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Ferroptosis in AS progression: role of miRNA

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Abstract. – We review the relationship between miRNAs associated with ferroptosis and the evolution of AS. Even though, more evidence is asked to determine the role of miRNAs associated with ferroptosis in the AS, this review will help us understand the role of miRNAs in ferroptosis and AS and may provide new insights for probing new biomarkers for the diagnosis and treatment of AS for the time to come.

This is a narrative essay. Using PubMed as the main source, a literature search strategy was randomly implemented to index Scopus articles. No specific terminology is used.

Studies have shown that ferroptosis plays a crucial role in the development of AS, and a large amount of ferroptosis in cells can lead to the progression of AS. MicroRNAs (MiRNAs) have been proved to be taken part in the biological course of ferroptosis and thus the process of AS is affected. The exact regulatory mechanism behind this appearance remains unclear. In order to clarify this, a growing number of studies have concentrated the regulatory role of miRNAs in the process of generation and development of ferroptosis, as well as the function of ferroptosis in the progression of AS.

MiRNAs play a significant role in the process of ferroptosis and are incredibly significant in the occurrence, development, clinical diagnosis, treatment and prognosis evaluation of AS.

Key Words:
Atherosclerosis, Ferroptosis, MicroRNAs, Programmed cell death (PCD).

Introduction

AS is a chronic inflammatory disease characterized by the formation of lipid plaques on the walls of large and medium-sized arteries[1]. It is caused by the accumulation of low-density lipoprotein (LDL) under the subcutaneous skin, accompanied by the proliferation of smooth muscle cells and fibrous matrix, gradually forming atherosclerotic plaques[2]. AS is the main cause of internal vascular related death worldwide[2,3]. Understanding the underlying mechanisms fundamental to the pathological development of AS is essential for solving clinical problems and developing new therapeutic strategies[3].

Cell death plays a crucial role throughout life. Apoptosis was the first mechanism discovered in programmed cell death (PCD). Ferroptosis is a new type of PCD, first proposed by Dixon et al[4] in 2012, which relies on reactive oxygen species (ROS) production and iron overload[5]. The morphological characteristics of ferroptosis are reduction or loss of the mitochondrial crest[4], condensation of the mitochondrial membrane[6] and rupture of the outer mitochondrial membrane[7]. Biochemical features of ferroptosis are deficiency depletion or inactivation of glutathione peroxidase 4 (GPX4) activity, leading to intracellular glutathione (GSH) depletion, iron accumulation and lipid peroxidation[8]. The genetic characteristics of ferroptosis are mainly manifested in iron metabolism, lipid metabolism and amino acid metabolism. As shown in Table I, ferroptosis is significantly different from autophagy, apoptosis, pyroptosis and necroptosis in several aspects (Table I).

Non-coding RNAs (ncRNAs) were once taken for rubbish molecules, but because of their fundamental characteristics in gene expression and translation regulation[13]. Recently, there has been considerable interest and new insights about this[14] MicroRNAs (MiRNAs) are the major members of

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non-coding RNAs and play a crucial part in genetic expression and physiological processes[15,16]. MiRNA is a kind of non-coding single stranded RNA molecule with a length of 21-24 nucleotides in cells, which is encoded by endogenous genes and plays an important regulatory role. MiRNAs were first discovered by Lee in Caenorhabditis elegans in 1993[17] and can regulate a variety of human metabolic pathways at the level of translation and transcription[18]. It has been reported that the regulation method of miRNAs also exists in the regulation of ferroptosis[16].

In recent years, ferroptosis has been found to promote the occurrence and development of AS, and miRNA plays an important role in regulating ferroptosis. This paper summarizes the regulatory mechanism of ferroptosis and the relationship between miRNA and ferroptosis, providing new ideas for the study and future application of targeted AS molecules.

Mechanisms of Ferroptosis

The regulatory mechanisms of ferroptosis are complexed, referring a various of signal molecules and metabolic pathways (Figure 1). In this review, we summarize the vital function of iron metabolism, lipid metabolism, and amino acid metabolism in the pathogenesis of ferroptosis.

Table I. Characteristics of the different types of PCD.

First author, year	RCD (year of discovery)	Morphological features	Biochemical features	
Dixon et al[4]	Ferroptosis (2012)	Cell swelling, mitochondrial contraction, dense mitochondrial membrane, reduced or missing mitochondrial crest, mitochondrial outer membrane rupture, normal nucleus, lack of chromatin condensation	Iron overload and lipid peroxidation inhibit xCT, decrease GSH and GPX4	
Degterev et al[9]	Necroptosis (2005)	The cytoplasm and organelles expanded rapidly, the plasma membrane ruptured, and chromatin moderately condensed	Pro-inflammatory response, ROS production, decreased ATP content,RIP1, RIP3 and MLKL activation	[9]
Cookson et al[10]	Pyroptosis (2001)	The cells swell, forming vesicles from the plasma membrane and nuclear pyknosis	Release of pro-inflammatory cytokines, inflammatory caspase	[10]
Kerr et al[11]	Apoptosis (1972)	Cell shrinkage, plasma membrane blistering, nuclear fragmentation, chromatin condensation and marginalization, pseudopodia retraction, apoptotic bodies formation, cytoskeleton disintegration, no significant changes in mitochondrial structure	Caspase activation, phosphatidylserine externalization, oligonucleic DNA fragmentation	[11]
De Duve et al[12]	Autophagy (1966)	Formation of autophagic vacuoles, bimembrane autophagosomes, lack of changes in plasma membrane, and chromatin aggregation, including macroautophagy microautophagy and co-protein-mediated autophagy	Increased lysosomal degradation and recovery of damaged proteins and organelles	[12]

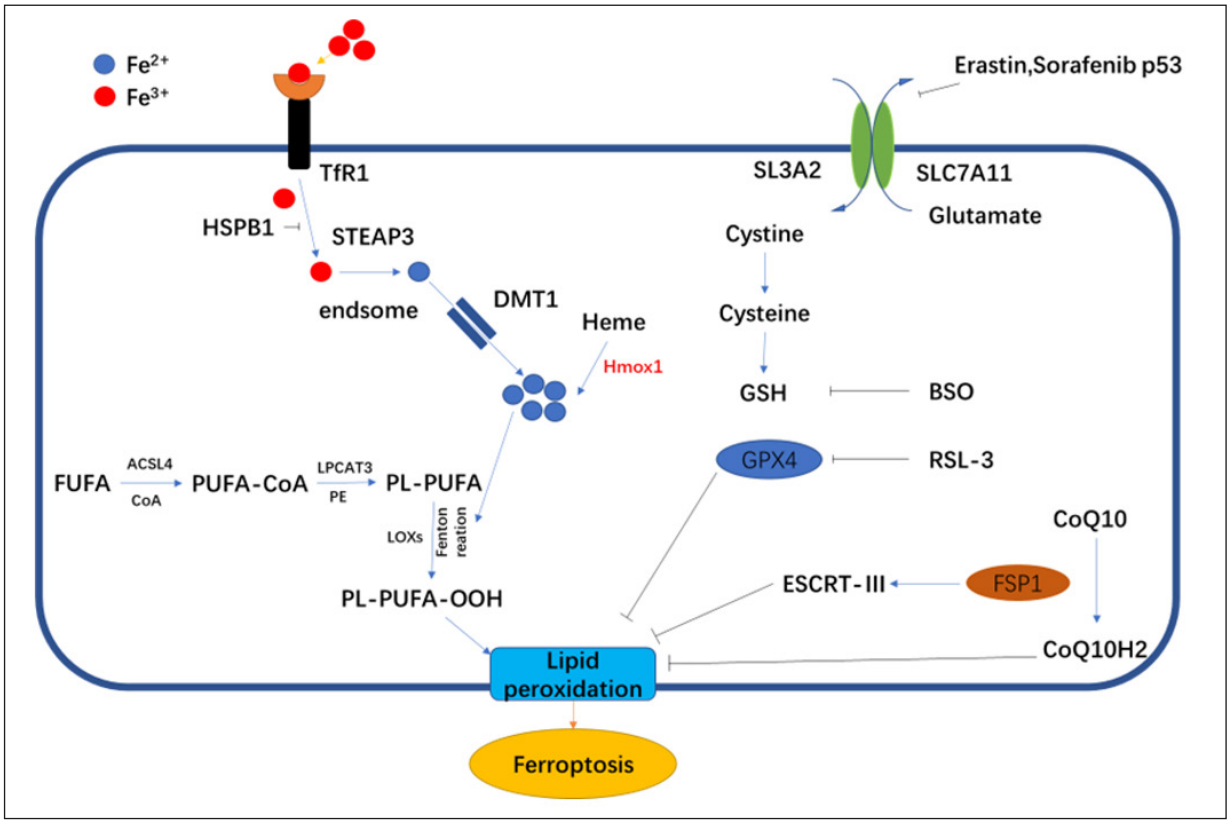

Figure 1. Mechanisms of ferroptosis.

Iron Metabolism and Ferroptosis

Iron homeostasis is essential for many biological processes and cellular viability. Ferroptosis is caused by excess iron, which leads to lipid peroxidation and cell death. Although the exact mechanism between iron metabolism and ferroptosis remains to be fully elucidated, there is no doubt that iron metabolism plays an important role in ferroptosis. Erastin-induced death depends on iron in cells rather than on other metal ions; ROS accumulation and ferroptosis can be inhibited by co-treatment with the iron chelating agent deoxyamine[19]. Transferrin receptor 1 (TfR1) allows Fe^{3+} into cells. Then, in the endosome, the six transmembrane epithelial antigens of the prostate 3 (STEAP3) can be converted into Fe^{2+} and released from endosomes via divalent Metal Transporter 1 (DMT1). Fe^{2+} is stored in unstable iron pools (LIP) and ferritin and is exported via ferroportin-1 (FPN1). If the balance between iron absorption, utilization, and circulation is interrupted, free iron ions in the presence of hydrogen peroxide (H_2O_2) may aggregate and catalyze the Fenton reaction, leading to the formation of lipid peroxides and ultimately ferroptosis[20]. In this process, silencing the gene encoding TfR 1 prevented erastin-induced ferroptosis, while deletion of FPN1 increased cell sensitivity to ferroptosis[21].

Recent studies have found that several regulatory factors of iron metabolism are involved in the course of ferroptosis. CDGSH iron - sulfur domains 1 and 2 (CISD1 and 2) are regulatory factors of iron in mitochondria. CISD1 inhibition increases iron-mediated mitochondrial lipid peroxidation and contributes to erastin-induced ferroptosis[22]. CISD2 deficiency increases mitochondrial iron and lipid ROS levels and also promotes sulfasalazine-induced ferroptosis[23]. Iron is a cofactor included enzymes in many metabolic processes; excess iron promotes mitochondrial ROS production surplus and ferroptosis. Ferritin is a highly conserved ferritin storage protein complex composed of two subunits of heavy chain (FTH) and light chain (FTL)[24], which plays an important role in iron metabolism by storing extracellular iron[25]. In Hippo mutant cells, the increased expression of ferritin heavy chain can prevent ROS

accumulation and inhibit ferroptosis, while the loss of cardiac ferritin heavy chain can promote cardiomyocyte death and heart failure through ferroptosis[26]. Ferritin autophagy is an important mechanism to hold intracellular iron balance. It can cause ferroptosis by accelerating unstable iron overload and lipid peroxidation[27]. Commanding iron levels in cells by obstructing ferritin autophagy may be a new therapeutic target for inhibiting ferroptosis in the future. Nuclear receptor Coactivator 4 (NCOA4) is a cargo receptor for ferritin degradation. It also maintains intracellular iron homeostasis by stopping ferritin autophagy[28]. The silencing of NCOA4 can decrease the accumulation of reactive iron and reactive oxygen species, thereby inhibiting cell death[29]. Heat shock protein beta-1 (HSPB1), a member of small heat shock proteins (HSPs), is a class of functionally relevant stress proteins and has the ability to inhibit iron uptake[30]. Upregulation of HSPB1 inhibited erastin-induced ferroptosis. HSPB1 phosphorylation guards' cells from ferroptosis by decreasing the production of iron-dependent lipid ROS[31]. Hmox1 is an essential enzyme for heme catabolism, which can decompose heme into iron, biliverdin and carbon monoxide. Hmox1 knockout mice had iron amassing in the liver and kidney, suggesting that Hmox1 was referred to iron metabolism. Dyshomeostasis of iron, covering iron missing and iron accumulation, can injure natural heart function and result in multifarious cardiovascular diseases[32].

Lipid Metabolism and Ferroptosis

Recent studies have shown that lipid peroxidation metabolism has relations with the formation of ferroptosis, which is involved in the building of membrane micelles and pores[33]. Now it is deemed that the formation of lipid hydroperoxides is concerned with the autooxidation and enzymatic reactions catalyzed by lipoxygenase (LOXs), but not to cyclooxygenases (COXs)[34]. At present, studies on lipid peroxidation related to ferroptosis mainly focus on enzyme-catalyzed lipid peroxidation. The peroxidation of polyunsaturated fatty acids (PUFAs) seems to be mainly regulated by LOXs and GPX4 during ferroptosis[35]. LOXs is an iron-containing non-heme dioxygenase, which promotes free and esterification of PUFAs by directly catalyzing lipid peroxidation[35], while GPX4 indirectly inhibits lipid peroxidation[36]. LOX, especially 12/15-LOX, which plays a core role in lipid peroxidation and ferroptosis[37]. Phosphatidylethanolamine binding protein 1 (PEBP1) is a small scaffold protein inhibitor of the protein kinase cascade that forms complex with 15-LOx to promote ferroptosis[38]. In contrast to PUFAs, monounsaturated fatty acids (MUFAs) play an anti-iron role by inhibiting lipid peroxidation. A study has shown that overexpression of stearoyl-CoA desaturase1 (SCD1), an essential enzyme for MUFAs biosynthesis, inhibits ferroptosis in ovarian cancer cells[39]. Friedmann Angeli et al[40] found that multiple LOXs were related to PUFA peroxidation, and the accumulation of oxidized PUFAs could lead to ferroptosis in cells when GPX4 was inhibited[41]. In addition, typical inhibitors of ferroptosis such as liproxstatin-1 (LIP-1), ferrostatin-1 (Fer-1), and inhibitors of LOXs such as vitamin E, flavonoids inhibit ferroptosis by inhibiting LOXs activity[42]. Arachidonic and adrenoic acids are groups of PUFAs, their metabolism is associated with two important enzymes acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), both of which are involved in the long PUFAs entry into the lipid membrane. Several studies have demonstrated that genetic and/or pharmacological inhibition of ACSL4 and LPCAT3 can protect cells from ferroptosis under certain circumstances[43]. PUFAs can be altered to PUFA-CoA under the catalysis of acyl-CoA synthase. Arachidonic acid (AA) is preferentially esterified by ACSL4, and subsequently participates in the formation of phospholipids, which are oxidized to form phospholipid-ethanolamine, predisposing cells to ferroptosis[42].

Doll et al[43] emphasized that the inactivation of ACSL4 gene and the pharmacological inhibition of ACSL4 by using different thiazolidinediones (TZDs) namely rosiglitazone (ROSI), pioglitazone (PIO) and troglitazone (TRO) can effectively prevent the occurrence of ferroptosis, because it hinders the assembly and movement of PUFAs-OOH. These results suggest that suppression of ACSL4 is a feasible treatment to stop ferroptosis-related diseases.

Amino Acid Metabolism and Ferroptosis

The Cystine-glutamate reverse transporter system Xc^- is a heterodimer related to a disulfide bond consisting of a light chain XCT and a heavy chain 4F2, namely, substrate specific subunit SLC7A11 and regulatory subunit SLC3A2[44].

Its main function is to exchange cystine and glutamate through cell membrane. Cysteine is transported from the outside of the cell through system Xc^- to the inside of the cell. Once it is absorbed by system Xc^- and transported into cells, it will be reduced to cysteine, which is an essential amino acid for biosynthesis of glutathione (GSH) and inhibits the uptake of cysteine, generating the accumulation of lipid peroxidation products[45].GSH is an effective antioxidant with strong reducibility and is mainly used for remove baleful lipid hydrogen peroxide generated by cell metabolism while decreasing lipid hydrogen peroxide to innocent lipid alcohols[46]. GSH protects important cellular components from ROS damage, including free radicals, lipid peroxides, and heavy metals[47]. GPX4 is a member of glutathione peroxidase (GPXs), which is a GSH dependent antioxidant enzyme. With two glutathione donors, GPX4 can reduce the lipid hydroperoxides (PUFAs-OOH) into corresponding alcohols, thereby inhibiting oxidative stress-induced ferroptosis[48]. It is considered to be a key regulator of ferroptosis[49]. System Xc^- /GSH/ GPX4 axis is thought to be the main pathway referred to ferroptosis. Some studies[50-52] analyzed the compounds and genes involved in this amino acid metabolic pathway.

Erastin is an RSL compound that inhibits system Xc^-, leading to depletion of GSH, which in turn inhibits GPX4 activity and promotes lipid ROS formation, leading to ferroptosis in cells[53]. BRCA1-associated protein 1 (BAP1) and OTU deubiquitinase, ubiquitin aldehyde-binding 1 (OTUB1) are also involved in ferroptosis by regulating xc^- expression[54]. Like erastin, sorafenib is a multikinase inhibitor approved for the treatment of liver cancer[55] that lead to ferroptosis by obstructing GSH synthesis[56]. Buthiionine subfoximine (BSO), which has been researched as an adjunctive therapy for cancer, causes ferroptosis by lowering GSH levels. Tumor suppressor gene p53 also plays a significant role in ferroptosis by down-regulating the expression of SLC7A11 and inhibiting systemic Xc^-, thereby affecting the activity of GPX4 and contributing to increased lipid peroxidation and ferroptosis in cells[57]. Ras-selective Lethal 3 (RSL3) was the first described GPX4 inhibitor[58]. RSL3 binds to the nucleophilic active site of GPX4, effectively reducing the expression level of GPX4[59] and directly inhibiting GPX4 without consuming GSH. DPI7 and DPI10 also act directly on GPX4, thereby inactivating GPX4, resulting in fatal ROS accumulation and inducing ferroptosis. FIN56 consumes CoQ10 through squalene synthase activity (SQS)-mevalonate pathway, promotes GPX4 degradation[60], and also leads to ferroptosis[61].

In recent years, ferroptosis suppressor protein 1 (FSP1) has been considered as another effective factor to protect cells from ferroptosis. Bersuker et al[62] showed that a new ferroptosis inhibition pathway closely concerned with FSP1 is parallel to the typical GSH based GPX4 pathway. They also found that FSP1 protects cells from ferroptosis induced by GPX4-deficient cDNA in complementary overexpression, and that CoQ10, called ubiquitin, can be regenerated by NAD(P)H under the catalytic activity of FSP1. CoQ10 scavenge small lipophilic radicals such as ferostin-1 (Fer-1) and liproxstatin-1, resulting in the prevention of ferroptosis.

Role of MiRNA in Ferroptosis and AS Development

Function of MiRNA in Ferroptosis

MiRNA is a widely studied type of ncRNA, which is an endogenous small RNA with a length of 21-24 nucleotides and can be transferred between cells in a variety of ways (such as exosomes)[63]. More than 1000 miRNAs have been found in human tissue samples, and they are involved in the regulation of more than 50% of mammalian protein-coding genes[64]. It plays an important role in the regulation of many cell functions, including cell proliferation and cell death[65]. MiRNAs play a key regulatory role in the development and progression of disease by base pairing with complementary sequences within the mRNA molecule. MiRNAs function by binding to the 3 '-untranslated region of the target mRNA and inhibiting its expression[66]. Several studies have illustrated a relationship between miRNAs and ferroptosis Table II.

In particular, the accumulation of rich lipid ROS in cells is the most vital factor in striking ferroptosis. In contrast, ncRNAs directly or indirectly regulate lipid ROS-associated molecules, maintaining dynamics of oxidation-reduction during high levels of ROS production and reducing ROS levels below toxicity thresholds to avoid triggering ferroptosis[67]. A group of miRNAs that regulate post-transcriptional gene expression through RNA silencing has been shown to be included in the regulation of iron and ROS metabolism. MiR-9 inhibits ferroptosis by reducing the accumulation of lipid ROS by inhibiting erastin-and RSL-3[68]. MiR-148b and MiR-29b-1-5p promote ferroptosis

by augmenting intracellular ROS levels[69,70]. However, miR-155 and miR-378 can reduce intracellular ROS levels and inhibit ferroptosis process[71,72]. On the one hand, miR-365 and miR-125b, reduce NRF2 expression and on the other hand, increase intracellular ROS production, thus promoting ferroptosis[73,74].

In terms of lipid peroxidation, miRNAs regulate Xc- and GPX4, and a variety of miRNAs play important roles in lipid metabolism. Glutathione homeostasis is considered to be a key aspect in the occurrence of ferroptosis. Recent studies have emphasized the role of specific miRNAs in regulating intracellular GSH levels. As previously mentioned, SLC7A11 is an important side in protecting cells from ferroptosis because of the enhanced antioxidant effect of cystine uptake of cellular GSH metabolism[75]. Therefore, it is explicit that some miRNAs determine ferroptosis by influencing the expression of SLC7A11. MiR-k12-11 was found to induce the expression of SLC7A11 and persist in oxidative stress environments by inhibiting ferroptosis[76]. MiR-4715-3p inhibits ferroptosis by promoting the expression of GPX4[77]. In endothelial cells, miR -17-92 directly inhibits ACSL4 expression and protects endothelial cells from erastin-induced ferroptosis[78]. MiR-9-5p can inhibit glutamine metabolism and maintain REDOX homeostasis and inhibit ferroptosis of cells[79]. MiR-133b plays a role in regulating intracellular glutathione metabolism, leading to ferroptosis in cells[80]. MiR-103a-3p can inhibit glutamate transport, regulate glutamine metabolism, and inhibit ferroptosis of cells[81].MiR-122 regulates glutamine metabolism and promotes ferroptosis in cells[82]. MiR-375 leads to ferroptosis by regulating cystine metabolism[83]. MiR-27a promotes ferroptosis by regulating intracellular glutathione[84]. MiR-214-3p leads to ferroptosis by enhancing erastin-induced lipid peroxidation[85]. Therefore, several molecular

Table II. Summary of miRNAs involved in ferroptosis.

First author, year	miRNAs	Modulatory effect	Influence to ferroptosis	Reference/ Expression changes
Zhang et al[65]	miR-9	Inhibit lipid peroxidation, iron accumulation and inhibits erastin- and RSL3-induced ferroptosis	Suppression	[65]
Qu et al[66]	miR-148b	Increase intracellular ROS level	Promotion	[66]
De Blasio et al[67]	miR-29b-1-5p	Increase intracellular ROS level	Promotion	[67]
Gu et al[68]	miR-155	Decrease intracellular ROS level	Suppression	[68]
Skrzypek et al[69]	miR-378	Decrease intracellular ROS generation	Suppression	[69]
Gao et al[70]	miR-365	Decrease Nrf2 expression; Increase intracellular ROS generation	Promotion	[70]
Chen et al[71]	miR-125	Increase intracellular ROS level Suppress Nrf2 expression	Promotion	[71]
Qin et al[73]	miR-K12-11	Induces SLC7A11 expression and inhibits ferroptosis induced by oxidative stress	Suppression	[73]
Gomaa et al[74]	miR-4715-3p	Overexpression confers resistance to ferroptosis by promoting of GPX4	Suppression	[74]
Xiao et al[75]	miR-17-92	Suppresses erastin-induced ferroptosis by repression of ACSL4 expression	Suppression	[75]
Wang J. et al[76]	miR-9-5p	Inhibit glutamine metabolism and redox homeostasis	Suppression	[76]
Chen et al[77]	miR-133b	Modulate intracellular glutathione metabolism	Promotion	[77]
Niu et al[78]	miR-103a-3p	Inhibit transportation of glutamate Modulate glutamine metabolism	Suppression	[78]
Sengupta et[79]	miR-122	Modulate glutamine metabolism	Promotion	[79]
Wu et al[80]	miR-375	Modulate cystine metabolism	Promotion	[80]
Drayton et al[81]	miR-27a	Mediate regulation of intracellular glutathione	Promotion	[81]
Bai et al[82]	miR-214-3p	Enhance erastin-induced lipid peroxidation	Promotion	[82]

targets of glutathione metabolism may be known to be closely involved in the pathogenesis of ferroptosis.

Regulation of AS Progression by Ferroptosis

AS is a chronic progressive vascular disease characterized by a lipid metabolism disorder[86]. Endothelial injury, oxidative stress, inflammation, and immune dysfunction can promote the occurrence and development of AS[87]. The formation of AS plaque on the wall of the artery leads to narrowing of the lumen[88]. Ferroptosis is a newly discovered form of iron and lipid peroxidation dependent cell death associated with the development of AS. In addition, overexpression of GPX4 has been reported to reduce lipid peroxidation and inhibit inflammation in the aorta of ApoE $^{-/-}$ deficient mice, thereby alleviating atherosclerotic injury. Since the main characteristic of ferroptosis is overmuch lipid peroxidation, we have reason to deem that ferroptosis may be involved in the occurrence and development of As. Upregulation of GPX4 expression in vascular smooth muscle cells can effectively block oxidative stress, enhance arterial protection and delay the occurrence of AS. GPX4 activators are expected to offer new solutions for the treatment of atherosclerotic diseases mediated by inflammation and lipid peroxidation[89]. Recently, a study by Bai et al[90] verified the potential impact of ferroptosis on AS. The results showed that inhibition of ferroptosis inhibited lipid peroxidation in ApoE $^{-/-}$ mice and alleviated AS damage induced by high fat diet. In addition, ox-LDL leads to mitochondrial damage in mouse aortic endothelial cells (MAECs) and down-regulates the expressions of SLC7A11 and GPX4. Fer-1 inhibits ox-LDL-induced lipid peroxidation and endothelial dysfunction. They believed that ferroptosis may be involved in the pathological process of AS and may be the therapeutic target for AS[90]. In another study, the expression of genes associated with ferroptosis was studied in human coronary artery specimens. The results showed that in the late stage of AS, lipid metabolism was significantly enriched again and PTGS2, ACSL4 expression was up-regulated, GPX4 expression was down-regulated. The severity of AS was positively correlated with PTGS2 and ACSL4, but negatively correlated with GPX4[91].

PUFA-OOH is a major source of lipid peroxides that generate endothelial ROS to add, nitric oxide (NO) to reduce, Chronic inflammation of macrophages, Foam cell formation, ultimately contributing to the formation of atherosclerotic lesions. Beyond that, LDL peroxidation associated with ferroptosis degradation in endothelial cells can cause endothelial dysfunction and macrophage activation. Prior to the discovery of ferroptosis, GPX4 overexpression was reported to remove additional ROS and phospholipid hydroperoxide and markedly retard the progression of atherosclerotic plaques in ApoE$^{-/-}$ mice[92]. Iron catalyzed free radical reactions lead to oxidation of LDL in endothelial smooth muscle cells or macrophages, which may be a risk factor for the development of atherosclerotic lesions[93]. Ferroptosis and iron accumulation caused by oxidized low-density lipoprotein (OX-LDL) has been surveyed in mouse aortic endothelial cells, which can be reversed by ferroptosis inhibitors[90]. Transferrin, the primary plasma iron binding molecule, interacts with transferrin receptor protein 1 (TFR1) to transfer extracellular Fe^{3+} into cells, resulting in iron overload and increasing cell sensitivity to ferroptosis[94]. Ferritin and low-density lipoprotein-cholesterol levels were co-associated with the incidence of cardiovascular disease and death. LPO and iron deposition are important features of atherosclerotic plaques[95]. There is ample evidence that ferroptosis is related to the pathology of AS.

Role of MiRNA in AS Progression *via* the Ferroptosis Pathway

In the context of the world, leading cause of death is AS. In recent years, the study of AS has shifted from macroscopical to microscopical, and penetrated into effector cells, signal transduction, molecules and other fields. Ferroptosis plays a pivotal role in endothelial cell injury and the progression of atherosclerosis[96]. But the exact mechanism is still unclear. MiRNA is involved in the regulation of metabolism and other important biological processes and has potential application value in the treatment of AS[97].

Liu et al[98] showed that miR-132 is greatly expressed during the evolution of AS which is involved in lipid metabolism in endothelial cells and causes an abnormal increase of ROS in endothelial cells[98]. Mitochondrial dysfunction, such as changes in mitochondrial membrane potential, increased mitochondrial ROS, and opening of mitochondrial membrane channels, further leads to decreased intracellular GPX4 and increased oxidase NOX4, inducing ferroptosis, and ultimately promoting the development of AS. MiR-132 can

promote the occurrence and development of AS by inducing mitochondrial oxidative stress disorder and ferroptosis, which is expected to become a therapeutic target of AS[99].

A study by Xiao et al[100] believes that ACSL4/A20 mediates the deregulation of ferroptosis in endothelial cells, and the miR17-92 /A20/ACSL4 axis is involved in ferroptosis in endothelial cells, which is related to vascular diseases such as AS, which may provide a theoretical basis for the development of vascular diseases in the future. MiR17-92 is a multifunctional oncogenic miRNA cluster that plays an important role in tumor angiogenesis and tissue development. Overexpression of Mir-17-92 in human umbilical vein endothelial cells promotes GPX4 and inhibits ROS production by zinc lipoprotein (A20) -ACSL4 axis, which protects endothelial cells from erastin-induced ferroptosis[100].

Conclusions

Cell death is indispensable for natural metabolism in the body. Ferroptosis is a function of a newly discovered and unique form of programmed cell death and is closely related to various physiological processes and diseases, by iron relying on lipid peroxide and excessive accumulation of ROS, it plays a crucial role in the occurrence, progression and treatment of nervous system diseases, ischemia reperfusion injury, kidney injury, tumor development and other diseases. In recent years, studies on the role of ferroptosis in cardiovascular disease have attracted extensive attention. Understanding the molecular mechanisms of ferroptosis has made substantial progress and how AS drives sensitivity to ferroptosis, involving the expression of multiple molecular and components of a signaling pathway, of which iron metabolism, lipid metabolism and amino acid metabolism are vital regulatory mechanisms. Interventions targeting ferroptosis could be the basis for new treatment strategies for many diseases, including cardiovascular disease. In addition, miRNAs are extensive present in cells. In recent years, a great deal of studies has shown that miRNAs play a significant role in the process of ferroptosis and are great significant in the occurrence, development of AS. At the same time, exploring the regulation of miRNA in iron deficiency induced by AS much progress has been made.

In the past few years, more and more studies have uncovered the regulatory mechanism between AS and ferroptosis. However, the material regulatory mechanism of miRNA in regulating ferroptosis remains unclear and tissue specific expression of miRNAs and various off-target effects are major challenges. The mechanism by which miRNAs associated with ferroptosis regulate the progression and growth of AS remains to be thoroughly understood. Further studies are needed in the future and targeting these key miRNAs could reveal new diagnostic biomarkers and precise treatment regimens to inhibit the occurrence and progression of AS, providing more insights for the treatment of AS. Fundamental studies of miRNA, ferroptosis and AS are significant for their ultimate clinical relevance. Experimental studies need to evolve existing strategies to provide new treatment options for patients with AS. We have reason to believe that as science advances, the study of miRNA and ferroptosis will provide a solid theoretical foundation for the occurrence and development of AS.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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