

# Copper Homeostasis Imbalance and Cuproptosis in Secondary Brain Injury After Intracerebral Hemorrhage

Peijiang Wei<sup>1</sup>, Yanjun Li<sup>1</sup>, Yunsheng Xue<sup>2</sup>, Jianwen Zhi<sup>1</sup>, Bo Ning<sup>1,\*</sup>

<sup>1</sup> Department of Neurosurgery, Guangzhou Red Cross Hospital Affiliated to Jinan University, Guangzhou, Guangdong 510220, China

<sup>2</sup> Department of Neurosurgery, Guangzhou Red Cross Hospital, Guangzhou, Guangdong 510220, China

\* Corresponding author: Bo Ning (Email: ningbo1974@126.com)

---

**Abstract:** With high mortality and disability rates, intracerebral hemorrhage (ICH) impact patients' daily functional abilities. Secondary brain injury following ICH is a critical factor in the loss of daily functionality, involving multiple mechanisms such as blood-brain barrier disruption, brain edema, oxidative stress, mitochondrial dysfunction, and neuroinflammation, and activating various forms of cell death. Cuproptosis, a novel form of copper-dependent cell death, was introduced, which involves copper-dependent mitochondrial metabolic mechanisms. Recent studies have shown that cuproptosis is closely related to the progression and prognosis of ICH. However, the specific role of cuproptosis in ICH remains unclear, highlighting the importance of investigating the mechanisms of cuproptosis in secondary brain injury. This review summarizes the physiological functions of copper, the foundations of copper homeostasis, the mechanisms of cuproptosis, and its pathophysiological role in ICH, with a focus on the roles of neuroinflammation and mitochondrial damage. Finally, we explore future research directions in regulating copper homeostasis and inhibiting cuproptosis, particularly in relation to challenges in drug development, treatment windows, and target selection. Understanding the relationship between copper homeostasis, cuproptosis, and ICH offers new insights for the treatment of ICH and other neurodegenerative diseases.

**Keywords:** Copper Homeostasis; Cuproptosis; Intracerebral Hemorrhage; Secondary Brain Injury.

---

## 1. Introduction

Intracerebral hemorrhage (ICH) accounts for approximately 10%-15% of all stroke cases and is one of the subtypes with a high mortality and disability rate. ICH is characterized by its rapid onset, rapid disease progression, and a significant negative impact on patients' daily functioning [1]. Brain injury following ICH is typically divided into primary and secondary brain injuries. Primary brain injury occurs shortly after the hemorrhage, mainly caused by mechanical compression, elevated intracranial pressure, and local perfusion deficits resulting from hematoma formation. In contrast, secondary brain injury develops gradually over hours to days after the hemorrhage. Its mechanisms involve blood-brain barrier disruption, brain edema, oxidative stress, mitochondrial dysfunction, immune cell infiltration, neuroinflammatory responses, and activation of various forms of cell death [2].

## 2. Physiological Functions of Copper, Copper Homeostasis, and the Basis of Cuproptosis

### 2.1. Physiological Functions of Copper

Copper (Cu) is an essential trace element in the body, playing a crucial role in several key biological processes due to its strong coordination and binding abilities. Firstly, copper is closely linked to mitochondrial energy metabolism, it is an essential cofactor for the synthesis of respiratory chain complexes such as cytochrome c oxidase, and thus, copper is required to maintain the normal functioning of the cellular respiration chain [3]. In addition, copper also participates in maintaining redox homeostasis. On one hand, copper, as a

critical component of various enzymes, plays a role in the removal of reactive oxygen species and antioxidant defense. On the other hand, when copper homeostasis is disrupted and intracellular copper levels increase, it can trigger or amplify oxidative stress and molecular damage [4]. In the nervous system, copper is involved in regulating synaptic function and the physiological processes of neuronal death [5]. Therefore, it is crucial to control copper homeostasis within the normal physiological range.

### 2.2. Copper Homeostasis in the Nervous System

In the nervous system, the fine regulation of copper homeostasis is essential. Scientific research has shown that copper is involved in the regulation of synaptic function and can be released, bound, and regulated within the synaptic microenvironment [6]. Furthermore, copper may also influence neuronal protein homeostasis, affecting processes in the protein degradation system, thereby linking copper homeostasis to the pathology of neurodegenerative diseases [7]. On the other hand, copper can influence immune cell function and inflammatory signaling pathways. Copper exposure or disruption of copper homeostasis can induce or amplify inflammatory responses [8,9]. Thus, during the development of related neurological diseases, alterations in copper homeostasis may promote disease progression through multiple pathways, such as mitochondrial dysfunction, imbalance in oxidative stress, and amplification of inflammation [10]. From the perspective of homeostatic regulation, the intracellular copper levels are typically maintained by a network involving uptake, chaperone delivery, and export. After copper enters the cell, it is delivered to specific subcellular compartments and target

proteins with the assistance of copper chaperone proteins to exert its physiological functions. Meanwhile, the export system helps reduce copper accumulation and avoid non-specific coordination and redox damage. Therefore, for the central nervous system, the copper concentration in the brain and the function of copper transport proteins are crucial in maintaining a stable environment. Imbalances in these regulatory mechanisms may have acute or chronic adverse effects on neuronal function [10].

### **2.3. Definition and Core Mechanism of Cuproptosis**

Cuproptosis is a newly proposed form of regulated cell death driven by copper overload. Under conditions of copper homeostasis imbalance, intracellular copper accumulates and perturbs mitochondrial metabolism, ultimately leading to cell death. A key feature of cuproptosis is its dependence on an active mitochondrial tricarboxylic acid (TCA) cycle and on lipoylated TCA cycle proteins. In cells with high oxidative phosphorylation activity, copper preferentially binds to lipoylated TCA proteins, promoting their abnormal aggregation. This process is accompanied by loss of iron-sulfur (Fe-S) cluster proteins and proteotoxic stress, which together drive cell death. Subsequent studies further emphasized that the copper-lipoylated TCA protein axis distinguishes cuproptosis from apoptosis, ferroptosis, and necroptosis [11-13].

### **2.4. Specific Boundaries of Cuproptosis**

Copper-related cellular injury is not equivalent to cuproptosis. Disrupted copper homeostasis can damage cells through multiple pathways, including oxidative stress and inflammation. In contrast, cuproptosis refers to a more specific cascade characterized by copper accumulation, binding to lipoylated TCA proteins, protein aggregation, proteotoxic stress, and Fe-S protein loss [11-13]. Therefore, increased copper or copper toxicity alone is insufficient to infer that cuproptosis has occurred. A more cautious assessment should integrate evidence of copper overload with markers of lipoylated protein aggregation, proteotoxic stress, Fe-S protein perturbation, and dependence on mitochondrial metabolism [11-13].

Based on the core mechanism framework of Cuproptosis mentioned above, if there is a change in copper homeostasis after ICH along with mitochondrial metabolic abnormalities and disruption of protein homeostasis, Cuproptosis may contribute to the secondary brain injury process. Additionally, the bidirectional regulation between copper homeostasis and inflammation, as well as immune responses, may influence the progression of secondary brain injury after ICH [8-10].

## **3. Copper Homeostasis Imbalance and Cuproptosis After Intracerebral Hemorrhage**

### **3.1. Changes in Copper Homeostasis After Intracerebral Hemorrhage**

The most direct clinical evidence currently comes from studies analyzing serum copper homeostasis in hypertensive ICH patients. These studies measured indicators such as total copper (TCu), small molecular copper (SMC), and ceruloplasmin in ICH patients, comparing them with normal control groups [14]. The results indicated that hypertensive

ICH patients exhibit disturbances in serum copper homeostasis, with elevated SMC and later decreased Ceruloplasmin (Cp) levels being associated with poor outcomes [14]. This finding supports the view that copper metabolism may change after ICH and establishes a connection between changes in copper homeostasis and cellular damage mechanisms [14].

On the animal research side, most tissue evidence related to copper homeostasis has focused on the expression and function of copper-related proteins such as Cp. A previous study showed that after ICH, Cp levels were elevated in brain tissue, with expression observed in neurons and astrocytes. Moreover, exogenous Cp reduced brain injury and neurofunctional deficits in an iron-induced brain injury model [15].

At the same time, studies on secondary injury in ICH have pointed out that blood metabolic products after hemorrhage can activate microglia and astrocytes, leading to peripheral immune cell infiltration and the release of inflammatory mediators. There is a mutually promoting relationship between cellular inflammatory responses and metal metabolism disorders [16]. Therefore, from a pathophysiological perspective, changes in copper homeostasis after ICH are likely not a standalone biological event but part of a cascade reaction initiated by immune infiltration and the release of inflammatory mediators caused by the release of blood clot metabolic products, which subsequently leads to metabolic imbalance [16].

### **3.2. Potential Sources and Pathways of Copper Homeostasis Imbalance**

Based on the above research results and the pathological process of ICH, several possible pathways that lead to local copper homeostasis imbalance can be reasonably proposed. First, after ICH, blood enters the brain tissue and releases degradation products. The local metal ion environment and redox state are affected and change accordingly [16]. In this process, if copper ion concentrations increase or the copper transport state changes, conditions may be provided for copper-related toxicity reactions. Second, blood-brain barrier (BBB) disruption after ICH is an important component of secondary injury. Changes in BBB permeability may affect the delivery of metal ions between brain tissue cells, thereby altering the distribution of copper within the brain [15,16]. Third, after ICH, the activation and infiltration of immune cells can alter mitochondrial function and, through inflammatory signals, further affect metal ion transport [16]. This provides background support for the subsequent discussion of how copper homeostasis imbalance leads to mitochondrial metabolic-dependent damage, which then triggers the pathway of cell death.

### **3.3. Preliminary Evidence of Cuproptosis in ICH**

The canonical model of cuproptosis proposes that an increased intracellular copper load leads to copper binding to lipoylated proteins in the mitochondrial TCA cycle. This interaction promotes abnormal protein aggregation and is accompanied by loss of iron-sulfur (Fe-S) cluster proteins, resulting in proteotoxic stress and mitochondrial dysfunction that culminate in cell death [11-13]. In ICH-related studies, elevated copper levels after hemorrhage have been associated with copper homeostasis disruption and activation of cuproptosis-related signatures. Notably, activation of

PPAR $\gamma$  has been reported to mitigate copper toxicity and suppress cuproptosis by limiting copper influx and regulating the expression of cuproptosis-related factors [17]. In addition, transcriptomic analyses suggest that cuproptosis-related genes may correlate with immune activity and prognosis in ICH, and thus may represent potential intervention targets. However, transcriptional changes do not by themselves establish the occurrence of cell death and should be complemented by protein-level and functional validation. Future studies should strengthen the evidence chain in ICH, including assessments of lipoylated protein aggregation, Fe-S protein changes, metabolic dependence, key susceptible cell types, and the relevant time window [17,18].

#### **3.4. Mechanistic Inference of Cuproptosis in ICH**

From a pathophysiological perspective, cuproptosis has multiple potential intersections with secondary brain injury in ICH. First, mitochondrial dysfunction is widespread after ICH and is involved in several stages of secondary brain injury. Numerous studies emphasize the close relationship between mitochondrial structure and function changes, oxidative stress, cell death, mitochondrial dynamics imbalance, and abnormal clearance of damaged mitochondria [19-22]. Cuproptosis itself emphasizes its dependence on mitochondrial metabolic status, so in the ICH pathological environment, where mitochondrial damage dominates, cuproptosis may play a significant role [19,23,24]. Second, the neuroinflammatory response after ICH is believed to both exacerbate injury and potentially participate in repair [16,25]. Since metal metabolism and inflammation are mutually regulated, and metal homeostasis disruption can amplify oxidative stress and inflammatory signaling, changes in copper homeostasis provide the conditions for cuproptosis to occur [16,23,25]. Third, evidence of iron metabolism disorder and ferroptosis in ICH is relatively well-established, with enough studies suggesting that iron deposition in the hematoma zone, inflammation, and ferroptosis mutually promote each other [16,22,26]. For example, some studies indicate that microglial-related molecules can exacerbate neuronal ferroptosis by influencing iron deposition and inflammatory responses, further demonstrating how metal homeostasis imbalance triggers cell death [26,27]. Although the evidence chain for cuproptosis in ICH is still incomplete, the biological basis for the metal-related cell death network in ICH already supports multiple pathway interactions [16,22,28].

### **4. Cuproptosis, Mitochondrial Damage, and Neuroinflammation**

One of the key processes in secondary brain injury after ICH is mitochondrial dysfunction and neuroinflammatory responses. Current research indicates that mitochondrial damage not only directly leads to disruptions in cellular energy metabolism, but also exacerbates neuroinflammatory responses by regulating oxidative stress and certain cell death pathways, further impairing neuronal function [13,19,29]. On the other hand, neuroinflammation can further exacerbate mitochondrial damage through the release of inflammatory factors and activation of microglia, creating a vicious cycle of injury [14,30].

#### **4.1. Mitochondrial Damage and Energy Metabolism Disorders**

Mitochondria are the cell's energy factories, and their function is especially crucial in brain tissue to maintain cellular physiological activities. After ICH, due to the continued effects of hematoma and its breakdown products, local mitochondrial function undergoes significant changes, primarily manifested as the loss of mitochondrial membrane potential, decreased ATP synthesis, and dysfunction of mitochondrial respiratory chain complexes [15,31]. Furthermore, the excessive production of reactive oxygen species (ROS) and abnormal mitochondrial autophagy are also considered key mechanisms of secondary brain injury [17].

Cuproptosis is a copper-dependent form of regulated cell death tightly linked to mitochondrial metabolism. It is characterized by copper binding to lipoylated TCA cycle proteins, subsequent protein aggregation, Fe-S protein loss, and proteotoxic stress, rather than by nonspecific copper toxicity alone [11-13]. In experimental ICH models, some studies suggest that excessive copper accumulation is associated with aggregation of lipoylated mitochondrial TCA proteins, mitochondrial impairment, and cell death. These findings support the hypothesis that cuproptosis may contribute to mitochondrial-dependent cell loss after ICH, although direct mechanistic validation in relevant cell types and time windows remains limited [13,18].

#### **4.2. Interaction Between Neuroinflammatory Response and Mitochondrial Damage**

After ICH, the inflammatory response is a critical component of secondary brain injury. Studies have found that hematoma breakdown products activate microglia, macrophages, and astrocytes, which release a large number of cytokines, such as IL-1 $\beta$  and TNF- $\alpha$ , further exacerbating the neuroinflammatory response in neural tissue [30,32]. This inflammatory response not only directly damages neurons but also promotes mitochondrial damage through pathways like inflammasome activation, creating a vicious cycle of inflammation leading to mitochondrial damage and ultimately cell death.

The coupling of mitochondrial dysfunction and inflammation in ICH has been validated in several models. Research shows that ROS production induced by inflammation further damages mitochondria, while ROS generated by mitochondria can activate signaling pathways such as NF- $\kappa$ B, enhancing the inflammatory response [30]. Furthermore, the interplay between iron metabolism and copper metabolism is also considered a key factor in promoting this vicious cycle. Excessive iron ions exacerbate cell damage through ferroptosis, while copper homeostasis imbalance may also interact with iron metabolism through cuproptosis, amplifying the damaging effects [33].

#### **4.3. Interaction Between Copper Homeostasis Imbalance and Iron Metabolism**

In the pathological process of ICH, copper and iron metabolism are closely related. Existing research indicates that the homeostasis of copper and iron within cells is tightly regulated. Abnormal copper accumulation can affect iron transport, thereby increasing oxidative stress and the risk of cell damage [32]. Changes in copper levels may also activate signaling pathways associated with oxidative stress, such as

the MAPK and Nrf2 pathways, which are crucial in neuroinflammation and cell death in the central nervous system [23,34]. Therefore, copper homeostasis imbalance not only causes cell death through the direct mechanism of cuproptosis but also exacerbates secondary brain injury after ICH through its interactions with iron metabolism and oxidative stress.

## 5. Therapeutic Potential for Targeting Cuproptosis in Intracerebral Hemorrhage

Effective therapeutic options for ICH remain limited, particularly with respect to interventions targeting secondary brain injury. In recent years, dysregulation of copper homeostasis and cuproptosis have been proposed to contribute to injury progression in stroke and other central nervous system disorders, thereby providing a new perspective for therapeutic intervention in ICH-related secondary brain injury [23,34]. However, translating strategies that target copper homeostasis and cuproptosis into clinical practice still requires addressing multiple mechanistic and technical challenges.

### 5.1. Maintaining Cerebral Copper Homeostasis

The central aim is to prevent excessive intracellular copper accumulation, particularly by blocking pathological copper influx to reduce the likelihood of cuproptosis [23]. One study reported that activation of PPAR $\gamma$  attenuated brain injury after ICH and suppressed cuproptosis-related processes by limiting copper influx and modulating the expression of relevant factors, suggesting copper transport pathways as potential therapeutic targets [17]. Restoring copper homeostasis may not only reduce copper overload-associated cellular injury but also mitigate copper burden-related oxidative stress and mitochondrial dysfunction [34]. Clinically, serum indicators associated with copper homeostasis—such as ceruloplasmin and small-molecule copper (SMC)—have been linked to ICH severity and prognosis, providing a rationale for risk assessment and early intervention in copper dyshomeostasis [14].

### 5.2. Targeting Copper-Related Toxicity and Key Nodes of Cuproptosis

This approach focuses on directly reducing copper load to limit copper-associated toxicity. Evidence from other neurological disorders, such as Wilson's disease, suggests that copper chelation can effectively control brain copper ion levels and improve neurological function [35]. In stroke-related animal studies, copper chelators (e.g., ammonium tetrathiomolybdate, ATTM) have been reported to decrease copper-related toxicity and improve mitochondrial function, thereby alleviating brain tissue injury; however, their efficacy and safety specifically in ICH still require more direct validation in appropriate models and clinical studies [36]. Overall, copper chelation may exert protective effects by limiting copper entry into mitochondria-associated injury pathways and reducing the oxidative stress burden, yet key issues—including the therapeutic window, dosing regimen, and potential adverse effects—remain to be resolved.

### 5.3. Synergy with Mitochondrial Protection and Anti-Inflammatory/Antioxidant Strategies

Secondary brain injury after ICH is a multifactorial process, and single-target therapies often fail to cover the full spectrum of pathological mechanisms [2,37,38]. Mitochondrial protective strategies—by improving energy metabolism and reducing ROS generation—have shown potential benefits in studies of cerebral ischemia and brain injury, providing a direction for counteracting cuproptosis-associated mitochondrial metabolic disturbances [2]. Meanwhile, anti-inflammatory approaches can alleviate secondary injury by suppressing excessive inflammation, reducing microglial activation, and limiting cytokine release [39,40]. Therefore, combining copper homeostasis modulation with anti-inflammatory and antioxidant interventions may represent a promising therapeutic direction for ICH.

## 6. Conclusion and Outlook

Overall, copper homeostasis imbalance and cuproptosis may contribute to secondary brain injury after ICH. Given the impact of copper homeostasis imbalance on secondary brain injury, precise regulation of copper homeostasis may become a new therapeutic target for ICH. The development of copper chelators, copper homeostasis restoration drugs, and cuproptosis inhibitors will help improve neurological recovery following ICH. However, further research is needed to fully understand how the process of cuproptosis promotes the progression of secondary brain injury after ICH.

Currently, the detailed mechanisms linking copper homeostasis imbalance to cuproptosis in ICH remain unclear, including how copper triggers mitochondrial injury through interactions with lipoylated TCA cycle proteins and how this process contributes to neuronal and glial cell loss. Further research is needed to clarify these mechanisms and to evaluate their clinical relevance. In recent years, an increasing number of studies have highlighted a potential role of cuproptosis in ICH. Current ICH management mainly includes medical therapy, surgical intervention when indicated, and post-acute rehabilitation. However, due to the heterogeneity and complexity of ICH, outcomes remain suboptimal in many patients. Future neuroprotective and immunomodulatory strategies, together with approaches targeting copper homeostasis and cuproptosis, may offer new therapeutic directions.

## Acknowledgments

Funding Project: The Impact and Mechanism of CD63/SLC2A3-Mediated Neuronal Ferroptosis on Rehabilitation after Intracerebral Hemorrhage (2025A03J35 95).

## References

- [1] Zille Marietta, Farr Tracy D., Keep Richard F., et al. Novel targets, treatments, and advanced models for intracerebral haemorrhage [J]. *EBioMedicine*, 2022, 76:103880.
- [2] Shao Linqian, Chen Sichao, Ma Li. Secondary Brain Injury by Oxidative Stress After Cerebral Hemorrhage: Recent Advances [J]. *Frontiers in Cellular Neuroscience*, 2022, 16:853589.
- [3] Llases María-Eugenia, Morgada Marcos N., Vila Alejandro J. Biochemistry of Copper Site Assembly in Heme-Copper Oxidases: A Theme with Variations [J]. *International Journal of Molecular Sciences*, 2019, 20(15):3830.

- [4] Cobine Paul A, Brady Donita C. Cuproptosis: Cellular and molecular mechanisms underlying copper-induced cell death [J]. *Molecular Cell*, 2022, 82(10):1786-1787.
- [5] Gong Rui, Kong Ying, Pan Limin, et al. To explore the acupuncture intervention mechanism for vascular dementia based on the theories of copper death and angiogenesis [J]. *Journal of Clinical Acupuncture and Moxibustion*, 2023, 39(06):1-6.
- [6] D'Ambrosi Nadia, Rossi Luisa. Copper at synapse: Release, binding and modulation of neurotransmission [J]. *Neurochemistry International*, 2015, 90:36-45.
- [7] Opazo Carlos M., Greenough Mark A., Bush Ashley I. Copper: from neurotransmission to neuroproteostasis [J]. *Frontiers in Aging Neuroscience*, 2014, 6:143.
- [8] Liu Yamei, Zhu Junlang, Xu Liangliang, et al. Copper regulation of immune response and potential implications for treating orthopedic disorders [J]. *Frontiers in Molecular Biosciences*, 2022, 9:1065265.
- [9] Deng Huidan, Zhu Song, Yang Huiru, et al. The Dysregulation of Inflammatory Pathways Triggered by Copper Exposure [J]. *Biological Trace Element Research*, 2023, 201(2):539-548.
- [10] An Yumei, Li Sunao, Huang Xinqi, et al. The Role of Copper Homeostasis in Brain Disease [J]. *International Journal of Molecular Sciences*, 2022, 23(22):13850.
- [11] Li Su-Ran, Bu Lin-Lin, Cai Lulu. Cuproptosis: lipoylated TCA cycle proteins-mediated novel cell death pathway [J]. *Signal Transduction and Targeted Therapy*, 2022, 7(1):158.
- [12] Tang Daolin, Chen Xin, Kroemer Guido. Cuproptosis: a copper-triggered modality of mitochondrial cell death [J]. *Cell Research*, 2022, 32(5):417-418.
- [13] Tsvetkov Peter, Coy Shannon, Petrova Boryana, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins [J]. *Science*, 2022, 375(6586):1254-1261.
- [14] Han Ming, Ding Shan, Zhang Yuan, et al. Serum Copper Homeostasis in Hypertensive Intracerebral Hemorrhage and its Clinical Significance [J]. *Biological Trace Element Research*, 2018, 185(1):56-62.
- [15] Liu Hongwei, Hua Ya, Keep Richard F., et al. Brain Ceruloplasmin Expression After Experimental Intracerebral Hemorrhage and Protection Against Iron-Induced Brain Injury [J]. *Translational Stroke Research*, 2019, 10(1):112-119.
- [16] Ju Jia-Jun, Hang Li-Hua. Neuroinflammation and iron metabolism after intracerebral hemorrhage: a glial cell perspective [J]. *Frontiers in Neurology*, 2025, 15:1510039.
- [17] Zhang Wenying, Ma Wanyu, Ren Siying, et al. A pretest on cuproptosis: Activating PPAR $\gamma$  inhibits cuproptosis following intracerebral hemorrhage [J]. *Brain Hemorrhages*, 2025, 6(4):166-175.
- [18] Shen Xi, Zhu Jiandong, Gu Yuhang, et al. Prognostic Role of Cuproptosis-Related Gene after Intracerebral Hemorrhage in Mice [J]. *Cellular and Molecular Neurobiology*, 2025, 45(1):48.
- [19] Li Yuanyuan, Liu Haoqi, Tian Chao, et al. Targeting the multifaceted roles of mitochondria in intracerebral hemorrhage and therapeutic prospects [J]. *Biomedicine & Pharmacotherapy*, 2022, 148:112749.
- [20] Chen Weixiang, Guo Chao, Feng Hua, et al. Mitochondria: Novel Mechanisms and Therapeutic Targets for Secondary Brain Injury After Intracerebral Hemorrhage [J]. *Frontiers in Aging Neuroscience*, 2021, 12:615451.
- [21] Li Xiang, Chen Gang. Mitochondrial-Based Therapeutic Strategies for Intracerebral Hemorrhage [J]. *Translational Stroke Research*, 2022, 13(2):214-215.
- [22] Liu Mengnan, Li Binru, Yin Zhixue, et al. Targeting mitochondrial dynamics: A promising approach for intracerebral hemorrhage therapy [J]. *Life Sciences*, 2025, 361:123317.
- [23] Zhu Zhipeng, Song Min, Ren Jianxun, et al. Copper homeostasis and cuproptosis in central nervous system diseases [J]. *Cell Death & Disease*, 2024, 15(11):850.
- [24] Pan Chengliang, Ji Zhilin, Wang Qingxuan, et al. Cuproptosis: Mechanisms, biological significance, and advances in disease treatment—A systematic review [J]. *CNS Neuroscience & Therapeutics*, 2024, 30(9): e70039.
- [25] Mracsko Eva, Veltkamp Roland. Neuroinflammation after intracerebral hemorrhage [J]. *Frontiers in Cellular Neuroscience*, 2014, 8:388.
- [26] Liu Qi, Han Ziyi, Li Tao, et al. Microglial HO-1 aggravates neuronal ferroptosis via regulating iron metabolism and inflammation in the early stage after intracerebral hemorrhage [J]. *International Immunopharmacology*, 2025, 147:113942.
- [27] Han Ruili, Liu Lei, Wang Yuying, et al. Microglial SLC25A28 Deficiency Ameliorates the Brain Injury After Intracerebral Hemorrhage in Mice by Restricting Aerobic Glycolysis [J]. *Inflammation*, 2024, 47(2):591-608.
- [28] Li Pengpeng, Gao Yangyang, Liu Wei. Cuproptosis in stroke: Molecular mechanisms and therapeutic targeting of copper-mediated cell death [J]. *Brain Research Bulletin*, 2025, 232: 111614.
- [29] Jones Olivia A, Mohamed Saffwan, Hinz Rainer, et al. Neuroinflammation and blood-brain barrier breakdown in acute, clinical intracerebral hemorrhage [J]. *Journal of Cerebral Blood Flow & Metabolism*, 2024, 45(2):233-243.
- [30] Zhang Yan, Khan Suliman, Liu Yang, et al. Oxidative Stress Following Intracerebral Hemorrhage: From Molecular Mechanisms to Therapeutic Targets [J]. *Frontiers in Immunology*, 2022, 13:847246.
- [31] Yang Guang, Hu Rong, Zhang Chao, et al. A combination of serum iron, ferritin and transferrin predicts outcome in patients with intracerebral hemorrhage [J]. *Scientific Reports*, 2016, 6(1):21970.
- [32] Sun Yuanyuan, Li Qian, Guo Hongxiu, et al. Ferroptosis and Iron Metabolism after Intracerebral Hemorrhage [J]. *Cells*, 2023, 12(1):90.
- [33] Wei Yufei, Song Xiaoxiao, Gao Ying, et al. Iron toxicity in intracerebral hemorrhage: Physiopathological and therapeutic implications [J]. *Brain Research Bulletin*, 2022, 178:144-154.
- [34] Xing Liwei, Wang Zhifeng, Hao Zhihui, et al. Cuproptosis in stroke: focusing on pathogenesis and treatment [J]. *Frontiers in Molecular Neuroscience*, 2024, 17:1349123.
- [35] Socha Piotr, Jańczyk Wojciech, Zanetto Alberto, et al. EASL-ERN Clinical Practice Guidelines on Wilson's disease [J]. *Journal of Hepatology*, 2025, 82(4):690-728.
- [36] Mendonca BP, Cardoso JDS, Michels M, et al. Neuroprotective effects of ammonium tetrathiomolybdate, a slow-release sulfide donor, in a rodent model of regional stroke [J]. *Intensive Care Medicine Experimental*, 2020, 8:13.
- [37] Seiffge David J., Fandler-Höfler Simon, Du Yang, et al. Intracerebral haemorrhage — mechanisms, diagnosis and prospects for treatment and prevention [J]. *Nature Reviews Neurology*, 2024, 20(12):708-723.
- [38] Keep Richard F., Hua Ya, Xi Guohua. Intracerebral haemorrhage: mechanisms of injury and therapeutic targets [J]. *The Lancet Neurology*, 2012, 11(8):720-731.
- [39] Loan James JM, Kirby Caoimhe, Emelianova Katherine, et al. Secondary injury and inflammation after intracerebral haemorrhage: a systematic review and meta-analysis of molecular markers in patient brain tissue [J]. *Journal of Neurology, Neurosurgery & Psychiatry*, 2022, 93(2):126-132.
- [40] Yang Guoqiang, Fan Xuehui, Mazhar Maryam, et al. Neuroinflammation of microglia polarization in intracerebral hemorrhage and its potential targets for intervention [J]. *Frontiers in Molecular Neuroscience*, 2022, 15:1013706.