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Review

The mechanisms of ferroptosis and its role in atherosclerosis

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ABSTRACT

Ferroptosis is a newly identified form of non-apoptotic programmed cell death, characterized by the iron-dependent accumulation of lethal lipid reactive oxygen species (ROS) and peroxidation of membrane polyunsaturated fatty acid phospholipids (PUFA-PLs). Ferroptosis is unique among other cell death modalities in many aspects. It is initiated by excessive oxidative damage due to iron overload and lipid peroxidation and compromised antioxidant defense systems, including the system Xc^-/ glutathione (GSH)/glutathione peroxidase 4 (GPX4) pathway and the GPX4-independent pathways. In the past ten years, ferroptosis was reported to play a critical role in the pathogenesis of various cardiovascular diseases, e.g., atherosclerosis (AS), arrhythmia, heart failure, diabetic cardiomyopathy, and myocardial ischemia-reperfusion injury. Studies have identified dysfunctional iron metabolism and abnormal expression profiles of ferroptosis-related factors, including iron, GSH, GPX4, ferroportin (FPN), and SLC7A11 (xCT), as critical indicators for atherogenesis. Moreover, ferroptosis in plaque cells, i.e., vascular endothelial cell (VEC), macrophage, and vascular smooth muscle cell (VSMC), positively correlate with atherosclerotic plaque development. Many macromolecules, drugs, Chinese herbs, and food extracts can inhibit the atherogenic process by suppressing the ferroptosis of plaque cells. In contrast, some ferroptosis inducers have significant pro-atherogenic effects. However, the mechanisms through which ferroptosis affects the progression of AS still need to be well-known. This review summarizes the molecular mechanisms of ferroptosis and their emerging role in AS, aimed at providing novel, promising druggable targets for anti-AS therapy.

1. Introduction

Atherosclerosis (AS), the pathological foundation of coronary artery disease, is featured by chronic low-grade inflammation, lipid-rich core formation, plaque cell death, and vascular remodeling [1]. Dysfunction or abnormal death of plaque cells, i.e., vascular endothelial cell (VEC) [2], macrophage [3], and vascular smooth muscle cell (VSMC) [4] is mainly responsible for atherogenesis. Ferroptosis, a relatively new form of programmed cell death (PCD) identified by Dixon et al. in 2012, is featured by an iron-driven accumulation of reactive species oxygen (ROS) and lethal lipid peroxides (LPO) [5]. Cells that undergo ferroptosis have morphological, biochemical, genetic, and metabolic features distinct from those of previously identified PCD, such as apoptosis, pyroptosis, necroptosis, and autophagy [6]. Morphologically, ferroptotic cells displayed severe mitochondrial abnormalities, including reduced mitochondria crista, increased mitochondrial membrane densities, and outer membrane rupture. Biochemically, ferroptosis is usually accompanied by iron overload, glutathione (GSH) depletion, glutathione peroxidase 4 (GPX4) inactivation, and the peroxidation of membrane polyunsaturated fatty acid phospholipids (PUFA-PLs) [7]. Genetically, other kinds of PCD are always mediated by executional proteins, such as caspase-3/8 in apoptosis, gasdermins

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(GSDMs) in pyroptosis, receptor-interacting serine/threonine protein kinase 1/3 (RIPK1/3) in necroptosis, autophagy-related proteins in autophagy and PANoptosome in PANoptosis [8]. In contrast, ferroptosis occurs from the imbalance between the cell's oxidative damage and antioxidant defense systems [9] (Table 1). Recently, studies have disclosed that the pathogenesis of AS involves several ferroptosis features in plaque cells, such as severe iron loading [10], decreased GPX4 levels [11], and increased ROS [12]. Vinchi et al. found that iron-overload apolipoprotein E deficient (apoE$^{-/-}$) mice displayed massive iron deposits in VEC and VSMC, sustained endothelial activation, accelerated macrophage foam cell formation, and increased plasma lipid profile and inflammation, leading to the formation and destabilization of atherosclerotic plaques. Significantly, administering apoE$^{-/-}$ mice with deferasirox (an iron chelator) alleviated vascular iron accumulation, improved the inflammatory status, and reduced the aortic plaque area. In hemochromatosis patients, a category of humans with high serum iron levels, iron restriction also reduced the parameters of atherogenesis [10]. Marques et al. injected atherosclerotic mice with iron-dextran and observed that chronic iron loading significantly induced aortic iron deposits, increased endothelial dysfunction and oxidative stress, and intensified hypercholesterolemia, exacerbating plaque formation [2]. Another research disclosed that GPX4 overexpression markedly decreased the production of hydroperoxides and adhesion molecules in mouse aorta endothelial cells (MAECs) and ameliorated adhesion of monocytes to MAECs induced by the oxidized lipids lysophosphatidylcholine (LPC) and 7-ketocholesterol. In atherosclerotic mice, GPX4 up-regulation diminished lipid peroxidation and acellular areas in the aorta, resulting in smaller plaque areas [11]. Macrophages' excessive iron increases ROS production and promotes polarization toward the pro-inflammatory M1 phenotype [13]. Hepcidin is a hormonal stimulator of intracellular iron levels by repressing the iron-exporting activity of ferroportin (FPN) [14]. In low-density lipoprotein receptor-deficient (LDLR$^{-/-}$) mice, hemp (the gene encoding hepcidin) knockout decreased macrophage iron content and the number of pro-inflammatory M1 macrophages in the aorta, leading to less lipid accumulation in plaques [15]. Cai et al. reported that FPN deficiency-induced macrophage iron retention significantly promoted foam cell formation, increased oxidative stress in the aorta, and amplified systemic inflammation, causing larger lesion areas and unstable plaques in vivo [16]. These clues indicate a strong correlation between the ferroptosis of plaque cells and the development of AS. In this review, we summarize the molecular mechanism of ferroptosis and its role in atherogenesis, hoping to provide novel targets for developing pharmacotherapies for AS prevention.

Table 1
The characteristic morphology and biochemical features of various PCD.

Types	Morphology	Biochemical features	Key genes
Apoptosis	cell rounding; decreased cell size; nuclear condensation; membrane blebbing; apoptotic body formation	activation of caspases; phosphatidylserine exposure; DNA fragmentation	caspase-3/8, Fas, Bcl-2, Bax, p53
Necroptosis	cell swelling; rupture of cell membrane; chromatin condensation; nuclear and DNA fragmentation	drop in ATP levels; activation of RIPK1, RIPK3 and MLKL; cytosolic necrosome formation	RIPK1, RIPK3, MLKL, LEF1
Pyroptosis	cell swelling, bubbling, and lysis; pore formation on cell membrane; chromatin condensation with intact nucleus	Inflammasome formation, GSDMs cleavage, IL-1β and IL-18 production and secretion	NLRP3, caspase-1/4/5/11, GSDMs, IL-1β, IL-18
Autophagy	autophagic vacuolization; formation of double-membraned autolysosomes	enhanced lysosomal activity; increased autophagic flux	LC3, ATG5, ATG7, Beclin-1; DRAM3, TFEB
PANoptosis	containing the morphological features of apoptosis, pyroptosis and/or necroptosis simultaneously	PANoptosome formation	ZBP1, RIPK1, RIPK3, FADD, caspase-1/8
Ferroptosis	shrunken mitochondria; reduced mitochondria crista; increased mitochondrial membrane densities	iron accumulation; inactivation of GPX4; inhibition of system Xc$^-$; GSH depletion; lipid peroxidation	TFR1, xCT, FSP1, GPX4, NCOA4, ACSL4, LOXs, Nrf2

Notes: Fas, factor associated suicide; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; p53, tumor suppressor gene 53; ATP, adenosine triphosphate; RIPK, receptor-interacting serine/threonine protein kinase; MLKL, mixed lineage kinase domain-like pseudokinase; LEF1, lymphoid enhancer binding factor 1; GSDMs, gasdermins; NLRP3, nucleotide-binding domain and leucine-rich repeat protein 3; IL, interleukin; LC3, microtubule-associated protein 1 light chain 3; ATG, autophagy-related gene; DRAM3, damage-regulated autophagy modulator 3; TFEB, transcription factor EB; ZBP1, Z-DNA-binding protein 1; FADD, fas-associated death domain; GPX4, glutathione peroxidase 4; system Xc$^-$, cystine-glutamate antiporter; GSH, glutathione; TFR1, transferrin receptor protein 1; xCT, solute carrier family 7 member 11 (SLC7A11); FSP1, ferroptosis suppressor protein 1; NCOA4, nuclear receptor coactivator 4; ACSL4, acyl-CoA synthetase long-chain family member 4; LOXs, lipoxygenases; Nrf2, nuclear factor erythroid 2-related factor 2.

2. Molecular mechanisms of ferroptosis

2.1. Oxidative damage during ferroptosis

The core molecular mechanism of ferroptosis is the imbalance between oxidative damage and antioxidant defense. Iron overload and lipid peroxidation are the key events initiating oxidative membrane damage during ferroptosis [17,18] (Fig. 1).

2.1.1. Iron accumulation

Cellular iron homeostasis is controlled by iron uptake at the plasma membrane, distributions among cellular compartments, and iron export [19]. Iron is primarily circulated in the body as ferric ions (Fe^{3+}) in most mammalian organisms [20]. Circular Fe^{3+} binds apo-transferrin (apo-TF) to form holo-TF, which binds with high affinity to transferrin receptor protein 1 (TFR1) to create a holo-TF-TFR1 complex on the iron-consuming cell membrane [21]. The complex was subsequently internalized by clathrin-dependent endocytosis and acidified in the endosome, where six-transmembrane epithelial antigen of the prostate 3 (STEAP3) reduces Fe^{3+} to ferrous iron (Fe^{2+}), followed by delivering Fe^{2+} into the cytosolic labile iron pool (LIP) by divalent metal transporter 1 (DMT1) or transient receptor potential mucolipin 1 (TRPML1) [22,23]. With the disassembly of the holo-TF-TFR1 complex, apo-TF recycles back to the cell surface to repeat another cycle. When plasma iron exceeds the TF binding capacity, Fe^{2+} is directly transported into the cell by non-transferrin-bound iron (NTBI) transporters, including ZRT/IRT-like protein 14 (ZIP14) [24] and DMT1 [25]. Additionally, heme oxygenase-1 (HO-1)-mediated catalysis of heme is another source of labile Fe^{2+} [26]. In the cytoplasm, labile Fe^{2+} is stored in ferritin (FTN) or exported from the cell via FPN [27]. Finally, excessive labile Fe^{2+} acts as a catalyst to trigger the Fenton reaction, in which Fe^{2+} gives an electron in a reaction with hydrogen peroxide (H_2O_2) to produce the hydroxyl radical (·OH), one of the most reactive forms of ROS, causing non-enzymatic lipid peroxidation and ferroptosis [28].

FTN, which contains two subunits, i.e., FTL and FTH1, is the cells' main iron storage complex and is critical in ferroptosis regulation [29]. Additionally, intracellular iron status affects the expression of nuclear

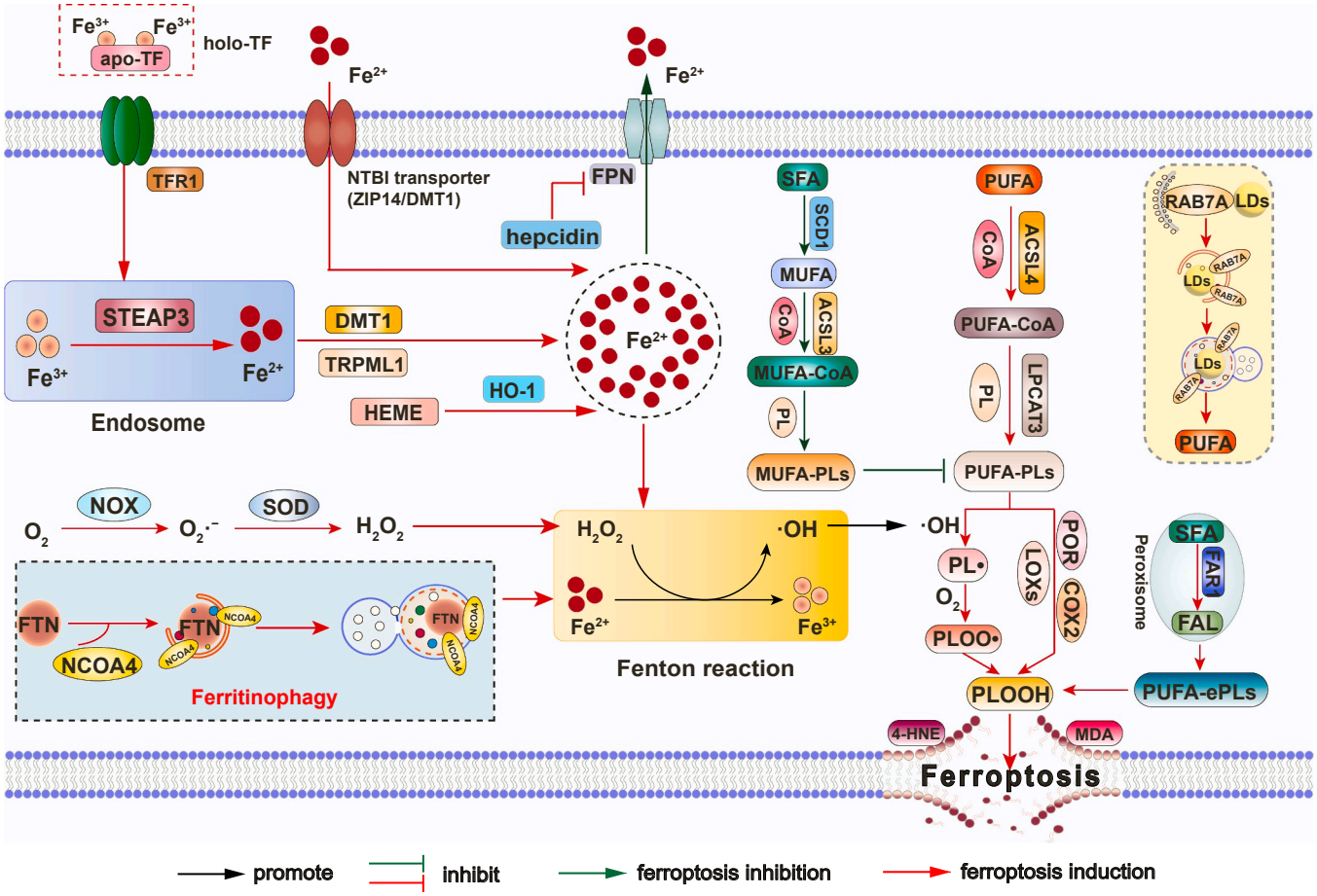


Fig. 1. Oxidative damage during ferroptosis. Oxidative damage during ferroptosis results from iron overload and lipid peroxidation. Excessive intracellular Fe^{2+} participates in the Fenton reaction with H_2O_2 to generate·OH that, in turn, converts PUFA-PLs to PLOOH. The enzymatic lipid peroxidation requires some dioxygenases, such as LOXs, POR, and COX2, which directly catalyze the oxidation of PUFA-PLs to produce PLOOH. PLOOH decomposes into 4-HNE and MDA, triggering ferroptosis. TF, transferrin; TFR1, transferrin receptor protein 1; STEAP3, six-transmembrane epithelial antigen of the prostate 3; LIP, labile iron pool; DMT1, divalent metal transporter 1; TRPML1, transient receptor potential mucolipin 1; NTBI, non-transferrin-bound iron; HO-1, heme oxygenase-1; FTN, ferritin; ACSL4, acyl-CoA synthetase long-chain family member 4; LPCAT3, lysophosphatidylcholine acyltransferase 3; LOXs, lipoxygenases; POR, cytochrome P450 reductase; COX2, cyclooxygenase 2; SFA, saturated fatty acid; MUFA, monounsaturated fatty acid; SCD1, stearoyl-CoA desaturase 1; FAL, fatty alcohol; FAR1, fatty acyl-CoA reductase 1; RAB7A, ras-related protein rab-7a.

receptor coactivator 4 (NCOA4), a protein on the surface of autophagosomes that targets FTN for destruction [30]. Upon iron depletion, the amount of NCOA4 in the autophagosomes increases. NCOA4 interacts directly with FTH1 via its conserved C-terminal domain and a critical conserved residue on FTH1, delivering FTN to the lysosomes for degradation and allowing the release of iron to the cytosol LIP, a process called ferritinophagy [31].

2.1.2. *Lipid peroxidation*

Unrestrained lipid peroxidation of the membrane lipid bilayer is the hallmark of ferroptosis. Compared with monounsaturated fatty acids (MUFAs), PUFA-PLs are most susceptible to peroxidation due to weak C-H bonds [32]. The biosynthesis of PUFA-PLs requires two membrane-remodeling enzymes, acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), as critical drivers of ferroptosis. ACSL4 preferably catalyzes long-chain PUFAs, such as free adrenic acid or arachidonic acid, with CoA to form the derivatives PUFA-CoA [33]. Then, LPCAT3 can re-esterify PUFA-CoA into PL, mainly phosphatidylethanolamine (PE) and phosphatidylcholine (PC), generating PUFA-PLs [34]. NADPH oxidases (NOXs) and mitochondrial respiratory chain disorders promote ROS (superoxide anion, $O_2\cdot^-$) production [35], which is catalyzed to H_2O_2 by superoxide dismutase (SOD) and converted to ·OH through the Fenton reaction. Non-enzymatic lipid peroxidation is initiated by ·OH-mediated removal of a bisallylic hydrogen atom from PUFA-PLs incorporated into lipid bilayers, producing PL radical (PL·). PL· then reacts with molecular oxygen to produce the PL peroxyl radical (PLOO·), which removes hydrogen from another PUFA, generating PL hydroperoxides (PLOOH). Subsequently, PLOOH and lipid free radicals, mainly PLOO· and alkoxyl PL radicals (PLO·), react with PUFA-PLs to propagate PLOOH production [36]. Eventually, this reaction chain leads to the accumulation of toxic lipid peroxides, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), triggering the breakdown of plasma membrane integrity and the rupture of organelle membranes [37]. Except for the non-enzymatic mechanisms through the Fenton reaction, the enzymatical lipid peroxidation process is also critical during ferroptosis. Some nonheme iron dioxygenases, including lipoxygenases (LOXs), prostaglandin synthase 2/cyclooxygenase 2 (PTGS2/COX2), and cytochrome P450 reductase (POR) directly oxygenate PUFA-PLs into PLOOH through their catalytic activities and promote ferroptosis [38].

In contrast, ACSL3 converts MUFAs into their acyl-CoA esters for incorporation into membrane phospholipids [39]. It is reported that stearoyl-CoA desaturase 1 (SCD1)-mediated MUFA production and an ACSL3-dependent enrichment of membranes with MUFAs protect against ferroptosis [40]. In addition to PUFAs, long-chain saturated fatty

acid (SFA) is another mediator of ferroptosis [41]. Specifically, the peroxisomal enzyme fatty acyl-CoA reductase 1 (FAR1) reduces SFA to fatty alcohol (FAL), which is incorporated into the sn-1 position of PLs containing PUFA in sn-2, generating polyunsaturated ether phospholipids (PUFA-ePLs) [42]. As newly identified substrates for lipid peroxidation in addition to PUFA-PLs, PUFA-ePLs can be hyperoxidized and induce ferroptosis [43]. Recently, the roles of selective autophagy pathways in lipid peroxidation and ferroptosis have been unraveled. Lipophagy is a process that delivers lipid droplets (LDs) by autophagosomes to lysosomes for decomposition, causing the release of free fatty acids [44]. Bai et al. unraveled that intracellular accumulation of LDs exhibits antioxidant effects on lipid peroxidation. Therefore, RAB7A (ras-related protein rab-7a)-dependent lipophagy can effectively promote ferroptosis by degrading LDs [45].

2.2. Antioxidant defense systems during ferroptosis

Activation of cellular antioxidant defense systems, including the system Xc^-/GSH/GPX4 pathway, the NAD(P)H/FSP1/CoQ10 pathway, the DHODH/CoQ10 pathway, and the GCH1/BH4/DHFR pathway, can mitigate the accumulation of lipid hydroperoxides and inhibit ferroptosis [46] (Fig. 2).

2.2.1. System Xc^-/GSH/GPX4 antioxidant pathway

As a significant PLOOH-neutralizing enzyme, GPX4 serves as a central suppressor and gatekeeper of ferroptosis [47]. It utilizes GSH as a substrate to detoxify PLOOH selectively to nontoxic phospholipid alcohol (PLOH) accompanied by glutathione disulfide (GSSG) production [48]. GSH is the cofactor for GPX4 and performs electrophile detoxification and ROS scavenging effects. It is a thiol-containing tripeptide consisting of glycine (Gly), cysteine (Cys), and glutamate (GLU) [49]. The synthesis of GSH requires the consecutive actions of glutamate-cysteine ligase (GCL), which contains the GLU-Cys ligase catalytic subunit (GCLC) and the GLU-Cys ligase modifier subunit (GCLM). GCL can conjugate Cys and GLU to produce γ-glutamylcysteine (GGC), further catalyzed to GSH by glutathione synthase (GS) [50]. Due to the limited concentrations of Cys within cells, Cys is the rate-limiting precursor in GSH synthesis. Although intracellular Cys can be de novo synthesized using methionine (Met) and glucose via the reverse transsulfuration pathway, most cells take up Cys primarily from the environment in its oxidized form (cystine, also known as Cys2) by the Cys2-GLU antiporter system Xc^- [51]. System Xc^- is a transmembrane protein complex comprising the solute carrier family 7 A member 11 subunit (SLC7A11; also known as xCT) and the SLC3A2 subunit (4F2HC). The SLC7A11 subunit mediates the transporter activity of the protein complex, whereas SLC3A2 acts as a molecular chaperone to stabilize SLC7A11. System Xc^- imports extracellular Cys2 and excretes intracellular GLU at 1:1 [52]. Then, the newly imported Cys2 is reduced to Cys in the cytosol by thioredoxin reductase 1 (TrxR1) [53]. In addition to system Xc^-, the alanine serine cysteine transporter 2 (ASCT2; also known as SLC1A5) can directly import Cys into the cytosol as another source of intracellular Cys [54]. GPX4 catalyzes the reduction of PLOOH mainly via a "ping-pong" mechanism, in which selenocysteine (Se-Cys) shuttles between oxidized selenic acid (SeOH) and reduced selenol (SeH) states [55]. This dynamic process especially involves the following steps: (1) PLOOH oxidizes the selenol form of Se-Cys (GPX4-SeH) into selenic acid intermediate (GPX4-SeOH), while PLOOH is reduced to PLOH; (2) GPX4-SeOH reacts with GSH to produce

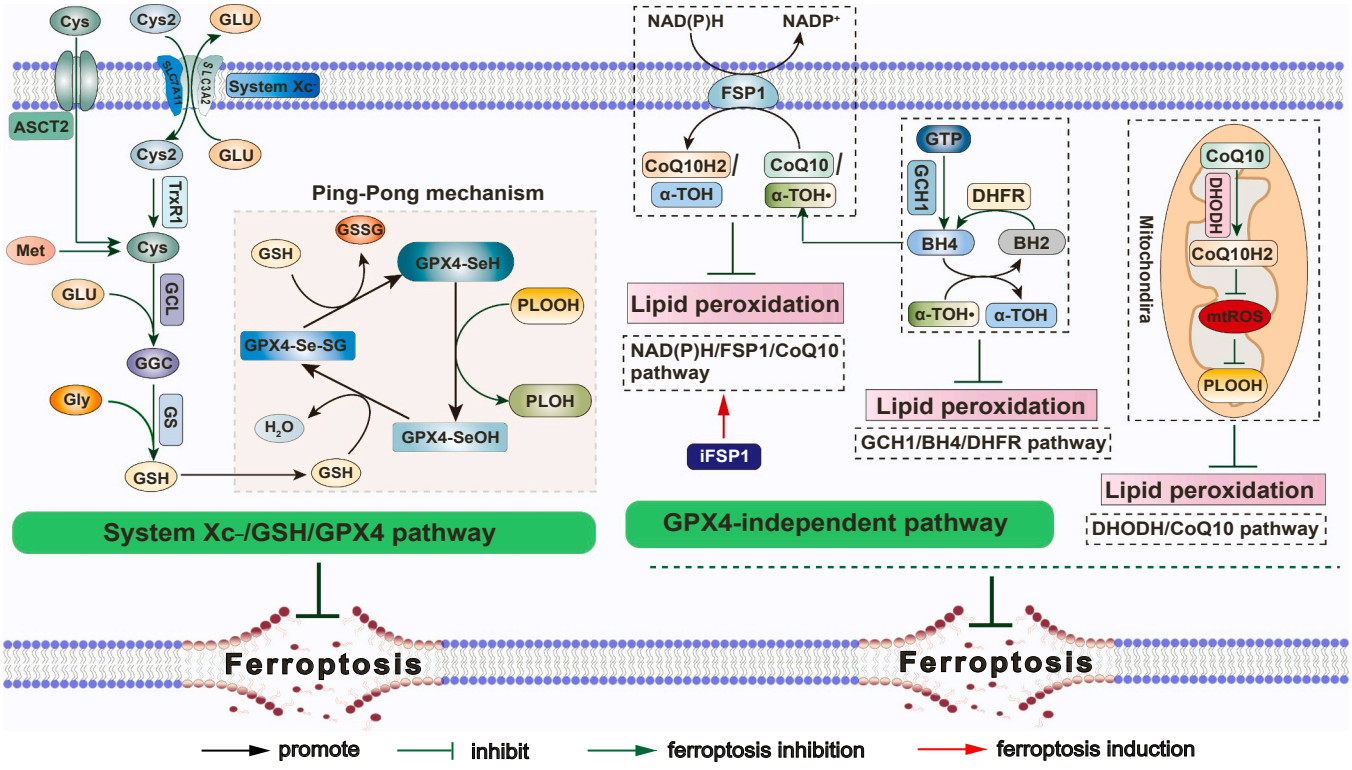


Fig. 2. Antioxidant mechanisms in ferroptosis. Antioxidant mechanisms in ferroptosis include GPX4-dependent canonical antioxidant mechanisms and GPX4-independent antioxidant pathways. The GPX4-dependent canonical antioxidant mechanisms entail de novo synthesis of GSH and the reaction of GPX4 with GSH to reduce toxic PLOOH to non-toxic PLOH through the "ping-pong" mechanism. Ferroptosis is also inhibited by some GPX4-independent antioxidant pathways, including the NAD(P)H/FSP1/CoQ10 pathway, the DHODH/CoQ10 pathway, and the GCH1/BH4/DHFR pathway. GPX4, glutathione peroxidase 4; Cys2, cystine; Glu, glutamate; TrxR1, thioredoxin reductase 1; Cys, cysteine; ASCT2, alanine serine cysteine transporter 2; GCL, glutamate-cysteine ligase; Gly, glycine; GGC, γ-glutamylcysteine; GSH, glutathione; GS, GSSG, glutathione disulfide; CoQ10, ubiquinone; CoQ10H2, ubiquinol; DHODH, dihydroorotate dehydrogenase; DHFR, dihydrofolate reductase; FSP1, ferroptosis suppressor protein 1; GCH1, guanosine triphosphate cyclohydrolase 1; BH4, tetrahydrobiopterin; BH2, dihydrobiopterin; RTA, radical-trapping antioxidant; α-TOH, α-tocopherol; α-TOH·, α-tocopherol radical.

H_2O and selenium-glutathione adduct (GPX4-Se-SG); (3) Finally, GPX4-Se-SG is converted back to GPX4-SeH to generate GSSG by reacting with the second equivalent of GSH [56].

2.2.2. Other antioxidant pathways

Recently, several GPX4-independent surveillance mechanisms of ferroptosis have been uncovered, including the NAD(P)H/FSP1/CoQ10 pathway, the DHODH/CoQ10 pathway, and the GCH1/BH4/DHFR pathway [57]. The ferroptosis suppressor protein 1 (FSP1) mainly localizes to plasma membranes and LDs, playing a critical role in scavenging deleterious PLOOH. Mechanistically, FSP1 reduces extra-mitochondrial coenzyme Q10 (CoQ10/ubiquinone) to ubiquinol (CoQ10H2) via NAD(P)H. CoQ10H2 acts as a lipophilic radical-trapping antioxidant (RTA) to either directly reduce lipid radicals or indirectly, via the recycling of α-tocopherol (α-TOH), nature's most important lipophilic RTA [58]. It is reported that iFSP1 (a highly specific FSP1 inhibitor) has ferroptosis-inducing capability [59]. Dihydroorotate dehydrogenase (DHODH) is localized to the inner mitochondrial membrane, where it catalyzes CoQ10 to CoQ10H2, diminishing the production of mitochondrial ROS (mtROS), and specifically detoxifying mitochondrial lipid peroxides [60]. Guanosine triphosphate cyclohydrolase 1 (GCH1) is the rate-limiting enzyme for tetrahydrobiopterin (BH4) synthesis. BH4 acts as a potent RTA requiring dihydrofolate reductase (DHFR)-mediated regeneration [61]. BH4 can also convert phenylalanine into tyrosine, which can be further converted to 4-OH-benzoate (a precursor of CoQ10), thus promoting CoQ10 synthesis and counteracting ferroptosis [62].

3. The role of ferroptosis in AS

3.1. VEC ferroptosis aggravates AS

Vascular endothelial cell (VEC) dysfunction is an initial event during the development of AS. VEC damages cause increased intimal permeability and leukocyte adhesion, accelerating AS progression and promoting thrombus formation [63]. Recently, the unfavorable role of VEC ferroptosis in atherogenesis has been well-demonstrated. Bai et al. found that oxidized-low-density lipoprotein (ox-LDL), a potent pro-atherosclerotic factor, could cause mitochondrial damage, increase the contents of iron and lipid ROS, and decrease levels of xCT and GPX4, thus inducing ferroptosis in MAECs. Compared to wild-type (WT) mice, high-fat diet (HFD)-fed $apoE^{-/-}$ mice displayed larger atherosclerotic lesion areas, severe iron overload, increased production of NOXs, and lipid peroxides (LPO), and decreased expression of xCT and GSH in thoracic aortic tissue. Specifically, the expression of GPX4 in CD31-positive VECs of the aorta was significantly reduced in HFD-fed $apoE^{-/-}$ mice. These phenomena were seriously compromised after injection with ferroptosis inhibitor, ferrostatin-1 (Fer-1) [64]. Li et al. found that injection of HFD-fed $apoE^{-/-}$ mice with endothelial progenitor cells-derived extracellular vesicles (EPC-EVs) carrying miR-199a-3p (EV-miR-199a-3p) decreased iron accumulation and lipid peroxidation, and increased the levels of xCT, GSH, and GPX4 in the aorta, leading to a smaller size of atherosclerotic plaques and lower serum levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Mechanistically, EPC-EVs transfer miR-199a-3p into MAECs, which targets specificity protein 1 (SP1) and suppresses ox-LDL-induced ferroptosis of MAECs [65].

Ferritinophagy-induced iron accumulation is an important promoter of VEC ferroptosis and atherogenesis. Wu et al. reported that treatment of human umbilical vein endothelial cells (HUVEC) with high-dose ionizing radiation (IR) markedly activated the p38/NCOA4 pathway-mediated ferritinophagy, which resulted in increased iron content, aggravated lipid peroxidation and decreased the expression of antioxidant indicators (GPX4, Nrf2, xCT, SLC3A2), causing severe VEC damage and ferroptosis. In HFD-fed $apoE^{-/-}$ mice, IR markedly aggravated plaque burden and vulnerability, with decreased GSH content and GPX4 activity in the aorta. IR increased the iron and LPO amounts in the carotid arteries and considerably reduced the $CD31^{+}GPX4^{+}$ and $CD31^{+}Nrf2^{+}$ area within the plaques [66]. Zinc oxide nanoparticles (ZnONPs) are widely used as a Zn supplement in food accelerating atherogenesis in vivo [67]. Treating HUVECs with ZnONPs decreased the contents of GPX4, FTH1, and GSH. It increased the cytosolic levels of LIP, IRP2, COX2, and MDA by activating mtROS/AMPK(AMP-activated protein kinase)/ULK1(unc-51like autophagy activating kinase 1)/NCOA4 pathway-mediated ferritinophagy, leading to ferroptosis and endothelial cytotoxicity [68].

Besides, enhancing antioxidant effects may be an effective way to protect against VEC ferroptosis and AS progression. Yang et al. disclosed that the serum level of prenyldiphosphate synthase subunit 2 (PDSS2), a key enzyme for CoQ10 synthesis, was significantly decreased in AS patients. Overexpression of PDSS2 in human coronary artery endothelial cells (HCAECs) significantly reduced the content of iron and total ROS and increased GSH levels by activating Nrf2 (nuclear factor erythroid 2-related factor 2), thereby suppressing the ferroptosis of HCAECs. Compared with WT mice, the atherosclerotic plaque area was significantly enlarged in $PDSS2^{-/-}Nrf2^{-/-}$ mice, while this was alleviated in $PDSS2^{-/-}Nrf2^{+/+}$ mice. They concluded that the PDSS2/Nrf2 axis protects against AS by inhibiting VEC ferroptosis [69]. Despite the absence of direct evidence, it is possible that ZnONPs could expedite the advancement of AS by augmenting VECs ferroptosis. Docosahexaenoic acid (DHA), a natural omega-3 fatty acid component of algae oil, is ubiquitous in marine foods and could prevent hypoxia-induced AS progression [70]. In angiotensin II (Ang II)-treated cardiac microvascular endothelial cells (CMECs), DHA markedly activated the IRF3 (interferon regulating factor 3)/xCT/ALOX12 (arachidonate 12-LOX) pathway, causing increased GSH levels, amplified activity of antioxidative enzymes (SOD, Mn-SOD, Cu/Zn-SOD, and GPX), and decreased contents of MDA and 12-hydroxyeicosatetraenoic acid (12-HETE), thus inhibiting ferroptosis [71]. DHA may serve as a potential therapeutic agent for atherosclerosis by inhibiting endothelial cell ferroptosis.

3.2. Macrophage ferroptosis exacerbates AS

Macrophage death is a double-edged sword in developing AS [72]. In the initial stage of AS, moderate macrophage death decreases the secretion of metalloproteinase (MMP) and alleviates the inflammatory response, while in advanced AS, unrestrained macrophage death and ineffective efferocytosis aggravates inflammation, promotes the formation of lipid-rich necrotic core, and destabilizes atherosclerotic plaques [73]. Bao et al. unraveled that atherosclerotic mice treated with cigarette tar had more severe iron deposits, increased 4-HNE levels, larger necrotic cores, and less collagen content in plaques. Specifically, cigarette tar increased the hepcidin levels and decreased the expression of FPN and xCT in macrophages of aortic plaques. In THP-1 macrophages, cigarette tar promotes ferroptosis via the hepcidin/FPN/xCT axis by stimulating the NF-κB signaling pathway, indicating the harmful role of macrophage ferroptosis in atherogenesis [74]. Hu et al. found that high uric acid (HUA) levels could decrease ox-LDL-induced ferroptotic events, including iron overload, GSH depletion, and accumulation of lipid and MDA in human THP-1 and mouse RAW264.7 macrophages. HUA also reduced the expression of xCT and GPX4 by inhibiting Nrf2-mediated autophagy, promoting ferroptosis and macrophage foam cell formation. In consistency with the in vitro findings, HUA diminished the activation of the Nrf2/xCT/GPX4 signaling pathway in atherosclerotic plaques, induced hypercholesterolemia, and accelerated atherosclerotic lesion formation in HFD-fed $apoE^{-/-}$ mice [75]. Compared to normal human arteries, smaller mitochondria and blurred mitochondrial cristae were observed in human atherosclerotic lesions. Significantly, GPX4 expression was mainly localized in the CD68-positive area and was negatively associated with the progression of atherosclerotic plaques, indicating that ferroptosis occurred predominantly in

macrophages during atherogenesis [76]. Macrophage ferroptosis exacerbates AS by promoting foam cell formation. Treatment of THP-1 macrophages with ox-LDL caused severe mitochondrial shrinkage, increased intracellular mtROS levels, and decreased GPX4 expression, leading to ferroptosis and foam cell formation. Further research revealed that ox-LDL promotes macrophage ferroptosis by up-regulating HIF-1α expression and suppressing autophagy [76].

Erythrophagocytosis (macrophages with phagocytosed erythrocytes)-induced macrophage iron overload and ferroptosis are another trigger for atherogenesis. Puylaert et al. reported that erythrophagocytosis by bone marrow-derived macrophages (BMDMs) significantly increased HO-1 and FTH1 levels, labile iron accumulation, lipid peroxidation, and finally, promoting ferroptosis. In apoE$^{-/-}$Fibrillin1$^{C1039G+/-}$(apoE$^{-/-}$Fbn1$^{C1039G+/-}$) mice, a model of advanced AS with intraplaque angiogenesis, the expression of HO-1 and FTH1 was robustly increased in erythrocyte-rich murine lesions. Subcutaneous administration of UAMC-3203 (a ferroptosis inhibitor) into apoE$^{-/-}$Fbn1$^{C1039G+/-}$ mice decreased intraplaque HO-1 and FTH1 expression and carotid plaque thickness, indicating that inhibiting erythrophagocytosis-induced macrophage ferroptosis is an effective way to prevent AS [77]. Liu et al. developed hyperlipidemic erythropoietin receptor Cre mice that express *Jak2*^{VF} in the erythroid lineage (VFEpoR mice). They found that VFEpoR mice showed increased phagocytosis of red blood cells (RBCs) by plaque macrophages, high iron, and 4-HNE contents, and more severe macrophage ferroptosis in plaques, leading to aggravated atherosclerotic plaque necrosis. These phenomena were more evident after selective induction of erythrocytosis and suppressed by ferroptosis inhibitor liproxstatin-1, respectively, suggesting that erythroid lineage *Jak2*^{VF} accelerates atherogenesis by enhancing erythrophagocytosis and macrophage ferroptosis [78].

Bacille-Calmette-Guérin (BCG) infection could increase atherosclerotic lesions in the *en face* aorta of LDLR$^{-/-}$ mice [79]. Treatment of RAW264.7 macrophages with BCG decreased cell viability and the expression of GPX4 and FSP1, increased mitochondrial membrane ridge breaks, and up-regulated intracellular HO-1, iron, and ROS levels, inducing lipid peroxidation and ferroptosis. These effects were potently reversed by HO-1 knockdown, suggesting that BCG may accelerate AS development by triggering HO-1-mediated macrophage ferroptosis [80]. Administration of β-caryophyllene (BCP) into hypercholesterolemic rats significantly lowered total cholesterol (TC) and LDL levels, increased high-density lipoprotein (HDL) levels, and enhanced the activity of antioxidant enzymes in the serum [81]. Wu et al. found that BCP treatment reversed RSL3-induced ferroptosis and inflammation in RAW264.7 macrophages and BMDMs, as reflected by ameliorated mitochondrial damage and lipid peroxidation, increased expression of GPX4 and FTH1 and reduced levels of TNF-α, PTGS2, AlOX5, and MDA, indicating that BCP may prevent AS by suppressing macrophage ferroptosis and inflammation [82]. Further data are necessary to test these hypotheses.

3.3. VSMC ferroptosis facilitates AS

The death of VSMCs in advanced atherosclerotic plaques triggers severe vascular inflammation and loss of collagen and extracellular matrix, leading to thinner fibrous caps and plaque rupture [83]. The osteogenic transdifferentiation and mineralization of VSMCs are critical in atherogenesis, causing vascular calcification and stiffening [84,85]. Xie et al. observed that intraperitoneal injection of Fer-1 into HFD-fed apoE$^{-/-}$ mice remarkably decreased TFR1 expression, increased the Nrf2, FSP1, FTL, and FTH1 levels in aortic VSMCs, and alleviated iron overload in plaques, leading to smaller plaque lesion areas. Similar phenomena were observed in Fer-1-treated human aortic ferroptotic VSMCs. Interestingly, unlike VECs and macrophages, the expression of xCT and GPX4 was not significantly changed in Fer-1-treated ferroptotic VSMCs in vivo and in vitro, suggesting that Fer-1 retards the development of AS by inhibiting VSMC ferroptosis independent of xCT/GPX4 axis, probably by activating the Nrf2/FSP1 pathway [86]. Oleoylethanolamide (OEA) could increase collagen content and decrease the necrotic core size in atherosclerotic plaques [87]. Chen et al. observed that treatment of rat primary VSMCs with OEA markedly amplified the anti-mitochondria dysfunction capacity and alleviated the PPARα (peroxisome proliferator-activated receptor α)/CGAS (cyclic GMP-AMP synthase)/STING1(stimulator of interferon response cGAMP interactor 1) signaling-induced ferritinophagy, leading to mitigated ferroptosis and VSMC calcification [4]. OEA may retard AS by suppressing VSMC ferroptosis and vascular calcification, which requires more in vivo data to validate. Recent studies have validated the involvement of ferroptosis in mediating this phenotypic transition of VSMCs [88,89]. Ye et al. showed that during high-calcium/phosphate-induced VSMC calcification, cellular PTGS2, lipid ROS, and MDA levels were significantly elevated, along with decreased cell viability and expression of xCT, GSH, and GPX4. Inhibition of ferroptosis ex vivo repressed calcification of VSMCs under pro-osteogenic conditions and attenuated rat and human arterial ring calcification [88].

As the primary cell type in the arterial vessel wall, VSMCs have a "contractile" phenotype that maintains the normal vessel structure and function under physiological conditions. In response to pro-atherogenic stimulators, contractile VSMCs switch to a dedifferentiated state ("synthetic" phenotype) to acquire proliferative, migratory, and synthetic capabilities [90]. Ji et al. reported that treatment of primary human aorta VSMCs (HASMCs) with derived growth factor BB (PDGF-BB), a growth factor that promotes VSMC dedifferentiation, significantly decreased GPX4 expression and increased the levels of TFR1, ACSL4, ALOX15, MDA, and 4-HNE. Moreover, ferroptosis inducer RSL3 increased, while GPX4 overexpression down-regulated the expression of synthetic VSMC markers (osteopontin and vimentin). Furthermore, ferroptosis inhibition suppressed the mitochondrial respiration chain, mtROS generation, and mitochondrial hyperpolarization and increased mitochondrial fusion in dedifferentiated VSMCs, indicating that ferroptosis promotes synthetic VSMC phenotype by disrupting mitochondrial homeostasis. Finally, they found that copper-diacetyl-bisN4-methylthiosemicarbazone (CuATSM), a positron emission tomography (PET) imaging tracer, prevented VSMCs switching toward synthetic phenotype, neointimal hyperplasia, and vascular inflammation by inhibiting ferroptotic stress in mice, suggesting that CuATSM may protect against AS by repressing the ferroptosis-induced synthetic VSMC phenotype [91].

In addition to the phenotype switch, VSMC inflammation is another threat to AS, as it reduces the flexibility of the artery walls and leads to further narrowing [92]. Sampilvanjil et al. reported that treatment of primary rat VSMCs with cigarette smoke extract (CSE), a significant risk factor for atherogenesis, caused lipid peroxidation, mitochondrial damage, and GSH depletion and increased pro-inflammatory cytokine production (IL-1, IL-6, TNF-α), inducing ferroptosis and inflammation. In ex vivo cultured aortas, CSE decreased the number of medial VSMCs among the elastic lamina. These effects were alleviated by Fer-1 and liproxstatin-1, suggesting that CSE may aggravate vascular inflammation and the development of AS by promoting VSMC ferroptosis [93]. Hypertension is a well-demonstrated pro-atherogenic factor [94]. Jin et al. found that GPX4 expression was significantly decreased in the aortic media of spontaneously hypertensive rats (SHR) and hypertensive patients. Compared with normal pressure, high hydrostatic pressure (HHP; 200 mmHg) increased iron accumulation, ROS production, and the expression of pro-ferroptosis genes (COX2, ACSL4, and NOX1) and decreased xCT and GPX4 levels in HASMCs, resulting in ferroptosis and VSMC inflammation. Mechanistically, HHP decreased GSH synthesis by suppressing the cystathionine gamma-lyase (CSE)/hydrogen sulfide (H_2S) pathway. HHP may accelerate AS progression by promoting VSMC ferroptosis and inflammation [95]. More studies are still warranted to unveil the role of VSMC ferroptosis in atherogenesis (Fig. 3).

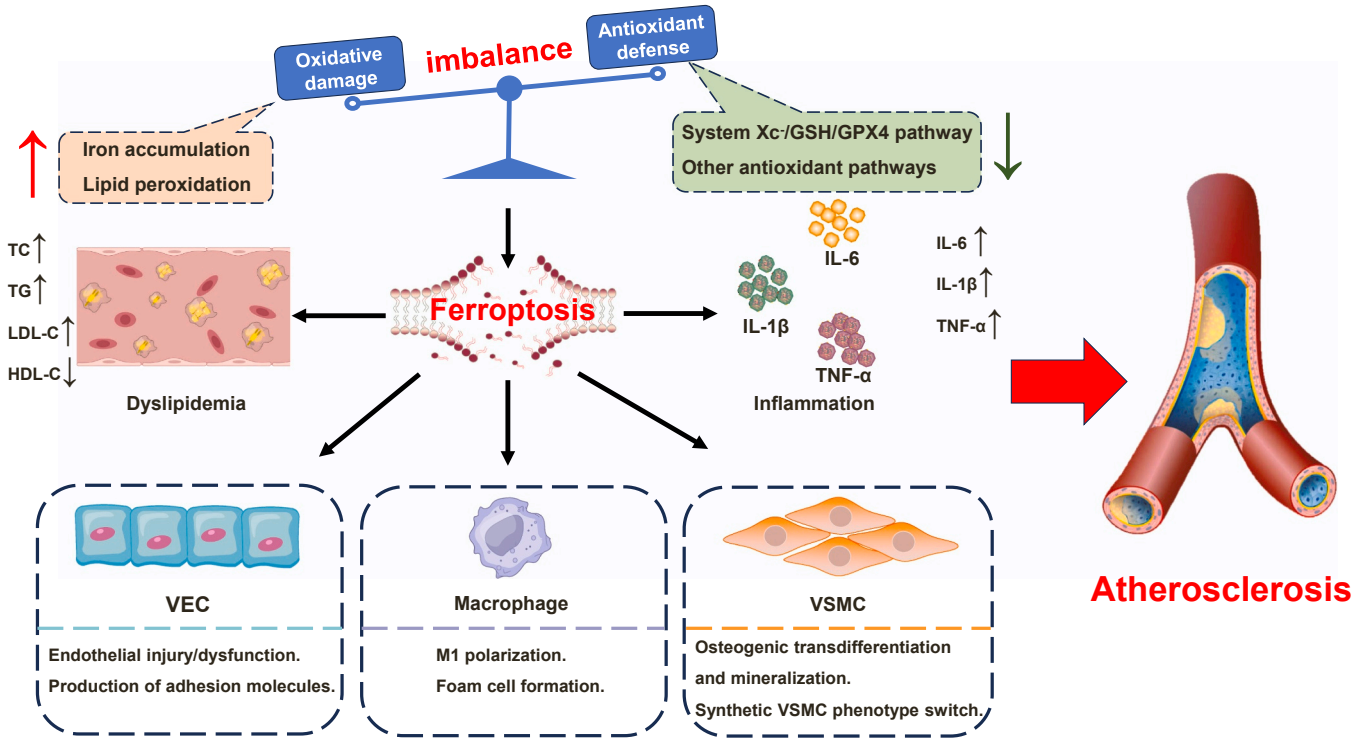


Fig. 3. The role of ferroptosis in atherosclerosis. Ferroptosis occurs from the imbalance between the cell's oxidative damage and antioxidant defense systems. Ferroptosis is implicated in many plaque cell activities, e.g., the stimulation of synthetic VSMC phenotypic switch, the facilitation of foam cell formation, and the enhancement of VEC impairment and inflammation. Further, ferroptosis promotes the release of inflammatory factors and dyslipidemia. Regarding the diverse crucial factors linked to the emergence and advancement of atherosclerosis, ferroptosis in plaque cells is the key promoter of atherogenesis. VSMC, vascular smooth muscle cells; VEC, vascular endothelial cells. TC, total cholesterol; TG, triglycerides; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol.

4. Potential drugs and phytomedicine inhibit AS by suppressing plaque cells' ferroptosis

The development of AS is accompanied by abnormal programmed cell death of plaque cells. VEC injury, activation, and death can recruit monocytes and other circulating leukocytes for transendothelial migration. These monocytes in the endothelium can differentiate into macrophages and become foam cells by phagocytosing excess lipids. Besides, dying VEC can also promote the proliferation and migration of adjacent VSMC into the arterial intima, which increases the synthesis of extracellular matrix components, causing the formation of plaques and vasodilator dysfunction. Recent studies have identified many potential drugs/phytomedicine that retard atherogenesis by inhibiting plaque cells' ferroptosis, most of which are focused on VECs, as shown below.

4.1. Drugs/phytomedicine suppress AS by inhibiting VEC ferroptosis

Wang et al. reported that administrating Tongxinluo (TXL), a multifunctional Chinese medicine, into HFD-fed apoE$^{-/-}$ mice alleviated pulmonary microvascular endothelial barrier disruption, improved dyslipidemia, and decreased atherosclerotic plaque area. In human pulmonary microvascular endothelial cells (PMECs), TXL markedly enhanced GSH activity and increased the expression of GPX4 and FSP1. At the same time, the levels of ACSL4, MDA, and nitric oxide (NO) were decreased, indicating that TXL mitigates the progression of AS by inhibiting the ferroptosis of PMECs [96]. Icariin, a main active ingredient of the traditional Chinese medicine *Epimedium grandiflorum* Maxim, was demonstrated to improve dyslipidemia, inhibit inflammation, suppress ferroptosis in aortic tissue, and decrease the size of the atherosclerotic area in HFD-fed apoE$^{-/-}$ mice. Co-incubation of ox-LDL-treated HUVECs with icariin significantly enhanced autophagy, reduced ROS and Fe^{2+} levels, and increased the expression of GPX4 and FTH1, suggesting that icariin could mitigate AS by inhibiting VEC ferroptosis [97]. Besides, Rong et al. found that intraperitoneal injection of hydroxysafflor yellow A (HSYA), an active ingredient of *Carthamus tinctorius* L., into diabetic atherosclerotic mice caused a significant reduction in plasma lipid levels, aortic ferroptosis, and plaque lipid accumulation. Moreover, the incubation of HUVECs with HSYA markedly reversed high glucose and ox-LDL-induced ferroptosis, as reflected by increased cell viability and expression of xCT, GPX4, and GSH, and decreased levels of iron, ROS, MDA, and ACSL4. Further research unraveled that HSYA protects HUVECs from ferroptosis via the miR-429/xCT pathway, denoting that HSYA exerts atheroprotective effects by inhibiting VEC ferroptosis through the miR-429/xCT pathway [98].

Fluvastatin is a powerful cholesterol-lowering medicine with multifaceted anti-atherogenic effects [99]. Li et al. found that fluvastatin dose-dependently increased cell proliferation and migration, up-regulated the expression of xCT and GPX4, and decreased levels of 4-HNE, TNF-α, and IL-1α in ox-LDL-treated HUVECs, indicating that fluvastatin normalizes ox-LDL-induced endothelial dysfunction and inflammation via inhibition of ferroptosis [100]. Astragaloside IV (AS-IV), a critical component of Astragalus membranaceus, could attenuate atherosclerotic plaque vulnerability in vivo [101,102]. In LPC-treated HUVECs, AS-IV significantly improved mitochondrial morphology, reduced iron ion and lipid ROS levels, and upregulated the expression of xCT and GPX4, inhibiting cell senescence and ferroptosis [103]. Tanshinone IIA (TSA) is a diterpene quinone isolated from the Chinese herb Salvia miltiorrhiza and has pleiotropic anti-AS effects [104]. Treatment of HCAECs with TSA restored erastin-induced ferroptosis, as evidenced by decreased ROS levels, increased FTH1 levels, and enhanced expression of antioxidant mediators, including xCT, GPX4, GSH, SOD, and NAD(P)H quinone dehydrogenase 1 (NQO1). These effects were reversed mainly by Nrf2 inhibition, suggesting that TSA inhibits HCAEC ferroptosis via Nrf2 activation [105]. Fluvastatin, AS-IV, and TSA may retard the progression of AS by alleviating VEC

ferroptosis, but compelling evidence in vivo is still lacking.

4.2. Drugs/phytomedicine suppress AS by inhibiting macrophage and VSMC ferroptosis

Zhang et al. found that HFD-fed apoE$^{-/-}$ mice treated with Qing-Xin-Jie-Yu Granule (QXJYG) displayed fewer foam cells and smaller lesion areas in aortic plaques. QXJYG improved mitochondrial morphology, decreased total iron content, and increased xCT, GPX4, GSH, and SOD levels, thus inhibiting ferroptosis within plaques. Treatment of J774A.1 macrophage with QXJYG down-regulated cytoplasmic Fe^{2+}, LPO, and ROS levels, protecting against RAS-selective lethal 3 (RSL3)-induced ferroptosis [106]. Metformin has multiple anti-atherogenic effects [107], one of which is to prevent foam cell formation [108]. In ox-LDL-treated THP-1 macrophages, metformin incubation decreased the secretion of pro-inflammatory cytokines and the contents of HO-1 and MDA. It also up-regulated the levels of GPX4 and SOD via the AMPK/ERK signaling pathway, alleviating ferroptosis and lipid accumulation [109]. Metformin may protect against foam cell formation and AS by inhibiting macrophage ferroptosis. Zhang et al. found that administering echinatin into hyperlipidemia mice robustly mitigated arterial stiffening and AS. Mechanistically, echinatin improved cell viability, decreased intracellular Fe^{2+} and MDA levels, and increased the GCLC/GCLM expression and GSH levels by activating Nrf2 in arterial VSMCs, suppressing lipid peroxidation and ferroptosis. Echinatin-induced anti-ferroptosis effects of VSMCs reduced the expression of collagen type I alpha 1 chain (COL1A1), collagen type III alpha 1 chain (COL3A1), and tissue inhibitor of metalloproteinase 3 (TIMP3), thus yielding its matrix softening effects and preventing AS [110]. In addition, Ma et al. found that metformin could attenuate hyperlipidemia/palmitic acid (PA)-induced vascular calcification both in vivo and in vitro. PA decreased cell viability, GSH/GSSG ratio, and GPX4 expression and increased intracellular iron level and lipid peroxidation, thus inducing ferroptosis in primary VSMCs from the thoracic aortas of rats. The treatment of metformin or Fer-1 compromised these phenomena. Further research revealed that metformin inhibits PA-induced ferroptosis and subsequent calcium deposition of VSMCs via the periostin/p53/xCT pathway, suggesting that ferroptosis inhibition may be involved in metformin-elicited atheroprotection [89] (Table 2).

5. Conclusions and future perspectives

Ferroptosis, which involves the breakdown of the antioxidant system, disturbance of iron homeostasis, and accumulation of lipid peroxides, is a critical event in the initiation and progression of AS. Ferroptosis-induced AS involves three primary plaque cells, i.e., VEC, macrophage, and VSMC, leading to endothelial disruption, foam cell formation, adverse phenotypic switch, and escalated vascular inflammation [111]. Hitherto, research on the relationship between ferroptosis of plaque cells and AS is still in its infancy. The limitations of these studies are apparent, presented as follows: 1) most researchers have focused on ferroptosis in VECs and macrophages, whereas less is known regarding the role of VSMC ferroptosis in AS; 2) although various ferroptosis regulators of plaque cells have been identified, whether they are involved in plaque formation lacks direct evidence in vivo; 3) inactivation of xCT/GPX4 pathway is mainly responsible for ferroptosis within plaques, whereas the role of GPX4-independent antioxidant pathways in atherogenesis is rarely reported; 4) although the harmful role of ferroptosis in AS progression has been well demonstrated, whether ferroptosis of plaque cells play some beneficial effects under specific circumstances during atherogenesis need to be identified; 5) AS progression involves multiple cell types, thus the experiments designed in a single cell type cannot represent the disease in vivo; 6) solid clinical data that ferroptosis inhibition help treat AS patients are still deficient; 7) As gut microbiota is a vital source for iron and amino acids needed for our bodies, whether intestinal bacilli illness promotes the development

Table 2
Factors that regulate ferroptosis of plaque cells and atherogenesis.

Factors	Cell type	Ferroptosis-related indexes	Ferroptosis	AS	Refs
EV-miR-199a-3p	VEC	Iron↓, xCT↑, GPX4↑, MDA↓, ROS↓	↓	↓	[65]
IR	VEC	Iron↑, xCT↓, GPX4↓, NCOA4↑, Nrf2↓	↑	↑	[66]
ZnONPs	VEC	LIP↑, FTH1↓, GPX4↓, NCOA4↑, COX2↑	↑	↑?	[67,68]
PDSS2	VEC	Iron↓, GSH↑, ROS↓, Nrf2↑,	↓	↓	[69]
DHA	VEC	xCT↑, GSH↑, SOD↑, ALOX12↓, LPO↓	↓	↓?	[70,71]
TXL	VEC	FSP1↑, GPX4↑, GSH↑, MDA↓, NO↓	↓	↓	[96]
Icariin	VEC	Iron↓, FTH1↑, GPX4↑, ROS↓	↓	↓	[97]
HSYA	VEC	Iron↓, GPX4↑, GSH↑, MDA↓, ACSL4↓	↓	↓	[98]
Fluvastatin	VEC	xCT↑, GPX4↑, 4-HNE↓	↓	↓?	[99,100]
AS-IV	VEC	Iron↓, xCT↑, GPX4↑, ROS↓	↓	↓?	[101–103]
TSA	VEC	xCT↑, GPX4↑, SOD↑, NQO1↑, ROS↓	↓	↓?	[104,105]
Cigarette tar	Mφ	FPN↓, xCT↓, GPX4↓, GSH↓, 4-HNE↑	↑	↑	[74]
HUA	Mφ	Iron↑, xCT↓, GPX4↓, Nrf2↓, MDA↑	↑	↑	[75]
UAMC-3203	Mφ	HO-1↓, FTH1↓	↓	↓	[77]
EL Jak2^{VF}	Mφ	Iron↑, TFR1↑, GPX4↓, LPO↑, ROS↑	↑	↑	[78]
BCG	Mφ	Iron↑, HO-1↑, GPX4↓, FSP1↓, ROS↑	↑	↑?	[79,80]
BCP	Mφ	FTH1↑, GPX4↑, AlOX5↓, MDA↓	↓	↓?	[81,82]
QXJYG	Mφ	Iron↓, xCT↑, GPX4↑, LPO↓, ROS↓	↓	↓	[106]
Metformin	Mφ	HO-1↓, GPX4↑, SOD↑, MDA↓	↓	↓?	[107–109]
OEA	VSMC	LIP↓, FTH1↑, NCOA4↓, MDA↓	↓	↓?	[4,87]
HC/P	VSMC	xCT↓, GSH↓, GPX4↓, COX2↑, MDA↑	↑	↑?	[88]
CuATSM	VSMC	GSH↑, MDA↓	↓	↓?	[91]
CSE	VSMC	GSH↓, PTGS2↑, LPO↑	↑	↑?	[93]
HHP	VSMC	xCT↓, GPX4↓, COX2↑, NOX1↑	↑	↑?	[94,95]
Echinatin	VSMC	Iron↓, GCLC/GCLM↑, GSH↑, Nrf2↑, LPO↓	↓	↓	[110]
Metformin	VSMC	xCT↑, GSH/GSSG ratio↑, GPX4↑	↓	↓?	[89]

Notes: EV-miR-199a-3p, endothelial progenitor cells-derived extracellular vesicles carrying miR-199a-3p; VEC, vascular endothelial cell; xCT, solute carrier family 7 member 11 (SLC7A11); GPX4, glutathione peroxidase 4; MDA, malondialdehyde; ROS, reactive oxygen species; IR, ionizing radiation; NCOA4, nuclear receptor coactivator 4; Nrf2; nuclear factor erythroid 2-related factor 2; ZnONPs, zinc oxide nanoparticles; FTH1, ferritin heavy chain 1; LIP, labile iron pool; COX2, cyclooxygenase 2; PDSS2, prenyldiphosphate synthase subunit 2; GSH, glutathione; DHA, docosahexaenoic acid; SOD, superoxide dismutase; ALOX12, arachidonate 12-lipoxygenase; LPO, lipid peroxides; TXL, Tongxinluo; FSP1, ferroptosis suppressor protein 1; NO, nitric oxide; HSYA, hydroxysafflor yellow A; ACSL4, acyl-CoA synthetase long-chain family member 4; 4-HNE, 4-hydroxynonenal; AS-IV, astragaloside IV; TSA, Tanshinone IIA; NQO1, NAD(P)H quinone dehydrogenase 1; Mφ, macrophage; FPN, ferroportin; HUA, high uric acid levels; HO-1, heme oxygenase-1; EL Jak2^{VF}, erythroid lineage Jak2^{VF}; TFR1, transferrin receptor protein 1; BCG, Bacille-Calmette-Guérin; BCP, β-caryophyllene; ALOX5, arachidonate 5-lipoxygenase; QXJYG, Qing-Xin-Jie-Yu Granule; VSMC, vascular smooth muscle cell; OEA, oleoylethanolamide; HC/P, high-calcium/phosphate; CuATSM, copper-diacetyl-bisN4-methylthiosemicarbazone; CSE, cigarette smoke extract; PTGS2, prostaglandin synthase 2; HHP, high hydrostatic pressure; NOX1, NADPH oxidase 1; GCLC, glutamate-cysteine ligase catalytic subunit; GCLM, glutamate-

cysteine ligase modifier subunit; GSSG, glutathione disulfide; ↓, suppress; ↑, promote; ?, probably (not verified).

of AS by inducing ferroptosis requires exploration. Addressing these limitations will undoubtedly deepen our understanding of ferroptosis's role in AS and promote novel ferroptosis-based druggable therapies for treating AS.

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Data Availability

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CRediT authorship contribution statement

Xu Xi: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Xu Xiao-Dan:** Conceptualization, Methodology, Formal analysis, Writing – original draft preparation, Writing – review & editing. **Ma Meng-Qing:** Methodology, Investigation, Writing – review & editing. **Liang Yin:** Methodology, Formal analysis, Investigation. **Cai Yang-Bo:** Methodology, Formal analysis, Investigation. **Zhu Zi-Xian:** Methodology, Formal analysis, Investigation. **Xu Tao:** Methodology, Formal analysis, Investigation. **Zhu Lin:** Conceptualization, Writing – review & editing, Funding acquisition. **Ren Kun**: Conceptualization, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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