAMP2A, an isomer of LAMP2 and the receptor of CMA. Finally, CMA mediated by LAMP2A and HSPA8/HSC70 led to the degradation of GPX4 induced by erastin in HT-22 cells [102]. These results, combined with the discovery that HSPA5 increases the stability of GPX4 protein [103], support HSPs to play an essential role in iron poisoning.

4.4. Dependence of lipophagy on RAB7A

Lipophoagy is a selective autophagy that leads to the autophagic degradation of intracellular lipid droplets. LDs are a lipid-rich cell structure that regulates the storage and hydrolysis of neutral lipids (Fig. 3) [104], providing another potential possibility for regulating cell form. The hydrophobic core of neutral lipids, including triacylglycerol (TG) and cholesterol ester (CE), makes LDs the hub of lipid metabolism and energy balance [105]. RAB7A member RAS oncogene family (Rab7a) belongs to the RAS small molecule GTP superfamily, which is the mediator of in vivo transport and the central regulatory factor of liver lipophagy [106]. LDs protect cells from PUFA oxidation by transferring free fatty acids to their core, providing a defense mechanism under oxidative stress [107]. Studies have shown that LDs are negatively correlated with ferroptosis induced by oxidative stress [108]. During the ferroptosis of mouse hepatocytes and human hepatocyte line (HepG2) induced by RSL3, the level of LDs increased initially but decreased by with the gradual aggravation of ferroptosis [108]. More importantly, lipolytic degradation of LDs promotes lipid peroxidation during ferroptosis, which can be reversed by knocking out LDs cargo receptor RAB7A108 or ATG5 [108]. However, the up-regulation of tumor protein D52 (TPD52) can increase the formation of LDs, thus inhibiting the ferroptosis of hepatocytes induced by RSL3 [108]. LDs causing ferroptosis are still unclear, and adjusting ferroptosis according to lipid types is essential.

4.5. SQSTM1-reliant timepiece phagocytosis

The circadian clock is an endogenous and inducible rhythmic oscillation for about 24 h, which plays an essential role in the internal circulation of behavior, physiology, and metabolism [85]. Selective degradation of core circadian clock protein arene receptor-like nuclear translocation protein (ARNTL/BMAL1) promotes ferroptosis through autophagy, namely clock phagocytosis [109]. Ubiquitin-mediated ARNTL protein has been widely known [110–112], but it needs to be clarified whether the autophagy system can degrade ARNTL/BMAL [109] until the clocks are identified. In vitro, when used for ferroptosis induced by type 2 ferroptosis inducers (such as RSL3 and FIN56), the stability of the protein of ARNTL decreases, but for type 1 ferroptosis inducer 1 (such as elastin, sulfadiazine, and sorafenib), the stability of protein of ARNTL is not influenced [109,113]. Although clock phagocytosis requires several ATG proteins, such as ATG5 and ATG7, clock phagocytosis does not need ATG9A [109], which is different from classical autophagy in mechanism. As an autophagy receptor of clock phage, SQSTM1 mediates the degradation of ARNTL protein, which is a necessary condition for ferroptosis. Autophagic ARNTL is degraded by blocking hypoxia-inducible factor 1 subunit α(HIF1A). HIF1A is one of the leading transcription factors that regulate hypoxia response, and it plays a role in promoting survival in ferroptosis by up-regulating fatty acid binding protein 3(FABP3, muscle and heart) and fatty acid binding protein 3(FABP3, brain) to store fat [109]. Regarding mechanism, ARNTL antagonizes ferroptosis [109] by inhibiting the expression of Egl-9 family hypoxia-inducible factor 2 in vivo and in vitro and activating HIF1A, which is beneficial to survival. It is still unclear how the circadian rhythm disorder affects iron protease sensitivity.

4.6. Alterations in lysosomal membrane permeability mediated via STAT3

Recent studies show that lysosomes have a potential role in inducing ferroptosis [114,115]. In HT1080 cells, lysosomal inhibitors (such as ammonium chloride, bafilomycin A1, and antimycin A methyl ester) inhibited ROS production induced by erastin or RSL [115]. Erastin-induced lysosomal membrane permeability (LMP) and subsequent lysosomal death contribute to ferroptosis [114]. Mechanically speaking, the expression and release of CTSB (tissue protein B) mediated by STAT3 (signal transducer and activator of transcription 3) are necessary for ferroptosis [114]. The inhibition of lysosomal-dependent cell death by medicinal cathepsin inhibitor CA-074Me limited the ferroptosis of pancreatic cancer cells induced by erastin [114]. Notably, the activation of STAT3 mediated by integrins ITGA6 and ITGB4 promoted the survival of breast cancer cells in response to elastin, indicating that different pathways can converge on STAT3 to promote the induction of ferroptosis [116].

4.7. HMGB1

High-mobility group box 1(HMGB1) plays a position-dependent role in promoting autophagy [117]. Cell membrane HMGB1 can be combined with BECN1 to induce autophagy. Nuclear HMGB1 regulates the expression of heat shock protein family B member 1 (HSPB1) and promotes the reorganization of the cytoskeleton, which is necessary for mitosis [118]. Extracellular HMGB1 induces

autophagy by activating the PIK3C3 complex [119]. Extracellular HMGB1 is a molecular model related to injury, which induces inflammation and immune response during ferroptosis induced by RSL3 and elastin in vitro [119]. Interestingly, intracellular HMGB1 positively regulates the ferroptosis sinduced by erastin in leukemia cells by activating the up-regulation of TFRC expression downstream of mitotic-activated protein kinases (MAPK, such as MAPK/JNK and MAPK/p38) [120]. The broader correlation of HMGB1 in autophagy, ferroptosis, and immune response needs to be further elaborated.

5. Ferroptosis, autophagy, and tumors

5.1. Ferroptosis and tumors

It is found that many kinds of tumor cells are very sensitive to ferroptosis inducers. Ferroptosis can selectively induce the death of tumor stem cells and improve the sensitivity of tumor cells to chemotherapy drugs. Therefore, inducing ferroptosis has important anti-tumor potential.

5.1.1. Gene mutation

Both RAS-dependent and Ras-independent pathways can promote the death of iron-dead tumor cells [121]. In human rhabdomyosarcoma cells, RAS mutation may even cause ferroptosis resistance in some cases [122]. DNA damage accumulates in iron-death-sensitive $P53^{3KR}$ cells, resulting in aneuploidy, which is a sign of cancer-related genomic instability [123]. In addition, the sensitivity of ferroptosis is also affected by the mutant epidermal growth factor receptor (EGFR) [124] or the mutant IDH1 [125]. Generally speaking, the gene mutation is sensitive to the role of ferroptosis.

5.1.2. Ferroptosis and lung cancer

Studies have shown that high serum iron concentration and ferritin levels are positively correlated with the incidence of lung cancer [126]. Guo et al. found that erastin induced ferroptosis by depleting GSH and inactivating GPX4 and cooperated with cisplatin to inhibit the proliferation of lung tumor cells [127]. At the same time, Wang et al. found that tumors with high expression of related cytokine SOX2 were more resistant to ferroptosis, and the expression of SLC7A11 was positively correlated with SOX2 in mice and human lung cancer tissues [128]. Zhang et al. found that RNA binding protein RBMS1 increased in lung cancer, and its high expression was related to the decreased survival rate of patients. Through the direct interaction with translation initiation factor Eif3d, it bridges SLC7A11, causes cystine uptake mediated by SLC7A11, and promotes ferroptosis [129]. The latest research found that Nrf2 nano-regulators induced ferroptosis and stimulated the tumor microenvironment of lung cancer by down-regulating the mRNA expression of Nrf2 target genes (including SLC7A11, GPX4, SLC40A1, and AKR1 family genes) [130]. In addition, patients with lung adenocarcinoma with KRAS mutation are easily affected by the inhibition of SLC7A11, and the mutant-activated KRAS significantly increases the intracellular cystine level and glutathione biosynthesis [131]. Ubiquitin-specific protease 35 (USP35) overexpression did not affect tumorigenesis and ferroptosis under basic conditions, but reduced erastin/RSL3-triggered iron disturbance and ferroptosis, there facilitating lung cancer cell growth and tumor progress. Knocking out USP35 makes lung cancer cells sensitive to cisplatin and paclitaxel chemotherapy [132].

5.1.3. Ferroptosis and liver cancer

The changes in iron metabolism regulation play a role in the pathogenesis of HCC. Studies using HCC cell lines indicate that ferroptosis may be due to sorafenib inhibition of cystine/glutamate antiporter SLC7A11. Clinical studies have shown that the target gene of NFE2L2 MT1G is a biomarker and a contributing factor to sorafenib resistance. Knockout of MT1G can restore the anticancer activity of sorafenib by inducing ferroptosis in human HCC cells [[133] , [134]]. Sun et al. found that statins quiescin sulfhydryl oxidase 1 Gene increased the sensitivity of HCC to ferroptosis induced by sorafenib by inhibiting the activation of Nrf2 [135]. Yao et al. found that *anti*-LN2 therapy can improve the treatment of liver cancer by targeting ferroptosis, and the absence of LIFR can activate NF-κB signal transduction through SHP1, leading to the up-regulation of iron chelating cytokine LCN2, thus depleting iron and making ferroptosis inducer insensitive [136]. At the same time, branched-chain amino acid aminotransferase 2 (BCAT2) can regulate the ferroptosis of cancer cells. BCAT2, a critical enzyme that mediates the metabolism of sulfur-containing amino acids, regulates the intracellular glutamate level, activates the specific antagonistic system Xc-through ectopic expression, and protects HCC and PDAC from ferroptosis in vitro and in vivo [137]. In addition, the high intake of dietary iron will also increase the risk of liver cancer [138], which indicates that iron-chelating agents (such as deferoxamine) or drugs that increase iron-mediated toxicity (such as iron-induced drugs, sorafenib, statins, and artemisinin) can be used to treat cancer [12]. More and more evidence show that ferroptosis may effectively inhibit the growth of HCC cells, thus making ferroptosis a new strategy for HCC treatment.

5.1.4. Ferroptosis and pancreatic cancer

Ferroptosis can induce PDAC5 in two ways [5]. The exogenous pathway is mainly induced by inhibiting system Xc- (such as using elastin, sorafenib, or sulfasalazine) [15]. GSH, as an additional factor of GPX4, inhibits lipid ROS during ferroptosis [121]. Although proto-plasma biosynthesis dependent on peroxisome contributes to lipid peroxidation, producing polyunsaturated fatty acids mediated by ACSL4 and LPCAT3 provides ALOX-dependent lipid peroxidation [22,30]. The internal way is to reduce the expression activity of GPX4 through small molecular compounds such as RSL3, FIN56, or ML210. Or ferroptosis can be triggered or enhanced by autophagy degradation of intrinsic iron storage ferritin or intracellular export of SLC40A1 [139]. Lipophilic antioxidants (such as ferrostatin 1 and liproxstatin 1) and iron-chelating agents (such as deferoxamine) can block iron cell death. Therefore, the low expression of ACSL4 or

ALOX, or GPX4 may produce some ferroptosis resistance. In addition, some studies have found that PDAC is highly dependent on cysteine concentration. PDAC pumps cysteine through system Xc-to synthesize GSH and coenzyme A to resist ferroptosis.

5.1.5. Epithelial-to-mesenchymal transition

Epithelial-to-mesenchymal transition (EMT) is a process in which epithelial cells lose polarity and intercellular adhesion characteristics related to epithelial phenotype and gradually gain migration and invasion ability related to mesenchymal phenotype. Once EMT occurs in the tumor, it will produce drug resistance and be challenging to treat [140]. EMT-mediated tumor metastasis and drug resistance are stimulated by transcription factors, such as SNA1, TWIST1, and ZEB1, which are potential targets in oncology. The high baseline transcription level of ZEB1 is related to the sensitivity of cells to ferroptosis [140], partly due to the up-regulation of PPARγ induced by ZEB1, which is the primary regulator of liver lipid metabolism. ZEB1 found that it can regulate the sensitivity of mesenchymal cancer cells to the inhibition of GPX4 as an adipogenic factor, promote tumor invasion and treat drug resistance by inducing EMT in tumor cells [141]. The absence of tumor suppressor Merlin determines the dependence of the mesothelioma model on GPX4 by up-regulating various ferroptosis regulators, including ACSL4 and transferrin receptors [142]. The increase of CD44-dependent iron endocytosis will promote the activity of iron-dependent demethylase and the expression of genes related to EMT signal transduction, thus making breast cancer cells sensitive to ferroptosis [143]. These clinical data show that EMT-induced ferroptosis produces susceptibility.

5.2. Autophagy and tumors

Autophagy plays an essential role in many diseases, such as cancer, autoimmune diseases, and neurodegeneration, which helps the body to understand damaged cells, proteins, and pathogenic microorganisms [57]. Because autophagy is an essential part of the quality control mechanism to support cell balance, drugs or gene interventions that damage autophagy flux will damage the genome stability of healthy cells, thus inducing malignant transformation. However, a large amount of evidence supports the view that autophagy has a Jaanus-like influence on cancer biology, and autophagy can be regarded as a process of tumor inhibition or promotion according to cancer type, stage, driver gene mutation, and other variables [108,144–150]. This means that inhibiting autophagy in different periods is a new treatment direction.

5.2.1. Autophagy and its regulatory mechanism

There are many autophagy-mediated signal pathways in tumor cells. The following paths are known. First, the activation of PI3K/Akt/mTOR-mediated signaling pathway can inhibit autophagy, and PTEN, insulin, Sirt1, 5′AMP-activated protease (AMPK), mitogen-activated protein kinase (p38-MAPK), P53 and ROS-related pathways regulate it [151–153]. Second, the Ras/Raf/ERK signaling pathway acts as Ras or ERK in tumors [154,155]. Third, the c-Jun N-terminal kinase (JNK) signaling pathway is involved in post-translational modification and constitutive phosphorylation of Bcl-2, which dissociates Bcl-2 from Beclin1 and stimulates autophagy [156–158]. Finally, the intracellular calcification signal pathway exists in ER, mitochondria, and lysosomes. The release of Ca2+ is controlled by inositol 1,4,5-triphosphate receptor (IP3Rs) or RyRs, dual-pore channel 1/2 (TPC1/2), and transient receptor potential superfamily channels, such as transient receptor potential cation channel member 1 (TRPML1) and TRPM2. In addition, ER-derived Ca2+ released from IP3Rs can inhibit autophagy by inhibiting AMPK and stimulate autophagy 161–164 by activating AMPK or Beclin1 [159–162].

5.2.2. Autophagy and tumor development

Autophagy plays a dual role according to the development stage of cancer [163]. In the early stage of cancer, autophagy can prevent the occurrence of chronic tissue injury, cell injury, and inflammation by regulating the quality control function of protein and organelles and inhibiting the accumulation of P62 protein, thus preventing the proliferation and metastasis of the tumor [146,164,165]. EMT is very important for tumor migration and invasion. It has been reported that autophagy stimulation can reduce tumor invasion and metastasis by degrading EMT inducer [166,167]. However, in the late stage, autophagy can reduce DNA damage, enhance the comprehensive pressure signals of tumor cells, such as metabolic pressure, hypoxia, redox pressure, and immune signals, then maintain the metabolism, growth, and invasion of tumor cells, and finally lead to tumor progress and resistance to therapeutic drugs [164,168]. In advanced tumors, autophagy can protect tumor cells. In patients receiving radiotherapy, chemotherapy, and immunotherapy, autophagy can prevent the death of tumor cells after treatment so that tumor cells are dormant. Once activated, tumor cells quickly relapse or metastasize [169,170]. Therefore, just as proteasome inhibitors have been proven effective for multiple myeloma, it is also essential to determine the inhibitory effect of autophagy on cancer types with specific gene mutations [171]. For example, the indicators of autophagy dependence may be BRAF, KRAS, EGFR vIII, and LKB [147,172,173]. In addition, another tumor-promoting function of autophagy is maintaining the stability of blood arginine by reducing the level of arginase secreted by the liver [174]. Autophagy can inhibit the anti-tumor immunity mediated by $CD8^{+}$T cells and promote the survival and metastasis of latent cancer cells [175]. Therefore, it is very complicated to treat tumors by regulating autophagy.

Although it is still challenging to unravel the role of autophagy in tumor cells in tumor progression, people are increasingly interested in understanding the contribution of autophagy in host cells (especially immune cells). Under these circumstances, some studies have shown that inhibiting autophagy in host cells hinders the progress of tumors. For example, in the context of the established KRAS-driven lung malignant tumor, the deletion of host ATG7 may create an unfavorable metabolic environment for the hyperproliferative malignant cells and hinder the progress of the disease [176,177]. Similarly, the systemic deletion of ATG7 restricts the growth of tumor xenografts with arginine deficiency, which reflects the decrease of arginine level in circulation, which is caused by the

enhancement of arginine-releasing enzyme 1 (ARG1) released by autophagy-deficient hepatocytes [174]. The beclin1 gene was found in human hepatocellular carcinoma, breast cancer, ovarian cancer, and prostate cancer cells, which is an essential gene in the autophagy process [93,178–180]. In Beclin 1 ± mouse model, the spontaneous rate of tumor cells is high [181,182], which indicates that autophagy is a tumor inhibition mechanism [57,145,179,183]. ATG gene is also closely related to cancer. ATG2B, ATG5, and ATG12 were found in patients with gastric and colorectal cancer, and these genes may be involved in cancer development [184].

Notably, the non-autophagic driving function of the autophagy mechanism may also regulate the immune response of developing tumors [185]. For example, tumor cells bind to Toll-like receptors (TLRs), Fc receptors, or pro-apoptosis receptors after dying. T cell immunoglobulin and mucin domain containing 4 Gene(TIMD4), the LC3 binding mechanism is recruited to the phagocyte membrane, a process commonly called LC3-related phagocyte phagocytosis (LAP) [186], which limits the inflammatory reaction in phagocytes [187].

These conflicting functions may depend on the stage and background. In ATG knockout mice, only benign tumors occurred, such as hepatic adenoma in wild-type mice and pancreatic intraepithelial neoplasia in $KRAS^{G12D/+}$ mice, but these tumors were not wholly malignant [188–191]. The effects of autophagy may also depend on other factors, such as the mutation state of the P53 gene [190]. However, the evidence for this view is contradictory [172]. In addition, although autophagy gene mutation has been reported in human cancer, extensive genome analysis has not found the phenomenon of repeated occurrence in the ATG gene or human cancer driver gene mutation.

5.3. *Autophagy-related ferroptosis and tumors*

$KRAS^{G12D}$ is the most common mutation of KRAS mutation in pancreatic cancer. It has been found that the release of autophagy-dependent ferroptosis$KRAS^{G12D}$ from PDAC induced by oxidative stress is the initial step for KRAS to play a carcinogenic role [192]. The start-up and progress of PDAC are related to the oxidation pressure, that is, the imbalance between free radicals and antioxidants [193,194]. In order to determine whether oxidative stress can induce the release of cancer proteins, two human PDAC cell lines (PDAC1 and AsPC1) were used in the experiment, both of which carried $KRAS^{G12D}$ mutation. Hydrogen peroxide-induced the release of $KRAS^{G12D}$ from PDAC1 and AsPC1 cells and primitive human PDAC (pHs PDAC) in a time-dependent manner. These results indicate that oxidative stress induces the release of $KRAS^{G12D}$ from PDAC cells. In order to verify that H2O2-induced cell death affects the release of $KRAS^{G12D}$, autophagy ATG5, and ATG7 were knocked out by shRNAs, which limited the H2O2-induced cell death and the release of $KRAS^{G12D}$ from PDAC1 and AsPC1 cells, and proved that autophagy-dependent ferroptosis promoted the release of $KRAS^{G12D}$ protein during stress [192].

One study found that Zalcitabine, an antiviral drug, inhibited the growth of pancreatic cancer cells by inducing autophagy-

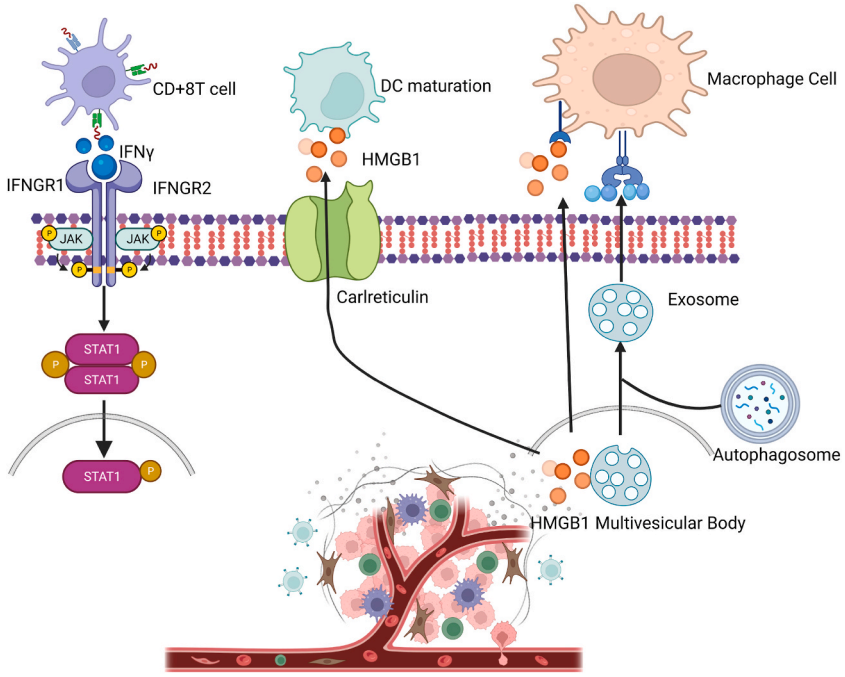

Fig. 4. Ferroptosis and tumor microenvironment a. $CD8^+$ T cells mediate the release of IFN γ, which activates the STAT1 pathway and inhibits SLC7A11 expression in tumor cells, thereby inducing ferroptosis in tumor cells. b. Tumor cell ferroptosis releases HMGB1, which promotes the maturation of DC cells, and mature DC cells activate $CD8^+$ T cells, thereby inducing ferroptosis in tumor cells. c. Tumor cell ferroptosis-mediated $KRAS^{G12D}$ binds to the advanced glycosylation basal product-specific receptor (AGER) on the surface of macrophages, triggering the polarization of M2-type macrophages and thus limiting antitumor immunity.

dependent ferroptosis in vivo and in vitro [195]. In terms of mechanism, these effects depend on the activation of the CGAS-STING1 pathway induced by mitochondrial DNA (mt DNA) pressure, which leads to autophagy-dependent ferroptosis through lipid peroxidation [195]. Mitochondria play an essential role in oxidative stress and cell death. On the one hand, the voltage-dependent anion channel is the direct target of erastin [196], and the oxidative stress caused by iron overload accelerates ferroptosis in cysteine deprivation in mitochondria [36,197,198]. On the other hand, mt DNA-depleted cancer cell line (ρ0 cell line) cultured with ethidium bromide for a long time showed the same sensitivity to ferroptosis inducer as its parent line [15]. On the contrary, some ρ0 cancer cells are more sensitive to cell death caused by hydrogen peroxide by promoting lipid peroxidation [199]. Mitochondrial dysfunction is related to tumors' occurrence, development, and drug resistance [200]. Mitochondrial changes, such as mt RNA damage and mutation, metabolic reprogramming, fission and fusion kinetics, and sensitivity to cell death, can provide unique therapeutic targets for cancer treatment [200].

Member 1 of Solute Carrier Family 40 (SLC40A1, also known as FPN1) is the only mammalian iron efflux protein found on the cell membrane, which mediates iron release from cells [201]. Recent studies have found that SLC40A1 [202] is involved in clock phagocytosis, which is beneficial to iron accumulation, lipid peroxidation, and plasma membrane damage, which is the main driving event of ferroptosis. Li et al. found that knocking out ATG5 or ATG7 can reverse the down-regulation of SLC40A1 protein induced by erastin. In addition, the drug inhibition of autophagy with CQ or bafilomycin A1 also prevented the down-regulation of the SLC40A1 protein induced by erastin. The anticancer activity of imidazole ketone elastin (IKE) was inhibited in SLC40A1 knockout genome [202]. This tumor inhibition mediated by SLC40A1 knockout is related to the increase of the mRNA content of MDA, iron, and prostaglandin-endoperoxide synthase 2 (PTGS2) in tumor [119]. Therefore, inducing autophagy degradation of SLC40A1 can restore the drug sensitivity of ferritin-resistant cancer cells. These findings emphasize the breakthrough of autophagy-mediated ferroptosis in tumor treatment.

6. Autophagy, ferroptosis, and tumor immunity

6.1. Overview of ferroptosis and tumor microenvironment

The tumor microenvironment is a dynamic network composed of malignant cells, non-malignant cells (stromal cells, immune cells, inflammatory cells, endothelial cells, Etc.), and an extracellular matrix, which affects the proliferation and development of tumor cells (Fig. 4) [203].

Monocytes can be polarized into classical proinflammatory (M1) macrophages and alternately activated (M2) macrophages (Fig. 4) [204]. In the early stage of tumorigenesis, proinflammatory cytokines promote M1-like macrophages to display iron chelate phenotype as an anti-tumor reaction [205,206]. In contrast, M2-like macrophages showed iron release phenotype, with higher expression of iron export protein FPN and lower expression of storage protein FT, thus increasing iron circulation and export to extracellular space. Iron transport to tumor cells may be completed by ferritin-mediated macrophage excretion, and then tumor cells take TFR1. Alternatively or in addition, lipocalin-2 secreted by macrophages can be used to transport iron to breast and other tumor cells [207]. Ferritin is an iron-containing protein secreted by macrophages. As mentioned above, it is also an iron transport mechanism [208]. In addition, because ferritin inhibits the cleavage of endogenous inhibitor HKa by kininogen, ferritin secretion may also affect endothelial cells and promote angiogenesis in the tumor microenvironment [209,210].

The iron itself may regulate the interaction between immune cells and tumor cells in TME by affecting the polarization of macrophages. For example, a high-iron diet promotes the polarization of M2 macrophages in vivo and inhibits inflammatory response [211]. On the contrary, the opposite result was observed in the mouse macrophage cell line and iron-induced polarization into the M1 type by increasing ROS [212]. In addition, the proliferation of tumors may not depend on iron, and macrophages can secrete FT into TME to stimulate the formation of tumors [213]. Interestingly, in the mouse lung cancer model, the TAM subgroup in the bleeding area showed iron overload and pro-inflammatory phenotype [214], which could clear tumor cells. Experiments have proved that this difference is absorbed by tumor blood vessels through damaged red blood cells. Clinically, the application of iron nanoparticles is related to M1 polarization and tumor inhibition in vitro and in vivo [214].

Iron overload or iron deficiency will adversely affect the adaptive immune response in the human body, so iron homeostasis is an essential determinant of effective T cell-mediated immune response [215,216]. On the one hand, iron metabolism disorder is related to the imbalance of T cell subsets [217]. Iron can also directly regulate T cell phenotype and down-regulate the expression of CD2 and CD4 phenotypes in vitro [218]. When iron uptake is inhibited by inhibiting TFR or using an iron complexing agent, Th1 cells are more susceptible to iron deficiency in vivo than Th2 cells [219,220]. On the other hand, T cells need iron in the process of immune response, such as infection or tumor. At the early stage of T cell differentiation, the activation of T cells is accompanied by the up-regulation of CD71, an IL-2-dependent pathway. On the contrary, in the mouse model, the induction of T cell energy is accompanied by the decrease of TFR surface expression [221]. Due to the increase of LIP and the expansion of ROS formation, deleting the FTH gene in hematopoietic cells reduces the number of T cells and B cells, indicating that iron in FT is necessary for adaptive immune response [222]. Therefore, T cell function is closely related to iron metabolism, but the extent to which iron imbalance in TME leads to immune deficiency and promotes tumor development needs further discussion.

6.2. Ferroptosis in tumor therapy: an immunological perspective

6.2.1. Ferroptosis and antitumor immunity

ICBs mainly include PD-1, PD-L1, and CTLA-4 inhibitors. Unlike traditional tumor treatment, ICBs have undergone revolutionary

changes in treating solid tumors [223]. ICBs cannot directly induce the death of tumor cells like traditional treatment. However, ICBs can indirectly lead to tumor cell death by enhancing cytotoxic T cells' activity [224].

Wang et al. reported that $CD8^+$T cells induced the iron formation of tumor cells in vivo [225], which opened a new direction for immune cells to regulate iron formation. $CD8^+$T cells activated by immunotherapy down-regulated the expression of SLC7A11, and IFN-γ produced by $CD8^+$T cells increased the binding of signal transduction signal and transcription activation signal (STAT1) to the transcription initiation site of SLC7A11 and inhibited its transcription. The lack of STAT1 in tumor cells abolished IFN-γ-mediated down-regulation of SLC7A11 and reversed lipid peroxidation and cell death induced by RSL3. On the contrary, tumor cells treated with iron protease or ferritin as inhibitors are insensitive to PD-L1 inhibitors [226,227]. Further, in vivo, experiments showed that T cells induced ferritin deposition in ovarian cancer mice. Immunohistochemical results showed that the level of CD8 was negatively correlated with the expression of Xc-complex, which indicated that the sensitivity to iron protease was parallel to the anti-tumor immunity. Subsequently, the same research group found that although IFN-γ is a well-known anti-tumor cytokine, IFN-γ activated by immunotherapy and ataxia mutation activated by radiotherapy synergistically induce the iron formation of human fibrosarcoma and melanoma [226]. Recent studies have shown that nanoparticles rich in RSL-3 can promote the immune death of tumor cells, and blocking the combination therapy of PD-L1 further enhances the infiltration of T cells in TME [228].

Immune tolerance is an inevitable result of tumor treatment. Recent studies have shown that iron protease is involved in T cell immunity and tumor immunotherapy [225]. Recent studies have shown that iron inhibin −1 promotes $CD8^+$T cells in tumors to produce high IFN-γ, and preventing ferroptosis of $CD8^+$ T cells by targeting CD36 enhances the efficacy of immunotherapy [229]. Jiang et al. also reported that inhibiting ferritin production is helpful for drug resistance treatment against PD-1/PD-L1 inhibitors [230]. Although some studies have shown that inducing ferritin production can help overcome the drug resistance of immunotherapy, this combination therapy may not be suitable for all treatment situations. The results of iron protease inducer on tumor immunity are different in tumors with different immunophenotypes. In addition, immune cells respond differently to different types of ferroptosis inducers and system Xc-inhibitors [231]. In addition, radiotherapy and immunotherapy can increase the sensitivity to iron protease. The anti-tumor effect of radiotherapy is not only related to DNA damage but also closely related to lipid peroxidation caused by iron deposition. Radiotherapy combined with immunotherapy can activate kinases ATM and IFN-γ through DNA damage and induce iron deposition in tumor cells [226].

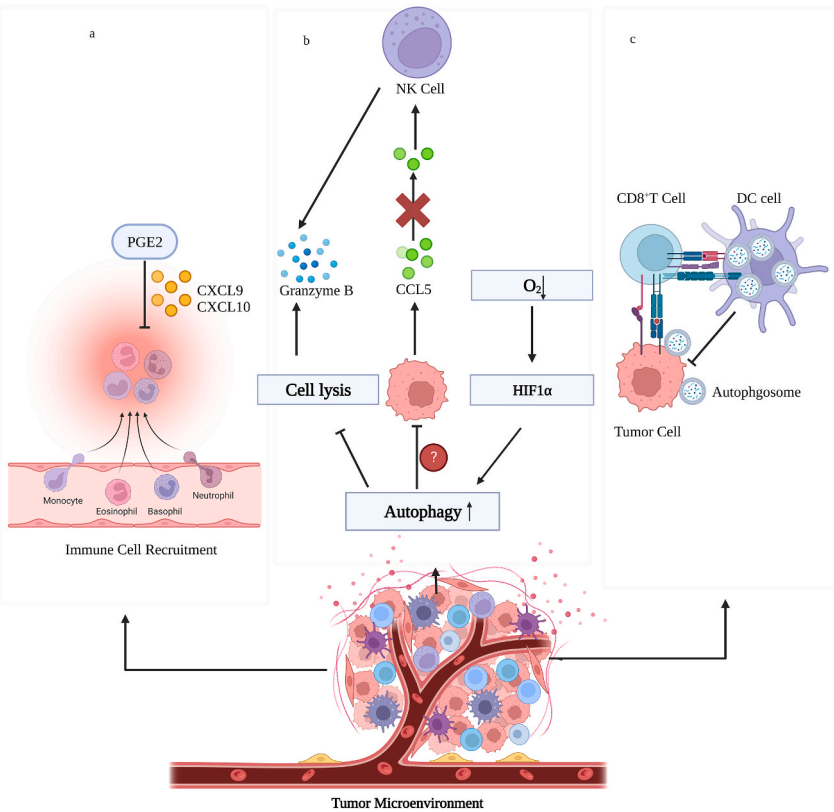

Fig. 5. Autophagy and tumor microenvironment a. Tumor cells block immune recruitment through autophagy; b. Hypoxia induces autophagy in tumor cells through HIF1α, granzyme B is secreted by NK cells, and autophagy enhances the degradation of granzyme B in tumor cells and blocks the NK cell tumor-killing effect; c. Autophagy in dead tumor cells promote DC cell-mediated cross-presentation by increasing autophagic vesicle production with antitumor antigens.

6.2.2. Role of DAMPs patterns in antitumor immunity

Damage-Associated Molecular Patterns (DAMPs) generated by dying cells play a dual role in antitumor immunity [12]. The release of DAMPs can facilitate immune cell death and enhance the immune response of tumor cells [232]. And yet, DAMPs trigger an inflammatory response that encourages the growth of tumor cells [233]. HMGB1 is released from cancer cells via ferroptosis, and it's binding to AGER promotes the inflammatory response of macrophages. Inhibitors of the HMGB1-AGER pathway inhibit the inflammatory response [119] mediated by ferroptosis (Fig. 6). In particular, PDAC can release $KRAS^{G12D}$ during iron phagocytosis by exosomes, which are subsequently picked up by macrophages (Fig. 6) [192]. This process is mediated by AGER, culminating in the M2-phenotype polarization of macrophages and the stimulation of tumor cell proliferation (Fig. 6) [140]. In contrast to pancreatic tumor suppressors mediated by SLC7A11 [234], GPX4 conditional depletion in the pancreas via iron damage-induced DNA release and subsequent STING in macrophages with inflammatory cell activation, thereby promoting KRAS-driven mutations in mice [235]. Clinically, the discovery of drugs targeting ferroptosis therapy helps to broaden the area of tumor treatment and may lead to the induction of hybrid RCD, which limits the proliferation of tumor cells.

6.3. Autophagy and the tumor microenvironment

Autophagy activation can promote or inhibit tumor development by regulating immune cells' dynamic balance, activation, proliferation, and differentiation. The primary human immune cells mainly include CD + T cells, Treg cells, and myeloid APCs, which affect tumor progression. In addition, autophagy promotes the development of DC and B cells, the differentiation of plasma cells, and the production of specific IgM and IgG by enhancing antigen presentation.

Autophagy plays a crucial role in the survival and proliferation of T cells. T cells deficient in ATG7 cannot proliferate effectively and cannot enter the S phase after TCR stimulation. CDKN1B, the primary negative cell cycle regulator, accumulates in naive autophagy-deficient T cells and cannot degrade after T cells are activated [236]. Autophagy not only participates in the survival and proliferation of T cells but also participates in the activation, differentiation, dryness, and effector function of T cells (Fig. 5). After TCR stimulation in vitro, $CD8^{+}$T cells induce autophagy (Fig. 5), which leads to the degradation of bcl-10 and protects against the adverse consequences of free NF-κB activation of cellular immunity [237]. PIK3C3 is a critical molecule in early autophagy. Compared with the wild type, the mitochondrion activity of PIK3C3-deficient T cells is decreased, and it is impossible to differentiate into effector T cells 241 when T cells are activated [238].

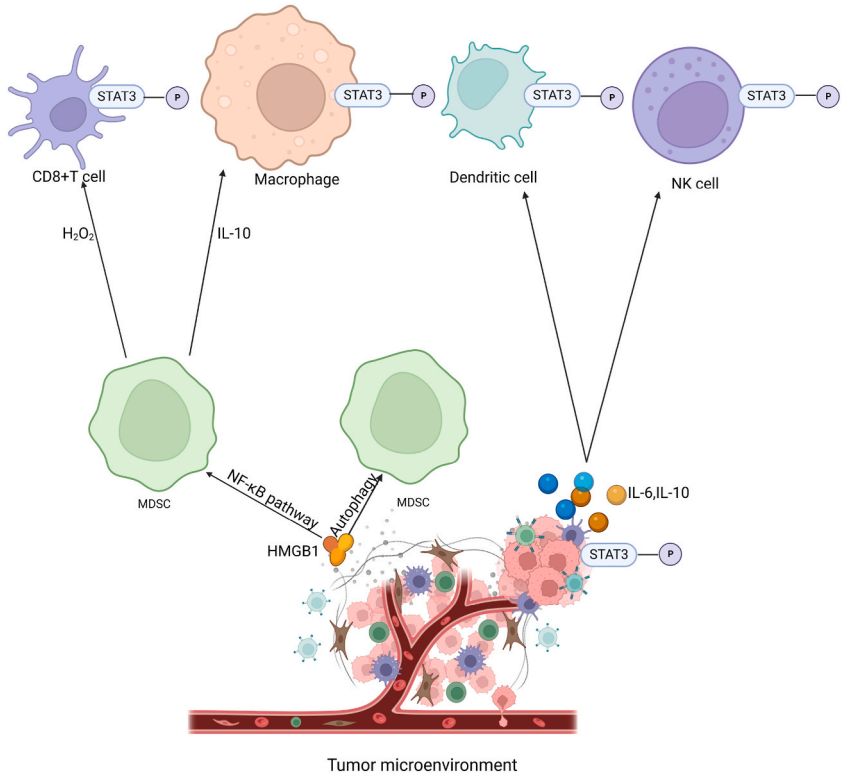

Fig. 6. Autophagy- Related Ferroptosis and Tumor Microenvironment. STAT3 activity in tumor cells supports multiple hallmarks of cancer, such as IL-6, IL-10 and EGFR. These hallmarks can activate related immune cells. STAT3 in $CD8^{+}$ T cells, natural killer (NK) cells, and neutrophils has been shown to induce suppressive anti-tumor cytolytic activity. HMGB1 activates MDSCs through the NF-κB and autophagy pathways. Under the influence of H_2O_2 and IL-10, MDSCs differentiate into $CD8^{+}$ T cells and macrophages.

The production of macrophages needs autophagy at different stages. Evidence shows that autophagy is the critical determinant of macrophage formation by regulating the maintenance of HSC, the differentiation of monocytes into macrophages, the recruitment of macrophages, and the polarization of macrophages [239,240]. Tumor-associated macrophages (TAMs) are usually the most abundant immune cells in TME, derived from tissue-resident macrophages and monocytes [241]. Macrophages absorb and process dead tumor cells and deliver TAA to T cells. Chemokine ligand 2(CCL2) has a significant recruitment effect on monocytes, which can up-regulate anti-apoptotic proteins and inhibit CASP8/caspase-8 cleavage from protecting monocytes from apoptosis in TME, and induce over-activation of TAMS autophagy [242]. When monocytes are stimulated to differentiate into macrophages, CSF1 will increase the expression and phosphorylation of ULK1, thus promoting the induction of autophagy [243]. In endometrial cancer and breast cancer, the transcription program of TAMs is different from that of monocytes and macrophages in their respective tissues, which is closely related to the survival of patients, which indicates that TME promotes the changes of TAMs in the process of tumor formation [244]. Autophagy also plays a crucial role in macrophage polarization. For example, Toll-like receptor 2-related ligands derived from the liver stimulate the differentiation of M2 macrophages by controlling the stability of NFκB relA protein (p65) through selective autophagy. Inhibition of autophagy can change the activity of NFκB and shape the phenotype of M2 macrophages polarized by hepatocellular carcinoma [245].

6.4. Autophagy in tumor therapy: an immunological perspective

6.4.1. Autophagy enhances tumor immunotherapy

Inhibition of autophagy may damage systemic immunity because autophagy is involved in developing the immune system and the survival and function of effector T cells [246]. The data show that the immune system tolerates a certain intensity of autophagy inhibition [247]. Because autophagy can regulate the immune response of tumor cells, it may increase the efficacy of immunotherapy and overcome the drug resistance of immunotherapy [248]. As an early immunosuppressant, high-dose IL-2 is used to treat renal cancer, which has a significant therapeutic effect and a wide range of stimulating effects on the immune system. However, a high dose of IL-2 may cause systemic autophagy syndrome induced by cytokines and the levels of IFNγ, IL-6, and IL-18 in serum increase significantly. In the advanced mouse model of metastatic liver cancer, the pairing of IL-2 and CQ limited the toxicity and enhanced the effect of immunotherapy [249]. It can be seen that autophagy may inhibit the growth of tumors by enhancing the proliferation and infiltration of immune cells in the liver and spleen and enhancing the effect of immunotherapy. In addition, autophagy plays a vital role in the presentation of MHC I and MHC II antigens [250]. For example, α -tocopherol (α-TEA), a semi-synthetic derivative of vitamin E, can stimulate autophagy and enhance the antigen cross-presentation of MCHI to CD 8 + T cells, which can strengthen the anti-tumor immune response and improve immunotherapy [251,252]. Shen et al. designed a new probe, and the vaccine based on DC cells promotes tumor immunotherapy by enhancing antigen presentation, a new treatment method. For example, autophagy induced by galactosylated N- alkyl polyethyleneimine encapsulated superparamagnetic iron oxide (SPIO) nanoparticles can enhance the function of the vaccine by inducing DC cells to mature [253]. In addition, autophagy induced by shikon in can directly promote the up-regulation of DAMPs and the activation of DC [254]. Triple-negative breast cancer (TNBC) is usually characterized by autophagy defect, and $CD8^{+}$T cells have a tumor-killing effect on triple-negative breast cancer cells by accumulating Tenascin-C. The increase of Tenascin-C is related to the poor prognosis of triple-negative breast cancer patients and negatively related to LC3B and CD + T cells [255]. Therefore, Tenascin-C inhibits the cytotoxicity of autophagy-deficient TNBC cells to T cells and enhances the efficacy of single *anti*-PD-1/PD-L1 [256].

It is reported that immunotherapy combined with radiotherapy or chemotherapy has a better therapeutic effect. Autophagy induced by radiotherapy or chemotherapy is helpful to increase the mannose-6- phosphate receptor (MPR) on the surface of tumor cells through autophagy transport, thus improving the sensitivity of immunotherapy to CTL of tumor cells [257,258]. For example, in colon tumors, mitoxantrone or oxaliplatin treatment can lead to autophagy of tumor cells, thus promoting the infiltration of DC and T cells [259]. In addition, autophagy may help ICD amplify radiotherapy's curative effect. Recent studies have found that ATP release induced by autophagy of compressed or dying tumor cells will trigger an anti-cancer immune response during radiotherapy [260]. In addition, autophagy can improve the efficacy of DNA vaccines by synthesizing tumor antigens encoded by intracellular vaccines [261].

6.4.2. Autophagy weakens the effect of immunotherapy

Activation of autophagy in hypoxic tumor cells can help tumor cells escape immune cell-mediated killing. STAT3 hypoxia-induced autophagy weakens immunotherapy by weakening CTL-mediated tumor cell lysis related to hypoxia-dependent phosphorylation of STAT3 [262]. In addition, hypoxia-induced autophagy eliminated Granzyme B derived from NK cells. It weakened NK cell-mediated lysis in vitro and in vivo because the accumulated HIF-2α was transferred to the nucleus and decreased ITPR1 expression of the sensor. This indicated that autophagy might counteract the immunotherapy that stimulated NK cells [263–265]. Many studies have found that tumor autophagy inhibition can be considered a strategy to improve tumor immunotherapy. HDIL-2 treatment increased autophagy in liver tissue collected from tumor-bearing mice, and the inhibition of autophagy by chloroquine combined with IL-2 significantly reduced the cytotoxicity of immune cells, promoted the infiltration of immune cells in the liver and spleen, and prolonged the survival time [249].

Autophagy also indirectly participates in the regulation of tumor immunity. When tumor cells undergo programmed cell death under the action of various cell death inducers, dying cells will release DAMPs to TME to stimulate the immune response [266]. Inhibition of autophagy will promote this process, indicating that the combination of autophagy inhibitor and cell death inducer can promote the anti-tumor effect of indirect immunotherapy, which has been verified in some animal experiments [267,268].

6.5. Autophagy-related ferroptosis and tumor immunity

6.5.1. Autophagy- related ferroptosis and tumor microenvironment

Tiny studies have been done on autophagy-associated ferroptosis and tumor immunity, and the field is still in its infancy. This offers a structured approach with the autophagy-associated ferroptosis mechanism and then examines its relevance in the tumor microenvironment. Overactivated STAT3 promotes the expression of immunosuppressive factors, including VEGF, IL-6, and IL-10, in tumor cells [269]. These tumor-derived substances are STAT3 activators and can be transduced into the tumor microenvironment (TME) (Fig. 6), consequently boosting STAT3 activation in multiple immune cell subpopulations including CAF [270]. In addition, excessive STAT3 activation plays a crucial role in DC cell maturation. DC cells are indispensable for launching T cell responses against tumor cells, whereas immature DC cells cause immune tolerance [271]. Overactivation of STAT3 in tumor cells can inhibit the expression of IL-12 and TNFα, thereby reducing the expression of Bcl-2 in DC cells [269]. As immature DC cells cannot activate T cells, STAT3-interfering $CD8^+$ T cells can produce more specific IFNγin mice with STAT3-depleted hematopoietic systems after immunization or tumor exposure [272]. It has been established that IFNγ produced by $CD8^+$ T cells inhibits the elimination of antigen-specific Treg cells [273]. IL-10 receptor signaling in $CD8^+$ T cells is required for Treg cell-mediated suppression, consistent with the involvement of STAT3 activation in the production and maintenance of tumor-associated Treg cells [273].

Several research have demonstrated that HMGB1 has an essential function in the dynamic interactions of other cells(Fig.6)F reshaping the TME and influencing the growth of tumors. In particular, HMGB1 features as a vital marker of ICD, contributing to the maturation of DC cells and presenting antigen to cytotoxic T cells (CTL) in order to stimulate CTL and clear adventitial cells [274]. In addition to the typical ICD, HMGB1 interacts with other TME components. Wang et al. reported a significant increase in the ability of CD62Ldim neutrophils to produce neutrophil traps (Nets) in peripheral blood and lung tissue in a mouse model of TNBC, and this ability was controlled by tumor-derived HMGB1/TLR2 signaling [275]. Hubert et al. also observed that inhibition of HMGB1 could reshape the microenvironment of breast cancer, including a significant decrease in monocyte/granulocyte myeloid-derived suppressor nucleus regulatory T cells, an increase in the M1/M2 ratio of tumor-associated macrophages, and activation of DC cells and plasma cell-like DC cells [275]. Because of the impact of HMGB1 on TME, the binding of HMGB1 to other immune cells represents a novel target for preventing breast cancer.

Chen et al. investigated the immediate relationship between autophagy-associated ferroptosis and TME in a systematic manner. High infiltration of $CD8^+$ T cells, a high autophagy potential index (API), and a high ferroptosis potential index (FPI) were associated with a positive diagnosis for survival of SCCs. In addition, it was unearthed that a high FPI and API were positively correlated with the efficacy of ICB treatments[1]. Recent experiments have shown that $CD8^+$ T cells mediate antitumor immunity and are associated with the tumor microenvironment (TME) by regulating changes in autophagy and ferroptosis to directly regulate antitumor immunity [276, 225].

6.5.2. Autophagy- Related Ferroptosis and immunotherapy

Autophagy-related proteins and antitumor immunity are still undergoing clinical studies, and combined therapy represents a novel immunotherapy technique. For instance, pancreatic and prostate malignancies exhibit ICB-resistance in certain tumors [277,278]. Combination therapy is therefore regarded a new way to improve tumor treatment, and the combination of STAT3 inhibitors with immunotherapy is an example of a combination strategy for combination therapy. Dasatinib, an indirect STAT3 inhibitor that targets SRC/ABL, facilitated *anti*-CTLA-4 immunotherapy in patients with head and neck squamous cell cancer [279]. The combination of IL-6 and PD-L1 reduced the development of pancreatic ductal adenocarcinoma in addition to hepatocellular carcinoma [280,281]. With JAK inhibition, resistance to PD-1 antibodies could be eliminated in mice with PDAC in situ [282]. Clonithiamine inhibited STAT3-induced PD-L1 transcription, thereby enhancing the efficacy of *anti*-PD-1/PD-L1 antibodies in non-small cell lung cancer [283]. In patients with unresectable advanced hepatocellular carcinoma, a phase III clinical trial demonstrated that the combination of bevacizumab plus atezolizumab significantly prolonged OS and PFS compared to sorafenib [284].

Among the existing HMGB1 combination treatment options, ICBs are utilized most frequently to stimulate adaptive antitumor immune responses in patients [285]. Hubert et al. discovered that inhibiting extracellular HMGB1 enhanced the effectiveness of *anti*-PD-1 immunotherapy. Anti-PD-1 antibodies and HMGB1 inhibitors considerably improved the rate of tumor cell death and tumor growth suppression compared to *anti*-PD-1 antibodies and HMGB1 inhibitors alone, as shown by a clinical trial employing human breast white tissue samples [286]. HMGB1 is implicated in the treatment of immunological ICBs in addition to standard PD-1/PD-L1 blockers. In breast cancer, for instance, the inhibitory receptor TIM-3 reduces antitumor immunity by suppressing CXCL9 synthesis by XCR1+ classical dendritic cells [274].

7. Summary

Research on ferroptosis has greatly expanded in the past few years. Ferroptosis can occur in two ways, exogenous or transporter-dependent and endogenous or enzyme-regulated [17]. Ferroptosis is a form of iron dependence, and regulatory cell death caused by excessive lipid peroxidation is related to the occurrence and treatment of various types of tumors [12]. However, the influence of ferroptosis on tumor biology is still unclear. Autophagy plays a key role in determining the survival or death of cells under various pressures.

In some cases, ferroptosis is considered a form of autophagy-dependent death. The relationship between autophagy and ferroptosis may be the relationship between metabolism and oxidative stress. Generally speaking, mixed cell death is more common in human diseases and dominant in a specific type of cell death. In this review, we expounded on the research mechanism of ferroptosis,

autophagy, and autophagy-related ferroptosis and also discussed their relationship with tumors and immunotherapy. In this case, non-apoptotic cell death has become a new strategy to improve immunotherapy in cancer treatment. Therefore, ferroptosis mediated immunotherapy nanotechnology has become a promising clinical treatment method because of its high accuracy, minor side effects, and non-invasive treatment. In clinics, designing relevant, effective drugs and reducing their drug resistance is an urgent problem.

Consent for publication

Not applicable.

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Statement

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Declaration of competing interest

All authors contributed to the study conception and design. YYX and YZ drafted the manuscript. JLW, YYR, and LJD prepared the figures. FL reviewed and revised the manuscript. All authors read and approved the final manuscript.

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