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Morphological Characteristics and Roles of Endoplasmic Reticulum in Ferroptosis: From Molecular Mechanisms to Disease Associations

Shuang He

Shangdong First Medical University & Shangdong Academy of Medical Sciences, Jinan, Shangdong, 250012, China

ABSTRACT
Ferroptosis is an iron-dependent form of cell death, which holds significant pathological implications in various diseases such as myocardial lesions, tumorigenesis, and intracerebral hemorrhage. The regulation of ferroptosis involves multiple factors, including interactions between subcellular organelles. Researchers are actively seeking inhibitors of ferroptosis to develop innovative cell protection strategies. The endoplasmic reticulum (ER) plays a critical role in protein synthesis and processing, as well as the accumulation of lipid peroxides, and exhibits high sensitivity to subtle changes in the intracellular environment. This review summarizes the association between ER morphological changes and the occurrence development of ferroptosis, as well as its roles in iron ion metabolism, lipid peroxidation, and the antioxidant system. Additionally, we focus on how ER stress participates in the regulatory network of ferroptosis by influencing the expression and regulation of related signaling molecules.

KEYWORDS
Endoplasmic reticulum stress; Ferroptosis; Lipid metabolism; Signaling pathways

1 Introduction

The concept of ferroptosis was first clearly defined in 2012. It is an iron-dependent form of cell death, characterized by an imbalance in intracellular iron metabolism, a decline in antioxidant defense capabilities, and abnormal lipid peroxidation.

The abnormal accumulation of intracellular iron leads to an imbalance in intracellular iron metabolism. The antioxidant system of cells is impaired, and it is unable to effectively scavenge reactive oxygen species (ROS), resulting in increased oxidative stress. During the process of ferroptosis, the peroxidation of unsaturated fatty acids within cells is exacerbated, generating a large number of lipid peroxides. Ferroptotic cells differ morphologically from other cell death modes such as apoptosis and necrosis, manifested as the disruption of the cell membrane and the release of cell contents. The molecular mechanism of ferroptosis has not been fully elucidated. However, numerous studies have indicated that it plays a crucial pathogenic role in a variety of diseases, including cancer, neurodegenerative diseases, and ischemic organ injuries.

The endoplasmic reticulum (ER) is an important organelle within cells with a complex structure and diverse functions. It plays multiple significant roles in cells. It is not only involved in protein synthesis and lipid metabolism but also closely associated with various biological processes such as cellular stress responses, calcium ion regulation, and cell death. The endoplasmic reticulum is highly sensitive to changes in the intracellular environment. Endoplasmic reticulum stress (ERS) can cause alterations in cell death patterns, including autophagy, apoptosis, ferroptosis, and pyroptosis. The endoplasmic reticulum is closely linked to ferroptosis. ERS may promote the onset of ferroptosis by affecting iron metabolism, lipid peroxidation, and the imbalance of the antioxidant system.

2 Endoplasmic reticulum morphology in ferroptosis

Functional differentiation and dynamic response the endoplasmic reticulum (ER) comprises rough endoplasmic reticulum (RER) and smooth endoplasmic reticulum (SER). RER contains ribosomes responsible for protein synthesis and primary folding, while SER lacks ribosomes but participates in lipid metabolism, calcium ion storage, and signal transduction. The ER membrane forms a continuous network extensively distributed throughout the cytoplasm, connecting to the nuclear membrane to provide a platform for protein synthesis, modification, transport, and signaling [4]. With diverse functions and clearly defined regions, its morphology and size adapt to cellular needs. Closely interacting with other organelles, the ER transports substances via vesicles and plays a crucial role in lipid metabolism and Ca2+ signaling. As the central processing unit for intracellular proteins, the ER's homeostasis is influenced by multiple factors including misfolded protein accumulation, elevated reactive oxygen species (ROS) levels, and abnormal Ca2+ signaling—collectively termed endoplasmic reticulum stress (ERS). The endoplasmic reticulum (ER) is highly sensitive to subtle environmental changes, particularly minor fluctuations in pH and viscosity, which can trigger its stress response [5]. Although studies have revealed the connection between ferroptosis and ER, the specific mechanisms by which pH regulates the relationship between ERS and ferroptosis remain incompletely understood.

During ferroptosis, membrane swelling is considered a direct consequence of lipid peroxide accumulation and closely associated with endoplasmic reticulum (ER) stress. ER stress not only accumulates iron ions and lipid peroxides but also promotes the ferroptosis process by upregulating ferroptosis-related genes. Additionally, ER inhibitors and inducers show

potential in regulating lipid peroxidation dynamics within ferroptotic cells. Changes in ER viscosity have also been observed during ferroptosis. Studies using specific fluorescent probes to track autophagy processes revealed altered viscosity during ferroptosis, further supporting the association between ER morphological changes (particularly membrane swelling) and viscosity alterations that influence ferroptosis progression.

Changes in ER luminal contents include lipid peroxide accumulation and increased ER iron content. Ferroptosis is mediated through NCOA4-dependent ferritin autophagy, while ER stress promotes ferroptosis by modifying mitochondrial and lysosomal functions—including regulating membrane potential, ROS production, enzyme release, and autophagy processes. Furthermore, ER-Golgi interactions in protein processing and their effects on nuclear function (including transcription factor activation and altered gene expression) play roles in ferroptosis regulation.

Ferroptosis affects lipid peroxide accumulation and pH levels on the ER membrane. Ferroptosis induces lipid peroxidation accumulation on the endoplasmic reticulum (ER) and its extension to the cell membrane, leading to decreased pH-potential and increased viscosity. These changes may be associated with the interaction between ER stress and ferroptosis. For instance, during erastin-induced ferroptosis, ER acidification and viscosity increase are particularly pronounced, while cells treated with the ferroptosis inhibitor ferrostatin-1 show no significant alterations. Alterations in ER membrane fluidity during ferroptosis correlate with cellular oxidative stress and imbalance in antioxidant defense systems, which subsequently affect ER function and cellular sensitivity to ferroptosis. Researchers have developed fluorescent probes to monitor ER membrane viscosity changes during ferroptosis, enabling deeper understanding of structural and functional modifications in the ER during this process.

Phospholipids undergo oxidation to form lipid peroxides. These peroxides alter membrane fluidity and permeability, thereby affecting endoplasmic reticulum (ER) function. The ferroptosis process disrupts phospholipid synthesis pathways in the ER, leading to alterations in membrane lipid composition. For instance, studies suggest that endoplasmic reticulum stress (ERS) may influence the ER membrane's lipid profile by regulating phospholipid synthesis-related gene expression. During ferroptosis, phospholipase activation triggers hydrolysis of ER membrane phospholipids, resulting in structural and compositional changes in the membrane.

3 Endoplasmic reticulum stress: The Molecular Switch for Ferroptosis

The double-edged sword effect of the Unfolded Protein Response (UPR) pathway when cells encounter adverse external stimuli, they trigger endoplasmic reticulum stress and the unfolded protein response (UPR). As an adaptive cellular response to ER stress, UPR activation helps alleviate protein folding burdens, reduces misfolded protein accumulation, and maintains cellular homeostasis by promoting protein degradation and enhancing antioxidant capacity . ERS-activated UPR regulates cell survival through three pathways: PERK-eIF2α, IRE1-XBP1, and ATF6.

The PERK-eIF2α pathway stands as a critical signaling cascade that plays pivotal roles in regulating protein synthesis and coping with protein folding stress. During ER stress, PERK becomes activated and induces eIF2α phosphorylation through its kinase activity. While phosphorylated eIF2α inhibits most protein synthesis, it selectively activates ATF4 to drive the expression of pro-oxidant genes like CHOP, thereby exacerbating lipid peroxidation (Kumar et al., 2023). This includes CHOP (C/EBP homology domain protein), which is decisive in cellular adaptation to stress and determining cell fate.

IRE1 (inositol-requiring enzyme 1) is a kinase and endonuclease located on the endoplasmic reticulum membrane. It cleaves XBP1 mRNA to generate XBP1s, which enhance the expression of chaperones to alleviate endoplasmic reticulum stress. As a transcription factor, XBP1s can enter the nucleus and activate a series of eRS-related genes, thereby improving protein folding capacity, promoting degradation of misfolded proteins, and restoring endoplasmic reticulum homeostasis . However, sustained activation may upregulate iron transporters such as FPN1, leading to iron accumulation (Huang et al., 2024). This depends on cell type, stress intensity and duration, as well as interactions with other signaling pathways. For example, some studies suggest that sustained activation of the IRE1-XBP1 pathway may increase cellular ferroptosis sensitivity, while moderate activation may help cells resist ferroptosis.

The ATF6 regulatory network is a transcription factor located on the endoplasmic reticulum membrane. During endoplasmic reticulum stress response, ATF6 is transported to the Golgi apparatus, where it undergoes protease cleavage. The cleaved ATF6 fragment enters the nucleus to activate antioxidant genes (e. g., glutathione synthetase), but during excessive stress, it shifts toward pro-apoptotic/ferroptosis signaling (Ao et al., 2024).

Endoplasmic net-involved lipid metabolism and ferroptosis the endoplasmic net (EN) serves as the central site for phospholipid synthesis, where metabolic abnormalities directly determine cellular sensitivity to ferroptosis. For instance, increased cholesterol synthesis stabilizes membrane structures and inhibits lipid peroxidation. As a crucial component of cell membranes, cholesterol is essential for maintaining membrane fluidity and stability. The EN's involvement in cholesterol synthesis and metabolism may disrupt membrane integrity, thereby affecting ferroptosis. 鞘磷脂 (Sphingomyelin) hydrolysis releases ceramide, which amplifies ROS signaling through the mitochondrial-endoplasmic net axis (ER-Mitochondria Axis) (Li et al., 2024). Studies have also revealed that the TMEM147 gene promotes tumor-

associated macrophage (TAMs)M2 polarization by regulating cholesterol homeostasis, indirectly suppressing ferroptosis (Jingjing et al., 2023). Polyunsaturated fatty acids (PUFAs) play a pivotal role in ferroptosis due to their high susceptibility to peroxidation. The EN influences ferroptosis through regulation of PUFAs' synthesis and metabolism. Enzymatic systems within the EN participate in PUFAs 'metabolic processes, potentially modulating cellular ferroptosis sensitivity by altering PUFAs' composition and levels.

The role of the endoplasmic reticulum-mitochondria axis in ferroptosis the progression of ferroptosis is influenced by both endoplasmic reticulum (ER) stress signaling and mitochondrial functional regulation. ER stress can impair mitochondrial function by disrupting calcium ion uptake and ROS production, thereby exacerbating mitochondrial dysfunction. Conversely, mitochondrial dysfunction may intensify ER stress by increasing ROS generation and affecting iron metabolism, creating a vicious cycle that collectively drives ferroptosis. The interaction between ER stress and mitochondrial function regulates ferroptosis through lipid peroxidation and antioxidant system balance. ER stress interacts with ferroptosis during membrane peroxidation, which destabilizes mitochondrial membranes. Ferroptosis is closely associated with iron metabolism disorders, accumulation of lipid peroxides, and oxidative imbalance. ER stress modulates ferroptosis by influencing antioxidant systems such as glutathione (GSH) metabolism. Additionally, ER stress induces various cell death modes including autophagy, apoptosis, and pyroptosis. ER stress (ERS) can regulate transitions between these cell death modes, further impacting ferroptosis. This demonstrates ER stress's crucial role in regulating cellular fate. The interaction between ER and mitochondria affects cellular redox balance and iron metabolism. The endoplasmic reticulum (ER) and mitochondria share specialized membrane contact sites called MAMs.These sites facilitate calcium-ion-lipid exchange, maintaining cellular redox balance. Calcium released from the ER activates mitochondria, triggering reactive oxygen species (ROS) production that plays a pivotal role in ferroptosis. Mitochondrial activation enhances oxidative phosphorylation, increasing ATP yield while intensifying oxidative stress responses, ultimately causing metabolic alterations. ROS-induced oxidative stress and lipid peroxidation culminate in cell death. Additionally, mitochondrial activation modifies metabolic pathways, particularly affecting glutathione (GSH) synthesis and iron metabolism, thereby influencing ferroptosis progression. The ER regulates iron death by modulating iron transport protein expression. At MAMs, phospholipid exchange impacts ROS generation: ATG2A protein promotes phosphatidylserine (PS) transfer to mitochondria, enhancing phosphatidylethanolamine (PE) synthesis. Since PE is prone to peroxidation, this process further accelerates ferroptosis.

4 The role of endoplasmic reticulum in ferroptosis-related diseases in neurodegenerative disorders

The interaction between endoplasmic reticulum (ER) stress and ferroptosis may influence disease progression. ER stress can trigger the expression of ferroptosis-related genes, promoting ferroptosis through iron ion accumulation and increased lipid peroxidation. It may also enhance ferroptosis by influencing lipid metabolism at ER-mitochondrial contact sites, thereby increasing the synthesis of oxidized phospholipids. In cardiovascular diseases, the connection between ER stress and ferroptosis has also been emphasized. For instance, ER stress may exacerbate myocardial cell damage during myocardial ischemia/reperfusion (I/R) injury and impair neuronal recovery after cardiac arrest. In oncology, the link between ER stress and ferroptosis holds significant therapeutic implications for cancer treatment. Both ER stress and the Unfolded Protein Response (UPR) play crucial roles in cancer cell resistance, while ferroptosis offers novel strategies for treating drug-resistant tumor cells. For example, certain compounds may enhance tumor suppression effects by activating ER stress and ferroptosis.

5 Conclusions and outlook

The endoplasmic reticulum (ER) plays a pivotal role in ferroptosis, involving lipid metabolism, stress responses, iron metabolism, and amino acid metabolism. By synthesizing, processing, and transporting key proteins, the ER regulates iron homeostasis and lipid peroxidation, influencing ferroptosis across cell types and physiological/pathological conditions. Although its mechanisms have been established, specific molecular pathways require further investigation. As a potential therapeutic target, the ER offers novel avenues for disease treatment. Research on ER-ferroptosis interactions could facilitate the development of effective drugs and interventions. Moreover, the ER's potential regulation of diverse cell death mechanisms warrants exploration of its role in apoptosis regulatory networks, with clinical applications to enhance disease diagnosis and treatment. Recent studies have increasingly linked ferroptosis to ischemia-reperfusion injury and neurodegenerative disorders, revealing the ER's evolving roles in these processes. Investigating ER-mediated ferroptosis mechanisms from this perspective provides fresh perspectives and innovative approaches for treating related diseases.

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