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Ferroptosis as an emerging target in inflammatory diseases

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Abstract

Cell survival or death is one critical issue in inflammatory responses. Ferroptosis, which is characterized by iron-dependent lethal lipid peroxidation, has been found to participate in the development of cancers, degenerative brain diseases and ischemia-reperfusion injuries. Incorporation of polyunsaturated fatty acids (PUFAs) into cellular membranes represents a vulnerability to invasion of microbials and sterile stimuli. In addition, the competition for iron in the battle between microbials and host cells underlies infection development. Although host cells have been equipped with complex antioxidant systems to combat lethal accumulation of lipid peroxidation, emerging evidence suggests several pathogens may target PUFAs in the cell membrane, and manipulate ferroptosis as a way for pathogen propagation. Moreover, ferroptosis takes part in the progression of sterile inflammations, such as cigarette smoke-induced chronic obstructive pulmonary disease, stroke and ischemia-reperfusion injuries. As iron-dependent oxidative stress and lipid peroxidation are common features for ferroptosis and inflammatory diseases, underlying mechanisms linking such pathological conditions will be discussed in this review. Progress in the research of ferroptosis may shed more light on the etiology and treatment of inflammatory diseases.

Previous Next

Keywords

Ferroptosis; Inflammation; Lipid peroxidation; Polyunsaturated fatty acids; Cell death; Iron

1. Introduction

As said by Lao Tzu, an ancient Chinese philosopher, *life and death are one thread, the same line viewed from different sides*. In response to various microbial components, chemical or physical stimuli, the innate immune system may respond by survival or cell death depending on the specific cue from the stimuli (Bolívar et al., 2019). By production of various chemokines, cytokines as well as growth factors, inflammatory responses may recruit defense cells, including neutrophils, monocytes and macrophages, to clear stimuli and facilitate the survival of host cells. Previously, dying cells were thought to be removed rapidly by circulating phagocytes with very limited significance in the progress of inflammation. However, diverse molecules released from the cytoplasm into the extracellular environment during cell death may profoundly affect their cellular environment and act as danger signals to further recruit defense cells (Fuchs and Steller, 2015). Therefore, cell death is not only a consequence of inflammation, but also a dynamic process that is tightly integrated into the development and progression of inflammatory diseases. Indeed, it has been shown that multiple regulated cell deaths, such as apoptosis, pyroptosis, necroptosis, autosis and NETosis, are involved in the development of infection and sterile inflammation (Vasilikos et al., 2017; Weinlich et al., 2017).

The term ferroptosis was coined in 2012 by Dixon et al. to describe the form of cell death induced by the small molecule erastin (Dixon et al., 2012). As a specific inducer of ferroptosis, erastin may inhibit cystine-glutamate antiporter system X_c^-, blocking transportation of cystine into cytoplasm. Failure to reduce excessive intracellular reactive oxygen species (ROS) due to depletion of the antioxidant glutathione may lead to lethal lipid peroxidation in the cell membrane (Yang et al., 2014). This unique cell death is characterized by iron-dependent ROS and oxidized lipid contents in the cell membrane. Cell death induced by specific inducers of ferroptosis can be suppressed by deferoxamine and deferiprone to chelate intracellular iron content, and inhibited by ferrostatins and liproxstatins to reduce lipid peroxidation (Stockwell et al., 2017). Several other key molecules also participated in the progress of ferroptosis, such as acyl-CoA synthetase long-chain family member 4 (ACSL4), which enrich cellular membranes with long polyunsaturated ω6 fatty acids (Doll et al., 2017), and glutathione peroxidase 4 (Gpx4), which reduces lipid peroxides in the cell membrane by reduced glutathione (Friedmann Angeli et al., 2014).

The physiological role of ferroptosis has been rarely explored. Continuous severe cold stress induces ferroptosis in multiple cell lines; therefore, ferroptosis may be present to maintain tissue homeostasis in a normal physiological environment (Hattori et al., 2017). Existing literatures support an important role of ferroptosis in the progress of tumor (Yang et al., 2014), ischemia-reperfusion injury (Li et al., 2019a, Li et al.,

2019) as well as degenerative neurological diseases, including Alzheimer's, Huntington's, and Parkinson's diseases (Do Van et al., 2016; Abdalkader et al., 2018). Although ROS is critical for the immune defense system to combat inflammatory stimuli, redundant ROS may cause excessive oxidative stress and deplete intracellular anti-oxidants, leading to excessive lipid peroxidation (Toufekoula et al., 2013; Kang et al., 2018). Indeed, ferroptosis has been shown to play roles in the pathogenesis of several types of microbial infections (Dar et al., 2018; Amaral et al., 2019) and sterile inflammation such as ischemia-perfusion injury and stroke (Guo et al., 2008; Yigitkanli et al., 2013; Tuo et al., 2017; Karuppagounder et al., 2018). The possible mechanism of ferroptosis development and its role in inflammatory diseases will be discussed in this review.

2. Defining ferroptosis

The complexity of regulated cell death (RCD) must be stressed before defining decisive features for ferroptosis. Different types of RCD are actually intertwined and mediated by a cascade of inter-correlated genes. For example, the state of caspase-8 determines whether a specific cell undergoes survival, apoptosis or necroptosis, and receptor interacting protein kinase 1 can interact with caspase-8 to induce apoptosis while coordinate with receptor interacting protein kinase 3 and mixed lineage kinase domain like pseudokinase to activate necroptosis (Weinlich et al., 2017). In contrast to the characteristic condensation and fragmentation of nuclei as well as fragmentation of chromosomal DNA in the apoptosis, defining other RCDs is hardly possible by ultrastructural changes. Employing antibodies to phosphorylated mixed lineage kinase domain-like protein facilitates specific detection of necroptosis, while utilizing antibodies to gasdermin protein helps determine pyroptosis and detection of cleaved caspase-3 contributes to ascertain apoptotic cells (Tonnus et al., 2019). Defining ferroptosis by certain decisive molecules has not been successful until now. However, several key biological features underlie the development of ferroptosis.

Ultrastructural morphological changes with vanished mitochondria cristae, condensed as well as ruptured mitochondrial membranes can be commonly found in the ferroptosis (Mou et al., 2019), whereas nuclear condensation or chromatin margination, which are key characteristics of apoptosis, are not observed in erastin-treated cancer cells (Dixon et al., 2012). In addition, ferroptosis is accompanied by excessive iron-dependent ROS accumulation, which depletes cellular glutathione (GSH). Failure in the intracellular redox system may lead to accumulation of lipid peroxidation products, the key events in the development of ferroptosis. Ferroptosis can be pharmacologically induced by several chemicals like erastin to block System X_c^- and RSL3 to inhibit Gpx4. System X_c^- is an amino acid antiporter in the cellular plasma membrane mediating import of extracellular cystine into cytoplasm and export of intracellular glutamate into extracellular space (Dixon et al., 2012), while Gpx4 is a selenium-containing enzyme that protects cells against oxidative damage by reducing lipid peroxides in the cell membrane by reduced GSH(Seiler et al., 2008). Ferroptotic cell death can be checked by several strategies: utilizing iron chelators, such as deferoxamine and desferrioxamine mesylate, to alleviate intracellular iron content, using ferrostatin and liproxstatin to lessen lipid peroxidation level (Dixon et al., 2012; Friedmann Angeli et al., 2014) and function

as radical-trapping antioxidants (RTAs) (Zilka et al., 2017), utilizing zileuton, one of LOX inhibitors, to exhibit effective radical-trapping activity and protect lipids from autoxidation (Liu et al., 2015; Shah et al., 2018) and employing lipophilic antioxidant vitamin E to reduce oxidative stress (Xie et al., 2016).

3. Glutathione metabolism in ferroptosis and inflammation

The intricate balance between the ROS and the antioxidant system maintains homeostasis of host cells to remove danger stimuli and contain detrimental oxidative stress. The cystine-glutamate antiporter system X_c^-, which consists of SLC3A2 and SLC7A11, regulates intracellular glutathione to balance redundant hydroxyl peroxides (Dixon et al., 2012). In normal physiologic conditions, System X_c^- antiporter imports extracellular cystine into the cytoplasm, while exports intracellular glutamate into extracellular space to maintain normal cell function. All available intracellular cystine can be converted into cysteine, which can be further transformed into reduced GSH in two steps by the ATP-dependent cytosolic enzymes glutamate-cysteine ligase and glutathione synthetase (Zhu et al., 2019).

GSH plays a crucial role in maintaining the intracellular redox balance, as it can be utilized by Gpx4 as a cofactor to eliminate membrane lipid peroxides and reduce oxidative stress (Seiler et al., 2008). In normal physiological context, Gpx4 achieved its peroxidase action by using the reduced form of GSH as an electron donor. Gpx4 may convert potentially toxic lipid hydroperoxides (L-OOH) to non-toxic lipid alcohols (L-OH) in the cell membrane (Fig. 1). Systemic Gpx4 knockout in mice leads to embryonic lethality, which may be correlated with mass neuronal cell loss in the nervous system (Ran et al., 2004); while increased cell death with enhanced lipid peroxidation was observed in conditional Gpx4 knockout models (Seiler et al., 2008; Yoo et al., 2012; Sengupta et al., 2013; Friedmann Angeli et al., 2014). Although the cell death was defined as apoptosis in these animal models, it is highly likely that ferroptosis occurred under such circumstances (Yang et al., 2014).

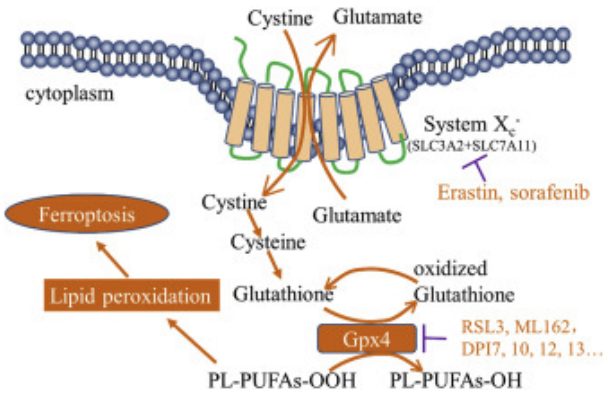

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Fig. 1. **System X_c^-, glutathione and Gpx4 antioxidant pathway in inhibiting lipid peroxidation and ferroptosis.** The cystine-glutamate antiporter system X_c^- transports the extracellular cystine into the

cytoplasm while it pumps intracellular glutamate into the extracellular space. Cystine can be further sequentially transformed into cysteine and glutathione. Gpx4 utilizes glutathione to reduce the elevated ROS in cells. Excessive lipid peroxidation can lead to ferroptosis of host cells. Several chemical agents can be utilized to induce ferroptosis, such as erastin and sorafenib that target System X_c^-, and RSL3, DPI12 as well as ML162 that blocks Gpx4.

Extracellular cystine deprivation, excessive accumulation of extracellular glutamate, malfunctioned antiporter System X_c^-, depletion of intracellular GSH and Gpx4 inactivation all contribute to onset of ferroptosis. Multiple agents have been utilized to elicit ferroptosis by targeting System Xc^-, GSH and Gpx4 (Stockwell et al., 2017). Erastin and its analogs (Dixon et al., 2012), sulfasalazine (Xie et al., 2016), glutamate, and sorafenib (Louandre et al., 2013) may inhibit System Xc-to induce ferroptosis. Disruption of System Xc^- by erastin may not only deplete intracellular cysteine and GSH, but also induce autophagy, especially nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy, which release ferritin-bound iron into the cytosol. Knockout or knockdown of autophagy related 5 (Atg5) and Atg7 reduced erastin-induced ferroptosis with decreased intracellular ferrous iron levels and lessened lipid peroxidation (Hou et al., 2016). RSL3 and ML162 may block Gpx4 (Yang et al., 2014) while FIN56 depletes Gpx4 protein (Shimada et al., 2016). FINO2 can stimulate lipid peroxidation and indirectly inhibit Gpx4 activity (Gaschler et al., 2018), while cystine/cysteine deprivation, BSO, DPI12, cisplatin can deplete GSH to activate ferroptosis (Yang et al., 2014; Roh et al., 2016).

ROS and oxidative stress are common features accompanying inflammation. Deficient cytoplasmal GSH may cripple the activation of mammalian target of rapamycin-1, NFAT as well as Myc, thereby compromising sufficient energy production and damaging Myc-dependent metabolic reprogramming (Mak et al., 2017). Therefore, GSH deficiency may lead to a failure in the switch from oxidative phosphorylation to glycolysis and disrupt glutaminolysis under pathologic stimuli. Moreover, T-cell-specific ablation of murine glutamate cysteine ligase cripples antiviral defenses, but helps lessen autoimmune diseases (Mak et al., 2017). In addition, Gpx4 expression participates in the pathogenesis of Hepatitis C virus (HCV)-induced hepatitis. Gpx4-silencing reduces the specific infectivity of HCV by up to 10-fold (Brault et al., 2016). By alleviating ROS level, Gpx4 activation intricately lessens damages in inflammatory conditions by regulating activation of NF-κB and oxidation of arachidonic acid (Brigelius-Flohé, 2006). Therefore, the perturbation in the system X_c^--Gpx4-GSH axis may predispose the infected or inflamed cells to the onset of ferroptosis in certain circumstances.

In addition to the canonical glutathione-based GPX4 pathway, FSP1-CoQ10-NAD(P)H pathway functions as a stand-alone parallel system, which cooperates with GPX4 and glutathione to suppress phospholipid peroxidation and ferroptosis. The ferroptosis suppressor protein 1 (FSP1) (previously known as apoptosis-inducing factor mitochondrial 2 (AIFM2)) reduces coenzyme Q10 (CoQ) as an oxidoreductase using NAD(P)H, trapping excessive radicals and impeding the exorbitance of lipid peroxides (Bersuker et al., 2019; Doll et al., 2019).

4. Iron in ferroptosis and inflammation

Iron-dependent lipid peroxidation is one key characteristic in the development of ferroptosis. Several chemicals, including 2,2-bipyridyl, deferoxamine as well as ciclopirox, can protect cells from erastin- and RSL3-induced ferroptosis by chelating intracellular iron (Dixon et al., 2012). On the contrary, addition of bioavailable forms of iron, such as ferric ammonium citrate, ferric citrate, iron chloride hexahydrate as well as transferrin-bound iron, may sensitize cells into development of ferroptosis when treated with erastin (Gao et al., 2015).

The metal iron is crucial for the development of ferroptosis, because iron may generate ROS by Fenton reaction in both physiological and pathological conditions (Schaible and Kaufmann, 2004). In the circulation system, iron is transported to vertebrate cells in the form of ferric iron (Fe^{3+}) by the transferrin protein, and iron is vitally important for maintaining normal cell function. Transferrin can be recognized by transferrin receptors (TFRs) on the cell membrane and transferred into intracellular endosomes (DeGregorio-Rocasolano et al., 2019). In the acidic environment of endosome, Fe^{3+} is dissociated from the transferrin–receptor complex and further transformed into ferrous iron (Fe^{2+}) by the reductase STEAP3. Following the reduction process, Fe^{2+} is further transferred into the labile iron pool (LIP) in the cytoplasm by SLC11A2. This low-molecular-weight pool of weakly chelated Fe^{2+} and Fe^{3+} can rapidly passes through the cell, catalyzing formation of highly damaging hydroxyl radical through the Fenton reaction (Robello et al., 2009). Despite its redox-active nature, LIP represents only a minor fraction (5%) of the total cell iron (50–100 μM) in quiescent conditions, while the major iron is stored in the ferritin (Kakhlon and Cabantchik, 2002). In normal conditions, intracellular iron can be efficiently pumped into extracellular space by ferroportin, a protein in the cell membrane. Then the exported Fe^{2+} can be oxidized into Fe^{3+} by ferroportin-associated ceruloplasmin, a copper-containing ferroxidase with homology to the intestine-specific enzyme hephaestin (Fig. 2). In addition to donating electrons to oxygen to generate ROS and lipid peroxides, which is also called autoxidation, iron is also indispensable for the enzyme-mediated peroxidation process by lipoxygenases (Shah et al., 2018). The reactivity of lipoxygenase (LOX) depends on its active site structure around a mononuclear, non-heme iron center (Gaffney et al., 1993). LOX catalyzes oxidation of PUFAs to their hydroperoxyl intermediates, including hydroperoxyeicosatetraenoic acid, in the case of arachidonic acid (Shintoku et al., 2017). It must be noted that although LOX activity may contribute to the cellular pool of lipid hydroperoxides that initiate ferroptosis, spontaneous peroxyl radical-mediated lipid peroxidation (autoxidation) may play a critical role in driving ferroptosis (Shah et al., 2018).

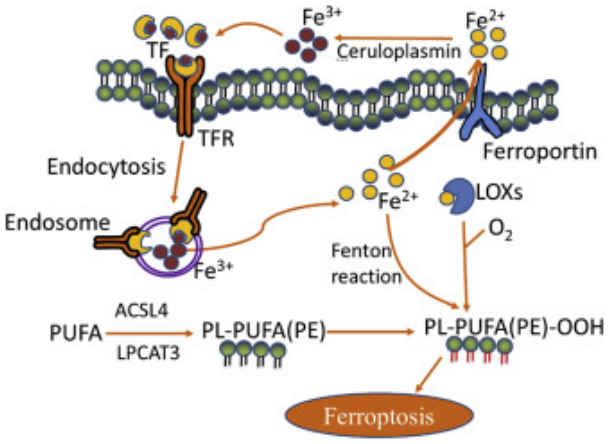

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Fig. 2. **Iron metabolism in ferroptosis.** Ferroportin and transferrin receptor (TFR) maintains iron homeostasis by pumping Fe^{2+} and Fe^{3+} into extracellular space and into cytoplasm respectively. Fe^{3+} was transferred into the endosome by TFR-transferrin complexes, and Fe^{3+} is reduced to Fe^{2+} by STEAP3 in the endosome, then Fe^{2+} is released into a labile iron pool. Fe^{2+} that is exported into the extracellular space can be oxidized by ceruloplasmin into Fe^{3+}, which can be taken up by transferrin. Fe^{2+} is crucial in the development of ferroptosis by oxidizing lipids in the cell membrane through Fenton reaction and catalyzing lipid peroxidation through lipoxygenases (LOXs). Lipid peroxidation is the key events in ferroptosis. LPCAT3 and ACSL4 also participate in the pathogenesis of ferroptosis by regulating polyunsaturated fatty acid (PUFA) metabolism.

Being an integral part of the innate antimicrobial defense, iron catalyzes the generation of reactive oxygen species (ROS) to clear stimuli. In the progress of inflammation, iron homeostasis may be disrupted, generating excessive ROS which results in detrimental effects in cells and tissues. To gain irons that are indispensable for cell survival, competition for iron underlies the battle between vertebrate cells and microbials. In response to lipopolysaccharide and lipoteichoic acid, levels of intracellular iron content are increased in neuroblastoma SH-SY5Y cells and BV-2 microglia, leading to iron accumulation in neurological tissues (Pandur et al., 2018). In addition, by chelating intracellular iron content, DIBI reduces excessive inflammatory responses and improve outcome in an experimental endotoxemia model (Thorburn et al., 2017). Increased iron levels in the cytoplasm can also be observed in macrophages in the infection process of *Bacteroides fragilis*, a commensal bacterium in the intestine (Verma et al., 2019). Such iron accumulation may be closely related to downregulated ferroportin in macrophages, and the effects of the iron chelator deferoxamine were compromised in *Salmonella*-induced IL-6 and IL-1β production (Verma et al., 2019). Therefore, disruption in the iron metabolism in the infection and sterile inflammation underlies the development of inflammatory diseases. Whether such disturbance would predispose cells to oxidative stress or ferroptosis in particular regions is still to be clarified.

5. ROS and lipid peroxidation in the ferroptosis and inflammation

ROS plays multiple roles in physiological and pathological conditions, mainly including three groups of oxygen-containing molecules: superoxide (O_2•$^-$), peroxides (H_2O_2 and ROOH) and free radicals (HO• and RO•) (Spooner and Yilmaz, 2011). ROS is generated as a natural byproduct of oxidative phosphorylation by the electron transfer system in the mitochondria to reduce oxygen. In addition, ROS can be produced by NADPH oxidases. ROS is of critical importance for neutrophils and monocytes to clear pathogens, including bacteria, fungi and viruses, by respiratory burst. Moreover, ROS can act as intracellular signaling molecules, mediating inflammation, apoptosis and pyroptosis in multiple cells (Latunde-Dada, 2017). Excessive ROS production may cause cellular oxidative stress, and damage DNA, proteins as well as lipids.

In addition to intracellular iron accumulation, disrupted lipid metabolism underlies the onset of ferroptosis. Phospholipids are major components in the cell membrane to its fluidity. Polyunsaturated fatty acids (PUFAs) within phospholipids such as phosphatidylcholine, including arachidonic acid and docosahexaenoic acid, may mediate intracellular signal transduction, and they are most susceptible to undergo peroxidation in the course of ferroptosis (Yang et al., 2016). When the iron-dependent ROS is exorbitantly elevated, redundant peroxidation of PUFAs occurs, leading to malfunctioned cell membrane and propelling cells toward iron-dependent cell death (Doll et al., 2017). Cyclooxygenases, cytochrome p450 as well as lipoxygenases are the three most characterized types of lipid oxidation enzymes; however, it has been demonstrated that lipoxygenases rather than cyclooxygenases participated in erastin-mediated ferroptosis (Yang et al., 2016). In the course of ferroptosis, 15-lipoxygenase-1 translocates to cell membrane and interacts with PUFAs to induce ferroptosis; moreover, siRNA-mediated silencing of ALOX15 and several inhibitors of lipoxygenases can block erastin-and RSL3-induced cell death in cancer cells (Shintoku et al., 2017).

In addition to lipid peroxidases, several genes that regulate synthesis of PUFA and maintain integrity of the normal cell membrane may also impact ferroptosis development. Presently, it has been shown that lysophosphatidylcholine acyltransferase 3 (LPCAT3) and ACSL4, which are responsible for insertion of the unsaturated arachidonic acid into phosphatidylethanolamine in the cellular phospholipid membrane, fuels ferroptotic cell death and aggravates erastin- and RSL3-induced ferroptosis in cancer cells (Shintoku et al., 2017).

Lipid peroxidation can be observed in multiple physiological conditions, such as cellular apoptosis and inflammatory processes (Dixon et al., 2012). Lipid peroxidation is one key feature in atherosclerotic plaques progression. Oxidized low density lipoprotein may trigger sterile inflammation in macrophages and formation of foam cells, and it is well recognized as the culprit in hyperlipidemic atherosclerosis progress. Moreover, lipid peroxidation has long been reported to participated in the pathogenesis of bacteria, viruses and fungi infection (Martynenko et al., 1990; Deighton et al., 1999; Toufekoula et al., 2013). More specifically, elevated membrane lipid peroxidation can be observed in $CD4^+$ and $CD8^+$ T cells in response to TCR ligation during infection progress; the crucial selenoenzyme Gpx4 may scavenge excessive ROS and

reduce phospholipid hydroperoxides, thereby maintaining immunological homeostasis by regulating survival and expansion of both $CD4^+$ and $CD8^+$ T cells (Matsushita et al., 2015). Moreover, Gpx4 deficiency is closely correlated with gasdermin D-mediated pyroptosis in lethal polymicrobial sepsis. Conditional Gpx4 knockout in myeloid lineage cells propels lipid peroxidation, caspase-11 activation and gasdermin D cleavage, promoting rupture of the cell membrane and release of danger associated molecule pattern such as high mobility group box 1, alarmin and pro-IL-1β(Kang et al., 2018). Therefore, lipid peroxidation may bridge the pathological process of ferroptosis and microbial infection. Multiple agents have been utilized to block lipid peroxidation, such as ferrostatins, liproxstatins, deuterated polyunsaturated fatty acids, CoQ10, vitamin E, alpha-tocopherol and Trolox. Whether such agents can lessen inflammatory responses in inflammation should be further explored.

6. Ferroptosis in the infection

In response to invasion of microbials, host cells utilize a wide array of pattern recognition receptors (PRRs), including Toll like receptors (TLRs), C-type lectin receptors and RIG-1 like receptors, to identify pathogen-associated molecular patterns (PAMPs), such as lipoteichoic acid, peptidoglycan and lipopolysaccharide (LPS). Following ligation of PRRs with PAMPs, the danger signals are transmitted into the nucleus, initiating a cascade of cellular events, including production of cytokines, chemokines and ROS. Profuse generation of ROS is vital for clearing toxic stimuli while excessive ROS may cause oxidative stress and tissue damages in infection-related diseases in both experimental animals and human subjects (Atabay et al., 2017). Two of the best defined sources of ROS during host cell-microbe interactions are the membrane associated NADPH oxidase complex and mitochondrial electron transport chain with the latter one being the primary source of ROS (Spooner and Yilmaz, 2011). For example, lipopolysaccharide from *P. gingivalis*, one major putative pathogen for chronic periodontitis, may elicit mitochondrial dysfunction, high ROS production and oxidative stress (Bullon et al., 2011). Typical mitochondrial dysfunction is characterized by decreased mitochondrial protein, mitigated mitochondrial mass and reduced membrane potential. Except for its profound roles in inflammation, apoptosis and pyroptosis, prolonged elevation in ROS levels in tissues may also deplete the anti-oxidant pool in the cystine-GSH-Gpx4 pathway (Zhu et al., 2019).

Phospholipids in the cell membrane stands at the first line of defense against the microbial stimuli by maintaining homeostasis of host cells. Microbials with the capability to produce lipoxygenases may attack lipid contents on the cell membrane. Indeed, *Pseudomonas aeruginosa*, a common encapsulated, Gram-negative, rod-shaped bacterium can induce cell death by ferroptosis (Dar et al., 2018). Although *P. aeruginosa* itself is not equipped with arachidonic acid–phosphatidylethanolamines (AA-PE) in its cell membrane, the bacteria synthesizes lipoxygenases (Vance et al., 2004). Similar to cytoplasmic lipoxygenases in mammalian cells, secretable lipoxygenases from *P. aeruginosa* may target arachidonic acids in the cell membrane of host cells, and transform it into 15-hydroxyeicosatetraenoic acid (15-HETE). Clinical *P. aeruginosa* isolates from patients with persistent lower respiratory tract infections was dependent on the level and enzymatic activity of lipoxygenases. Lipoxygenases-deficient mutant bacteria failed to induce ferroptosis in human

bronchial epithelial cells (Dar et al., 2018). It must be noted that except some types of marine bacteria, prokaryotic bacteria do not gain the capability to metabolize PUFA lipids (Horn et al., 2015); the conserved PUFA metabolism in *P. aeruginosa* indicated that bacteria may manipulate a variety of mechanisms to attack host cells, and ferroptosis may participate in other types of infection that remains to be unraveled.

As previously described, ferroptosis is characterized by iron-dependent ROS and lipid peroxidation in the dying cells. Therefore, increased iron levels in inflamed cells and tissues may predispose infected cells to undergo ferroptosis. *Mycobacterium tuberculosis* can induce heme oxygenase-1, a host enzyme that degrades heme to free iron (Andrade et al., 2013; Costa et al., 2016). Elevated levels of iron is accompanied by exacerbated inflammation and augmented bacterial loads in lung tissues of patients and animals with *M. tuberculosis* infection (Schaible et al., 2002; Boelaert et al., 2007). *M. tuberculosis*-induced macrophage necrosis is characterized by reduced levels of GSH and Gpx4, increased free iron, mitochondrial superoxide, and lipid peroxidation, all of which are important hallmarks of ferroptosis (Amaral et al., 2019). In addition, ferrostatin-1 and iron chelators reduced necrotic cell death in *M. tuberculosis*-infected macrophage cultures. Reduced Gpx4 expression as well as increased lipid peroxidation can be observed in lung lesions during acute *M. tuberculosis* infection, whereas Fer-1-treated animals exhibited remarkable reductions in bacterial load (Amaral et al., 2019). Together, these findings indicate that ferroptosis may participate in the progression of certain type of microbial infection diseases.

Iron is indispensable for survival of both bacterium and vertebrate cells (Schaible and Kaufmann, 2004). Therefore, by storing iron in the cytoplasm in the battle against microbials during infection, the host cells can deprive microbials of iron for growth; in addition, host cells can also utilize iron to generate reactive species to clear microbials (Lewis, 2010). The elevated iron level in the cytoplasm may lead to excessive oxidative stress and lipid peroxidation, which may in turn result in iron-dependent cell death. Cells die not for nothing. Dying cells may release profuse danger signals, while invading microbials may acquire nutrients such as iron which is vital for microbial growth. Therefore, the complexity in the competition for iron nutrient underlies the progression of microbial infections, and iron-related ROS accumulation leads to onset of iron-dependent ferroptosis in host cells.

In addition to above-mentioned lipoxygenase-mediated and free iron-mediated lipid peroxidation by *P. aeruginosa* and *M. tuberculosis* infection, lipid peroxidation itself may drive the process of pyroptosis. Kang et al. demonstrated that depletion of Gpx4 results in increased septic lethality (Kang et al., 2018). Myeloid-specific conditional knockout of Gpx4 enhances caspase-11 activation and subsequent Gasdermin D cleavage, leading to activation of pyroptosis of macrophages (Kang et al., 2018). Such results stressed that different types of RCD are actually correlated and intertwined, and bacteria may manipulate various strategies to avoid host defense system and cause cell death as well as tissue damage.

7. Ferroptosis in the atherosclerosis

Accumulation of ROS underlies the onset and progression of multiple pathological conditions, such as lethal

cancers (Wang et al., 2019), cardiovascular diseases (Baba et al., 2018), diabetes (Bruni et al., 2018), stroke (Alim et al., 2019), Alzheimer's and Parkinson's disease (Do Van et al., 2016). When lipid level is elevated in the peripheral circulatory system, free radicals in the arterial wall may trigger a cascade of innate immune responses characterized by endothelial activation, inflammatory mediator production, monocyte recruitment and foam cells formation (Martinet et al., 2019). Excessive peroxidation of low-density lipoprotein in the endothelium may activate oxidative stress in macrophages. Diverse types of regulated cell death in lipid-laden macrophages have been reported, such as classical programmed cell death (apoptosis) (Gonzalez and Trigatti, 2017), recently defined necroptosis (Karunakaran et al., 2016), pyroptosis (Hoseini et al., 2018), and NETosis (Wang et al., 2017). Lipid peroxidation as well as iron deposition are common features of advanced atherosclerotic plaques (Martinet et al., 2019); therefore, it may be assumed that ferroptosis in macrophages may participate in the progression of atherosclerotic plaque destabilization.

Although definite evidence of ferroptosis has not been reported, it must be noted that the term ferroptosis was newly coined in 2012 to define the specific cell death induced by the small molecule erastin (Dixon et al., 2012). Indeed, overexpression of Gpx4 significantly lessens lipid modifications by superoxide and impedes progression of atherosclerotic plaque in $ApoE^{-/-}$ mice (Guo et al., 2008), indicating that ferroptosis may potentially underlie the progress of cardiovascular diseases. Using GPX4 knockout animal model may better unveil whether ferroptosis decisively participated in the progress of atherosclerosis.

The role of iron overload in atherosclerosis is controversial. Atherosclerotic process is significantly accelerated in iron-laden $ApoE^{-/-}$ $FPN^{wt/C326S}$ mice in comparison to normo-ferremic $ApoE^{-/-}$ mice. Non-transferrin bound serum iron causes iron overload, induces reactive oxygen species production and apoptosis in cultured vascular cells, and stimulates massive MCP-1-mediated monocyte recruitment, resulting in vascular oxidative stress and plaque formation (Vinchi et al., 2019). However, enhanced atherosclerosis has not been observed in flatiron mice that bear macrophages over-loaded with iron (Kautz et al., 2013). Indeed, being defense cells against microbial invasion and oxLDL accumulation, macrophages are equipped with efficient antioxidant defense to balance the oxidative stress after engulfing large quantities of microbials and oxidized LDL. Therefore, iron overload itself may not be related to the progress of atherosclerosis, but oxidative stress in endothelial cells from non-transferrin bound serum iron may be the culprit of aggravating the progress of atherosclerosis.

8. Ferroptosis in the ischemia-reperfusion injury

Ischemia reperfusion injuries in organs or tissues are featured by an initial phase of severe reduction or cessation of vital blood flow, deprivation of oxygen consumption and metabolic reprogramming from oxidative phosphorylation to anaerobic glycolysis, and a second phase of re-oxygenation with outpouring oxidative stress (Feigin et al., 2014). Ischemia-reperfusion injury (IRI) underlies the progress of several types of sterile inflammation, such as organ transplantation, stroke, and myocardial infarction. Multiple pathological events are correlated with the detrimental effects of IRI, among which the outburst of free radicals during reperfusion after the ischemic period is the major culprit. Outpouring of hydroperoxides

contributes to malfunctioned protein, damaged DNA and peroxidized lipids, which may lead to eventual cell death. Depletion of anti-oxidant enzyme Gpx4 aggravates acute renal injury in mice, while liproxstatin-1 reduces cellular iron-dependent cell death and mitigates IRI-induced hepatic injuries in $Gpx4^{-/-}$ mice (Friedmann Angeli et al., 2014). Conditional kidney tubule-specific ablation of FADD and caspase-8 do not sensitize newly isolated renal tubules from necroptosis hypoxic injury, and necrostatin-1, a classic RIPK1 inhibitor, did not guard the tubules from hypoxia injury, while ferrostatin rescued tissues from IRI (Linkermann et al., 2014). Blocking glutaminolysis reduces intracellular glutamate levels, decreases ferroptotic cell death sensitivity and lessens IRI-induced heart injury (Gao et al., 2015), while ferrostatin-1 and iron chelation ameliorated heart failure induced by both acute and chronic IRI in mice (Fang et al., 2019).

Regulated cell death actually is an integral part of self-defense system. By releasing damage signals such as alarmins, heat shock proteins and pro-IL-1β, cell death triggers sterile inflammation for the host defense system to counter the imminent stimuli (Weinlich et al., 2017). By reducing lethal lipid peroxidation, Fer-1 treatment inhibits damage signals from dying cardiomyocytes and reduces neutrophil recruitment after heart transplantation, which contributes to a reduced infarct size, improved left ventricular systolic function and reduced left ventricular remodeling in myocardial IRI (Li et al., 2019a, Li et al., 2019). In addition, Fer-1 treatment impacts Toll like receptor 4- Toll/IL-1 receptor domain-containing adaptor inducing IFN-beta (TRIF)-type I interferon signaling pathway (Li et al., 2019a, Li et al., 2019). Ferroptosis not only occurs in the reperfusion stage, but also participate in the ischemia phase. Inhibitors of ACSL4, a key enzyme in elongation of PUFAs in the cell membrane, protected mice against ferroptotic cell death, and blocking ferroptosis by liproxstatin-1 ameliorated IRI in the intestine (Li et al., 2019a, Li et al., 2019).

9. Ferroptosis in stroke

The ischemic stroke is one leading cause of death as a result of obstruction of arteries that supply sufficient blood to the brain. Depletion of oxygen and nutrients activates excessive oxidative stress, mitochondrial impairment and ultimate cell death (Brouns and De Deyn, 2009).

Iron is a double-edged sword in the homeostasis of brain tissue. On one hand, iron is indispensable for catalyzing generation of profuse ATP for a normal brain function; on the other hand, the brain is highly vulnerable to iron-dependent oxidative stress (DeGregorio-Rocasolano et al., 2019). Levels of iron are increased in aging neurological tissues (Ayton et al., 2015). In addition, iron accumulation is well recognized in neurons in the phase of reperfusion in both clinical cases and animal models of ischemic stroke (Ding et al., 2011; Park et al., 2011; Domínguez et al., 2016). An early and transient increase in iron content can be observed in ischemic cerebral tissues (Millerot-Serrurot et al., 2008). Iron-chelation agents ameliorate brain edema, reduces neuronal death and impedes brain atrophy in the process of intracerebral hemorrhagic stroke (Hua et al., 2008; Zeng et al., 2018; Hu et al., 2019). Lysis of erythrocytes floods the cerebral tissue with excess of heme in the hemoglobin, and hemin has been shown to induce iron-dependent cell death in neuronal cells, while N-acetylcysteine, a FDA–approved cysteine prodrug, blocks oxidation activity of ALOX,

thereby reducing ferroptosis development (Karuppagounder et al., 2018). Transient middle cerebral artery occlusion enhances iron accumulation in the mice brain, while reduces expression of Tau, a protein primarily found in neurons in the central nervous system. Decreased iron accumulation and reduced IRI can be observed in Tau knockout mice after ischemic stroke; moreover, liproxstatin and ferrostatin ameliorated infarct size after experimental stroke (Tuo et al., 2017).

In addition to disruption in the iron homeostasis in stroke, malfunction of GSH and lipid peroxidation also underlies the development of stroke. Anti-oxidant GSH level was remarkably reduced whereas lipid peroxidation was enhanced in ischemic brain lesions in a mouse model of ischemic brain stroke (Ahmad et al., 2014). LOX-mediated generation of lipid hydroperoxides has been suggested to be involved in ferroptosis (Li et al., 2018). A novel inhibitor of 12/15-lipoxygenase, LOXBlock-1, decreases neuronal oxidative stress, reduces tissue plasminogen activator and protects mice from IRI (Yigitkanli et al., 2013).

10. Conclusions and perspectives

Since the discovery of ferroptosis, compelling evidence has shown that ferroptosis has been involved in the development of brain degenerative diseases (Abdalkader et al., 2018) and carcinogenesis (Yang et al., 2014). Depletion of Gpx4 and GSH, elevated lipid peroxidation products, as well as disrupted iron metabolism are shared features in ferroptosis and inflammatory diseases. Ferroptosis has been observed in *P. aeruginosa* and *M. tuberculosis* infection as well as non-infection inflammatory diseases, such as atherosclerosis, stroke, intracerebral hemorrhage and ischemia/reperfusion injury. The onset of ferroptosis may disrupt the integrity of tissue barrier and facilitate invasion of microbials (Fig. 3). However, it must be noted that currently we do not know in what condition ROS may induce lethal lipid peroxidation in inflammatory diseases.

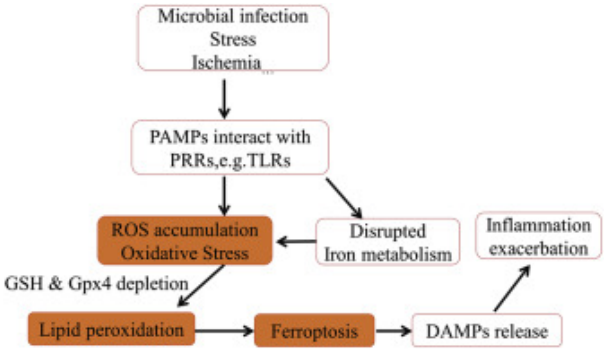

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Fig. 3. **Possible of role of ferroptosis in inflammatory diseases.** Various pathogen-associated molecular patterns (PAMPs), such as fimbriae, liposaccharide and lipoteichoic acid, may activate pattern recognition receptors (PRRs), notably Toll like receptors (TLRs), on the cell membrane to generate ROS production and accumulation, which may further induce oxidative stress as well as depletion of GSH&Gpx4. Elevated iron

levels in certain diseases may further facilitate lipid peroxidation, the core element in ferroptosis development. Excessive lipid peroxidation may result in ferroptosis, leading to release of damage-associated molecular patterns (DAMPs), activation immune cells and aggravation of inflammation. The release of DAMPs and inflammatory response may further exacerbate tissue destruction, disrupt tissue barrier and allow microbial entry.

Vertebrate cell membrane stands at the first line of defense against various microbial invasion; therefore, phospholipids in the cell membrane inherently maintain the integrity and homeostasis of host cells. However, present researches indicate that pathogens may manipulate several strategies to attack weakness in phospholipids, PUFAs. For example, *P. aeruginosa* may directly attack PUFAs in the cell membrane by lipoxygenases to induce lipid peroxidation and ferroptosis, while *M. tuberculosis* may induce iron accumulation in the cytoplasm, which in turn oxidize lipid content in the cell membrane. More studies are needed to explore whether ferroptosis is restricted to certain microbials.

Many questions regarding ferroptosis in inflammatory diseases should also be further investigated. By competing for iron in the inflammatory progress, host cells may store iron in the cytoplasm for ROS generation while decrease iron availability for pathogens. However, how the elevated iron levels in the cytoplasm may trigger ferroptosis is currently uncertain. In addition, the significance of ferroptosis should be further explored, such as whether it is an adaptive process to eliminate infected cells and release invading intracellular microbials into the extracellular environment for immune recognition, whether it induces release of damage-associated molecular patterns (DAMPs), including alarmins, DNAs and mitochondria, to alert the host of imminent severe danger signal, and provides invading microbials with plenty of nutrients. Moreover, why so many different ways for cell death are so closely entangled, by what mechanism the host cells choose to survive or to die, and what pathogenic factors actually induce ferroptosis are still uncertain. New techniques are needed to be discovered to detect ferroptotic cells specifically and determine whether a cell dies from ferroptosis or other forms of regulated cell death.

In summary, the newly discovered ferroptosis provides new insights into understanding the significance of life and death in inflammatory diseases. Better understanding of ferroptosis in infection and sterile inflammation may help provide individualized diagnosis and optimized treatment modalities for both infection and sterile inflammatory diseases.

Author contribution statement

HM and YZ wrote and edited the manuscript. LL and HL conceived the paper, and edited the manuscript.

Declaration of competing interest

The authors declare that there is no potential conflict of interest.

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