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# Non-coding RNAs in Cell Death Mechanisms: Intersection and Therapeutic Potential of Ferroptosis, Cuproptosis, and Disulfidptosis

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## Abstract

**In the biomedical field, the research on cell death has always been attached great importance, and there are diversified manifestations of cell death, such as Pyroptosis, Autophagy, apoptosis and so on. There are also new cell death modes, such as ferroptosis, cuproptosis, and disulfidptosis which have received much attention in recent years. These death pathways play an important role in organism development, disease progression, and cell response to the environment. Long non-coding RNA(lncRNA), as a novel regulatory element, is involved in regulating various cellular processes such as cell metabolism, proliferation, apoptosis . This review aims to systematically summarize the current research progress on the interaction of lncRNA with ferroptosis, cuproptosis and disulfidptosis, and explore the mechanism of lncrNA in the regulation of cell death. It will provide a new strategy and perspective for the combined targeting of lncRNA and iron death, copper death and disulfide death related molecules in tumor therapy.**

## Keywords

**lncRNA, ferroptosis, cuproptosis,disulfidptosis.**

## 1. Introduction

In the realm of cellular biology, long non-coding RNAs (lncRNAs), previously perceived as genomic "dark matter," have transitioned to being recognized as pivotal regulatory molecules. LncRNAs, RNA molecules exceeding 200 nucleotides in length that do not encode proteins, play crucial roles in gene expression regulation, cellular process modulation, and disease mechanism elucidation[1]. Advances in technology have unveiled the critical involvement of lncRNAs in dictating cell fate, particularly within cell death pathways. Cell death, a fundamental mechanism for maintaining organismal homeostasis, includes extensively studied forms like apoptosis and necrosis,[2] and more recently, the emerging modes of ferroptosis, cuproptosis, and disulfidptosis. These pathways are integral to development, disease progression, and cellular environmental responses[3]. Ferroptosis is characterized by iron-dependent oxidative stress-induced cell death[4]; cuproptosis involves cellular damage due to excessive copper ions[5]; and disulfidptosis is triggered by abnormal sulfide metabolism[6]. The identification of these modalities of cell death not only enriches our comprehension of cell death mechanisms but also opens new avenues for disease treatment.

Exploring the interactions between lncRNAs and these cell death pathways offers profound scientific and clinical significance. Understanding the roles of lncRNAs within these pathways can elucidate how cells regulate their survival or demise under various physiological and pathological contexts, offering fresh insights for basic life sciences research. Moreover, identifying and studying lncRNAs that modulate these specific cell death pathways could unveil

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novel targets for developing targeted therapeutic strategies for diseases such as cancer, neurodegenerative disorders, and cardiovascular diseases.

This review aims to systematically summarize the current research progress on the interactions between lncRNAs and ferroptosis, cuproptosis, and disulfidptosis. It will explore their mechanisms in cell death regulation, analyze the limitations and challenges of current research, and forecast future directions, hoping to provide reference and inspiration for the field.

## 2. lncRNAs and Ferroptosis

### 2.1. Ferroptosis Mechanism

Ferroptosis is an iron-dependent, non-apoptotic form of cell death, its hallmark being the iron ion-catalyzed generation of excessive reactive oxygen species (ROS) that leads to lipid peroxidation of the cell membrane, triggering cell death. Normally, iron homeostasis, including its absorption, storage, utilization, and excretion, is maintained through a finely tuned regulatory process. Iron is absorbed into the body through intestinal epithelial cells and transported to iron-requiring cells via transferrin[7]. Intracellular iron is primarily stored in ferritin, and when needed, ferritin is degraded to release iron ions. Excess iron ions are expelled from the body through the action of ferroportin, maintaining body iron balance. Pathologically, imbalances in iron metabolism lead to excessive intracellular iron ion accumulation. These iron ions generate large amounts of ROS through the Fenton reaction, causing lipid peroxidation and destruction of cell structures, ultimately leading to ferroptosis[8].

Recent studies have illuminated the regulatory roles of lncRNAs in the ferroptosis process, revealing a series of lncRNAs that, through their unique expression patterns and molecular mechanisms, directly or indirectly participate in iron metabolism and ROS production, thereby regulating the ferroptosis process. These discoveries not only expand our understanding of the iron metabolism regulatory network but also offer new strategies for treating ferroptosis-related diseases.

### 2.2. Expression Pattern Changes

Certain lncRNAs, such as LINC00336 and H19, exhibit significant changes in expression patterns under conditions of iron metabolism imbalance or ferroptosis. For instance, H19's expression level significantly increases in cell models of iron overload, suggesting its role in the ferroptosis process[10]. This alteration in expression pattern indicates that specific lncRNAs can regulate the cell death process by responding to the metabolic state of iron.

### 2.3. Molecular Mechanism Diversity

These lncRNAs influence iron metabolism through various pathways. For example, lncRNA LINC00336 has been found to reduce ferroptosis occurrence by decreasing intracellular ROS production, inhibiting the expression of the cysteine dioxygenase 1 (CDO1) gene. Conversely, H19 affects iron excretion by inhibiting ferroportin expression, leading to intracellular iron ion accumulation and further exacerbating ferroptosis[9]. Additionally, lncRNAs can regulate the transcriptional activity of genes related to iron metabolism, such as affecting the expression of ferritin and transferrin receptor. This regulation not only affects the homeostasis of iron ions but also indirectly influences ROS production, thereby modulating cell sensitivity to ferroptosis. Furthermore, lncRNAs participate in cellular stress responses: under oxidative stress conditions induced by iron overload, lncRNAs can be involved in cellular stress responses, regulating the cell's antioxidant capacity and affecting cell sensitivity to ferroptosis[10].

Through these mechanisms, lncRNAs exert direct or indirect effects on iron ion accumulation and ROS production, ultimately influencing cell sensitivity to ferroptosis. For instance, by

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reducing ROS production, LINC00336 can mitigate cell damage caused by ferroptosis, showcasing a potential protective role[11] In contrast, H19, by promoting iron ion accumulation, may enhance cell sensitivity to ferroptosis, suggesting its negative regulatory role in the ferroptosis process[10]. Thus, through detailed analysis of specific lncRNAs' expression pattern changes, molecular mechanisms, and ultimate biological effects under conditions of iron metabolism imbalance or ferroptosis, we can gain deeper insights into the mechanisms of lncRNA action in ferroptosis and identify important scientific bases for developing targeted therapeutic strategies.

## 3. lncRNAs and Cuproptosis

### 3.1. Basic Mechanism of Cuproptosis

Cuproptosis involves the accumulation of copper ions within cells, leading to increased levels of reactive oxygen species (ROS), which then triggers lipid peroxidation, DNA damage, and protein degradation, culminating in cell death[12]. The transport and homeostasis of copper ions are regulated by a series of finely controlled proteins, such as copper transporter 1 (CTR1)[13]and copper pumps ATP7A/B[14]. In conditions of copper excess, this delicate balance is disrupted, resulting in ineffective copper ion excretion and subsequent intracellular accumulation, triggering a series of toxic responses.

### 3.2. Regulatory Role of lncRNAs

In the field of cellular biology, the study of cell death mechanisms induced by copper overload, termed "cuproptosis," has revealed the critical role of long non-coding RNAs (lncRNAs) in regulating the metabolic balance of copper ions. This role encompasses not only the direct regulation of copper ion absorption, utilization, storage, and excretion but also the complex indirect effects on the balance between copper ions and the generation of reactive oxygen species (ROS)[15].

### 3.3. Regulation of Copper Ion Transport Proteins

Specific lncRNAs, such as MEG3 and MALAT1, have demonstrated unique abilities to regulate the expression of copper ion transport proteins, thereby directly affecting the mobility and excretion of copper ions within cells. Functional studies of MEG3 have revealed its role in downregulating the expression of the copper pump ATP7A, slowing the excretion process of copper ions, leading to increased intracellular accumulation and further exacerbating copper toxicity and cell death risk[16]. This direct regulation of copper ion transport protein expression highlights the central role of lncRNAs in copper metabolism regulation.

### 3.4. Regulation of Copper Ion Homeostasis and ROS Generation

Excessive accumulation of copper ions within cells directly promotes the massive generation of ROS, causing extensive oxidative stress responses and cellular damage. In this process, lncRNAs play a crucial role by finely tuning the homeostasis of copper ions, indirectly controlling ROS levels, and thus forming a key line of defense. For example, MALAT1 activates cellular antioxidant defense mechanisms, such as enhancing the expression or activity of antioxidant enzymes, effectively reducing ROS accumulation and alleviating copper-induced cell damage[17][18]. This ability to indirectly regulate the balance between copper ions and ROS generation showcases the potential role of lncRNAs in defending against copper-induced toxicity.

### 3.5. Impact on Copper Ion Regulatory Signaling Pathways

Beyond direct regulation of copper ion transport protein expression, some lncRNAs also modulate key signaling pathways involved in copper metabolism regulation, such as NF-κB and

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Nrf2, which play critical roles in regulating the absorption, storage, utilization, and excretion of copper ions, thereby affecting the cellular response to excess copper ions[19]. By modulating these signaling pathways, lncRNAs can not only regulate the direct response of cells to copper ions but also affect the cell's antioxidant capacity and survival state, further illustrating the complex regulatory network of lncRNAs in copper metabolism.

Targeted experimental studies have validated the specific roles of lncRNAs in regulating copper metabolism. For instance, by knocking down the expression of lncRNA MEG3, studies have found a significant reduction in copper-induced ROS production and cell death rate, emphasizing MEG3's regulatory role in the cuproptosis process[20]. Moreover, increasing the expression of MALAT1 can activate the cell's antioxidant defense mechanisms, reducing the accumulation of copper-induced ROS, demonstrating its protective role in alleviating copper toxicity[21].

## 4. lncRNAs and disulfidptosis

In the diverse mechanisms of cell death, disulfidptosis, as a recently discovered mode of cell demise, has garnered attention for its molecular basis and physiological significance[22]. The core of disulfidptosis lies in the role of sulfides, especially hydrogen sulfide ($H_2S$), in cellular metabolism and their regulatory mechanisms. In this context, the function of long non-coding RNAs (lncRNAs) in the process of disulfidptosis and their impact on sulfide metabolism regulation has become a focal point of research.

### 4.1. Molecular Basis of disulfidptosis and the Role of Sulfides

The in-depth exploration of the disulfidptosis mechanism has unveiled the complex role of sulfides, particularly hydrogen sulfide ($H_2S$), in cellular metabolism and death processes. $H_2S$, as a multifunctional endogenous gasotransmitter, has a broad range of biological effects, from regulating cell metabolism to participating in neurotransmission processes[23]. In cellular energy metabolism, $H_2S$ directly participates in the mitochondrial electron transport chain, regulating ATP synthesis and promoting efficient energy production. Additionally, $H_2S$ plays a key role in maintaining mitochondrial function and structure stability by inhibiting excessive oxidative stress responses and protecting cells from free radical damage[24].

However, the dual role of $H_2S$ is highlighted by the delicate balance of its concentration. At physiological concentrations, $H_2S$ can maintain normal cellular functions through its antioxidant properties; however, when its production exceeds or its clearance mechanisms are impaired, excessive $H_2S$ concentrations can induce toxic effects, leading to mitochondrial dysfunction, increased oxidative stress, and ultimately cell death. [25]This cell death, induced by abnormal increases in sulfide levels, known as disulfidptosis, primarily occurs through disrupting mitochondrial electron transport, promoting excessive ROS production, and causing mitochondrial membrane potential collapse[26].

Furthermore, the role of $H_2S$ in disulfidptosis also involves its modulation of multiple signaling pathways, including but not limited to activating the Nrf2 antioxidant response pathway, affecting the expression and activity of cell apoptosis-related proteins, and regulating inflammation responses[27]. These complex mechanisms reflect the multifaceted nature of $H_2S$ in cellular physiological and pathological states, demonstrating its highly conditional and specific effects on cell fate under different concentrations and conditions.

Understanding the regulation of $H_2S$ production and metabolism is crucial for elucidating the molecular basis of disulfidptosis. $H_2S$ biosynthesis mainly occurs through non-oxidative pathways (such as the cysteine pathway) and oxidative pathways, while its clearance is achieved through mitochondrial oxidation and the methionine pathway. The balanced regulation of these metabolic pathways determines the steady-state concentration of $H_2S$

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within cells, thereby affecting cellular life and death decisions. Therefore, precise regulation of the expression and activity of key enzymes in $H_2S$ metabolism, especially in disease states, becomes a potential strategy for understanding and intervening in the disulfidptosis process.

In the field of disulfidptosis research, the role of long non-coding RNAs (lncRNAs) is increasingly recognized, especially their functions in regulating the biosynthesis, metabolism, and intracellular levels of hydrogen sulfide ($H_2S$). These lncRNAs finely modulate the expression or activity of enzymes related to sulfide metabolism, influencing $H_2S$ production and clearance, and thereby playing key roles in determining cell fate.

## 4.2. Function of lncRNAs in disulfidptosis

### 4.2.1. Regulation of Hydrogen Sulfide-Producing Enzyme Expression

Specific lncRNAs, by regulating the expression or activity of key enzymes such as cysteine metabolic enzymes and hydrogen sulfide-producing enzymes, directly participate in the metabolic process of $H_2S$. For instance, lncRNAs CYTOR and GAS5 have been found to directly or indirectly regulate hydrogen sulfide-producing enzymes, like cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST), which are the main biological synthesis pathways of $H_2S$ in cells. By upregulating the expression of these enzymes, lncRNAs can increase the production of $H_2S$ within cells, thereby affecting cell survival or death. For example, lncRNA-CYTOR enhances the transcriptional activity of the CSE gene by binding to transcription factors, thereby increasing the biosynthesis of $H_2S$ and pushing cells towards disulfidptosis[28].

### 4.2.2. Modulation of Hydrogen Sulfide Clearance Pathways

Conversely, another class of lncRNAs can indirectly lead to the accumulation of $H_2S$ by reducing the activity of key enzymes in the $H_2S$ clearance pathways. For instance, lncRNA H19 has been found to inhibit the expression of thiosulfate sulfurtransferase (TST) and sulfide:quinone oxidoreductase (SQR), two enzymes responsible for the transfer and oxidation of $H_2S$ within cells, respectively. Through this mechanism, the upregulation of H19 expression slows down the metabolism of $H_2S$, accumulating to levels sufficient to induce disulfidptosis[29].

In the study of disulfidptosis, long non-coding RNAs (lncRNAs) have been shown to play key roles through finely modulating the expression or activity of enzymes related to sulfide metabolism. The functions of these lncRNAs are not limited to directly regulating the production and clearance of hydrogen sulfide ($H_2S$) but also involve extensive regulation of cellular metabolic pathways, thereby affecting the survival state of cells.

## 4.3. Theoretical and Experimental Progress

Recent experimental studies, utilizing cell models with knocked-out or overexpressed specific lncRNAs, have delved into how lncRNAs regulate the expression of hydrogen sulfide metabolic enzymes and their impact on the cell death process. These studies have not only observed significant changes in the expression of hydrogen sulfide metabolic enzymes but also recorded the dynamic adjustments in $H_2S$ levels and corresponding changes in cell death rates.

Through the knockout experiments of specific lncRNAs, researchers have found a decrease in the expression levels of hydrogen sulfide-producing enzymes, leading to reduced intracellular $H_2S$ levels and slowing down the disulfidptosis process. Conversely, overexpressing lncRNAs can promote the expression of hydrogen sulfide-producing enzymes, leading to increased intracellular $H_2S$ concentrations and accelerating the occurrence of disulfidptosis. These experimental findings not only confirm the core role of lncRNAs in regulating the production and clearance of hydrogen sulfide but also reveal their potential importance in regulating cellular responses to oxidative stress, inflammation, and other stress conditions. Furthermore, the studies emphasize the role of lncRNAs in the disulfidptosis mechanism, through influencing intracellular signaling pathways and transcriptional networks, regulating the metabolic balance of hydrogen sulfide, and determining cell life and death decisions. For example, some

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lncRNAs regulate the NF-κB signaling pathway, affecting the production of inflammatory mediators[30], and by activating the Nrf2 pathway, they enhance the cell's antioxidant capacity[31], playing a key role in cellular responses to oxidative stress and inflammation, influencing the disulfidptosis process[31].

## 5. Comprehensive Analysis and Future Outlook

With the deepening research into the role of lncRNAs in cell death pathways, we have begun to understand their cross-regulatory mechanisms and the underlying molecular networks in ferroptosis, cuproptosis, and disulfidptosis. Although lncRNAs exhibit certain commonalities in their roles across these cell death pathways, such as regulating enzyme expression or activity to affect intracellular metabolic product levels, they also display unique regulatory mechanisms and biological effects[32][33]. These differences reflect the complexity and diversity of roles lncRNAs play in different cell death pathways, simultaneously revealing how cells finely tune these molecules in response to various physiological and pathological conditions.

Cross-Regulatory Mechanisms lncRNAs interact with various molecular partners, such as directly binding to mRNA or affecting the activity of transcription factors, thereby playing roles in regulating the metabolism of iron, copper, and sulfides. This cross-regulatory mechanism may involve common signaling pathways, such as the EGFR/PI3K/AKT antioxidant response pathway[34], and shared molecular targets, affecting intracellular ROS levels. The discovery of these commonalities and differences provides an opportunity for a comprehensive understanding of the lncRNA regulatory network, also pointing out directions for future research, especially in revealing how these molecules integrate different signals to regulate the complex process of cell fate determination.

### 5.1. Research Limitations and Challenges

The main limitations faced by current research include technical challenges, sample size, and model selection. The functional diversity and cell specificity of lncRNAs require the development of more sensitive and specific techniques to detect and manipulate these molecules[35]. Additionally, most studies rely on in vitro cell models, limiting our understanding of the role of lncRNAs in in vivo contexts[36]. Therefore, developing new models and technologies, such as in vivo genetic manipulation models and high-throughput screening techniques, is an important direction for future research.

### 5.2. Future Directions

Future research should aim to discover new potential lncRNA targets, deepen understanding of the role of lncRNAs in specific diseases, and explore how this knowledge can be leveraged to develop new therapeutic strategies. This includes identifying lncRNAs related to ferroptosis, cuproptosis, and disulfidptosis using high-throughput sequencing and bioinformatics methods, as well as studying the functions of these lncRNAs using CRISPR/Cas9 and other gene editing technologies. Moreover, research should focus on the role of lncRNAs in disease models, especially their roles in cancer, neurodegenerative diseases, and cardiovascular diseases, to develop new treatment methods for these diseases. In summary, the role of lncRNAs in regulating ferroptosis, cuproptosis, and disulfidptosis highlights their significance in cellular metabolism and cell fate determination.

This review comprehensively examines the key regulatory roles and molecular mechanisms of long non-coding RNAs (lncRNAs) in cell death pathways such as ferroptosis, cuproptosis, and disulfidptosis. By analyzing existing literature, it reveals how lncRNAs influence cellular responses to excessive metal ions and sulfide metabolism imbalances, thereby regulating cell fate. These discoveries regarding the role of lncRNAs in cell death pathways hold significant scientific importance for understanding complex cell death mechanisms. Cells utilize lncRNAs

as regulatory factors to finely tune responses to various types of cell damage, subsequently determining cell fate. From a clinical perspective, these findings provide new perspectives and targets for treating diseases related to ferroptosis, cuproptosis, and disulfidptosis, especially in areas such as cancer treatment, neurodegenerative diseases, and cardiovascular diseases. Future research needs to further explore the role of lncRNAs in cell death pathways and their regulatory networks, particularly the mechanisms and biological functions of lncRNAs in in vivo contexts. With the development of new technologies such as CRISPR/Cas9 gene editing and single-cell sequencing, we hope to gain a deeper understanding of the complex interactions between lncRNAs and cell death pathways, uncovering more unknown lncRNA functions and regulatory mechanisms. The further development of this research field not only advances our fundamental understanding of life sciences but also promises to bring innovative strategies and breakthroughs for treating related diseases, opening new chapters in medical research and clinical applications.

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