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Mechanisms of Cuproptosis in Spinal Cord Injury Progression Associated with Copper Metabolic Dysregulation

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Abstract: ***This study aims to investigate the role of copper metabolic dysregulation in the progression of spinal cord injury, with a particular focus on the biological effects of cuproptosis. An animal model of spinal cord injury was established to examine the expression levels of SLC31A1 and ATP7B and to evaluate the association between copper metabolism and spinal cord injury. The results demonstrated that disruption of copper homeostasis markedly exacerbated spinal cord injury severity, characterized by enhanced neuronal apoptosis and heightened inflammatory responses. Further analysis revealed that cuproptosis plays a critical role in the pathophysiological process of spinal cord injury, as evidenced by the significant elevation of lipid peroxidation products, a hallmark of this cell-death pathway. SLC31A1 and ATP7B were identified as key regulators of copper metabolism; upregulation of SLC31A1 increased copper influx, while downregulation of ATP7B impaired copper efflux, leading to intracellular copper accumulation and activation of the cuproptosis pathway. The discussion section provides an in-depth analysis of the relationship between copper metabolic dysregulation and cuproptosis, elucidates the molecular mechanisms underlying cuproptosis in spinal cord injury, and examines the regulatory roles of SLC31A1 and ATP7B. These findings offer new insights into the pathological mechanisms of spinal cord injury and provide a theoretical basis for the development of clinical therapeutic strategies.***

Keywords: Copper metabolic dysregulation, Cuproptosis, Spinal cord injury, SLC31A1, ATP7B.

1. Introduction

Spinal cord injury (SCI), as a severe condition of the central nervous system, presents highly complex pathological mechanisms and has long remained a major focus of research in the field of neuroscience [1]. Secondary injury processes — characterized by mitochondrial dysfunction, inflammatory responses, and ionic imbalances—are key contributors to neurological deficits following spinal cord injury. Although extensive research has investigated these pathological mechanisms, the treatment of spinal cord injury remains highly challenging [2]. In recent years, dysregulation of copper metabolism and the associated process of cuproptosis have gained increasing attention due to their critical roles in various neurodegenerative diseases and cancers [3]. Cuproptosis is a distinct copper ion–dependent form of regulated cell death. Its underlying mechanism involves aberrant expression of copper transporters, including solute carrier family 31 member 1 (SLC31A1) and the copper-transporting P-type ATPase ATP7B, resulting in excessive intracellular copper accumulation that disrupts cellular function and viability [4].

Studies have demonstrated that excessive intracellular copper binds to lipoylated components of the tricarboxylic acid (TCA) cycle, leading to the loss of iron–sulfur (Fe–S) cluster proteins and the onset of proteotoxic stress, ultimately resulting in cell death. This mechanism has been extensively validated in neurodegenerative diseases, whereas its investigation in spinal cord injury remains at an early stage [5]. In view of the presence of mitochondrial dysfunction and inflammatory responses in the pathology of spinal cord injury, dysregulated copper metabolism and the resulting cuproptosis may play a critical role in secondary injury following spinal cord damage.

2. Theoretical Basis

2.1 Overview of Dysregulated Copper Metabolism

Dysregulation of copper metabolism, as a significant pathophysiological process, is underpinned by the dynamic balance of copper ions in the body and its regulatory mechanisms [6]. Copper is an essential trace element and a component of the active sites of various enzymes, playing critical roles in physiological processes such as oxygen transport, electron transfer, antioxidant defense, and neurotransmitter synthesis. Under normal conditions, copper homeostasis is maintained via a series of precisely regulated transport proteins and metabolic pathways, among which SLC31A1 and ATP7B, a copper-transporting P-type ATPase, are key regulators of copper uptake, transport, and excretion.

However, when copper metabolism is dysregulated, these regulatory mechanisms are disrupted, resulting in abnormal intracellular copper accumulation. These alterations are primarily associated with gene mutations, environmental factors, and metabolic pathway abnormalities, as exemplified by Wilson's disease caused by ATP7B mutations. Dysregulated copper metabolism not only impairs the activity of copper-dependent enzymes but also triggers cytotoxicity through multiple mechanisms. For example, excessive intracellular copper binds to lipoylated components of the tricarboxylic acid (TCA) cycle, leading to the loss of iron–sulfur (Fe–S) cluster proteins, inducing proteotoxic stress, and ultimately causing cell death, a process termed cuproptosis.

2.2 Mechanisms of Cuproptosis

Cuproptosis, as an emerging form of regulated cell death, is

copper-dependent and distinct from traditional pathways such as apoptosis and necrosis. Its underlying mechanism involves aberrant expression of key copper transporters, including solute carrier family 31 member 1 (SLC31A1) and ATP7B, a copper-transporting P-type ATPase. Overexpression of SLC31A1, a high-affinity copper transporter, leads to excessive copper influx, while dysfunction of ATP7B impairs copper efflux, resulting in intracellular copper accumulation. This copper overload disrupts cellular function and viability.

Specifically, excessive intracellular copper binds to lipoylated TCA cycle components, disrupting the stability of iron–sulfur (Fe–S) cluster proteins and leading to their loss. Fe–S cluster proteins play critical roles in cellular respiration and enzyme activity, and their loss results in proteotoxic stress and subsequent cell death. Furthermore, bioinformatics analyses indicate that metabolic dysregulation and oxidative stress induced by copper overload constitute key pathological events underlying cuproptosis.

2.3 Pathophysiology of Spinal Cord Injury

Spinal cord injury (SCI), as a severe central nervous system condition, is characterized by complex and multifactorial pathophysiology. Primary injury typically results from mechanical forces directly applied to the spinal cord, causing immediate neuronal and glial cell damage and death [7]. In contrast, secondary injury is the principal driver of progressive neurological dysfunction following SCI, initiating a cascade of pathological events.

Mitochondrial dysfunction is a critical contributor to secondary injury [8]. Following spinal cord injury, disruption of mitochondrial membrane integrity results in mitochondrial swelling and impaired oxidative phosphorylation (OXPHOS), thereby disrupting cellular energy metabolism. Evidence indicates that mitochondrial dysfunction not only compromises cellular energy supply but also increases the generation of reactive oxygen species (ROS), thereby exacerbating oxidative stress and promoting further neuronal and glial cell injury.

3. Materials and Methods

3.1 Animal Model Establishment

In studying the role of cuproptosis in spinal cord injury progression, the establishment of a reliable animal model is fundamental [9]. Adult male Sprague-Dawley (SD) rats, weighing 250–300 g, were used to ensure uniform physiological conditions [10]. The model was generated using the Modified Allen's Impact Method, which simulates clinically relevant acute spinal cord injury through precise control of impact force and angle.

The specific procedures were as follows: rats were deeply anesthetized via intraperitoneal injection of sodium pentobarbital (40 mg/kg). The animals were then secured on the surgical table, and the T10 spinal segment was exposed. A 10 g weight was dropped vertically from a height of 5 cm using a specialized impact device to induce a localized spinal cord contusion [11]. Muscle layers were sutured and the skin disinfected postoperatively to prevent infection. Postoperative care consisted of daily intraperitoneal antibiotic administration and bladder massage to maintain basic physiological functions.

3.2 Assessment of SLC31A1 and ATP7B Gene Expression

In studying the role of cuproptosis in spinal cord injury progression, the assessment of SLC31A1 and ATP7B gene expression is essential [12]. A range of advanced molecular biology techniques was utilized to guarantee the accuracy and reliability of the experimental data.

PCR was employed to quantitatively assess the mRNA expression levels of SLC31A1 and ATP7B. Total RNA was extracted from the spinal cord tissue of SCI model rats and reverse-transcribed into cDNA. Specific primers were then designed and synthesized, and amplification and quantification were carried out using a real-time quantitative PCR (qPCR) system. All procedures were performed under RNase-free conditions to prevent RNA degradation and ensure data integrity.

Western blotting was used to assess the protein expression levels of SLC31A1 and ATP7B. Proteins were extracted from spinal cord tissue and quantified using the BCA assay. The samples were separated by SDS-PAGE and transferred onto PVDF membranes. Membranes were incubated with specific antibodies, and bands were visualized by chemiluminescence and analyzed using an imaging system. Antibody dilution and incubation times were carefully optimized to minimize nonspecific binding and ensure result specificity.

3.3 Analysis of the Association Between Copper Metabolism and Spinal Cord Injury

From the perspective of copper metabolism disorder (CMD), to explore the role of copper-induced cell death (CICD) in the progression of spinal cord injury (SCI), it is essential to first understand the basic physiology of copper metabolism [13]. Copper is an essential trace element in the human body and is metabolized through the regulation of several key proteins and enzymes, such as the copper transporter SLC31A1 (Copper Transporter 1, CTR1) and the copper pump ATP7B (ATPase Copper Transporting Beta) [14]. SLC31A1 mediates the uptake of copper into cells, while ATP7B regulates its intracellular distribution and excretion. Dysfunction of these proteins can lead to copper metabolism disorders, resulting in abnormal intracellular Cu^{2+} levels.

Table 1: Multivariate analysis of the impact of copper metabolism disorders on spinal cord injury progression

Factor	Effect	correlation		
Inflammatory Response	Oxidative Stress	Cuproptosis		
SLC31A1 Expression	Lower	Lower	Copper Deposition	Positive correlation
ATP7B Expression	Lower	Lower	Neuronal Injury	Positive correlation
Extent of Copper Metabolic Dysfunction	Intensify	Intensify	Apoptosis and Necrosis	Positive correlation
Copper Ion Concentration	anormalous	anormalous	Lipid Peroxidation and Protein Thiol Oxidation	Positive correlation

The effects of copper metabolism disorders on spinal cord injury occur at multiple levels. Pathophysiological studies have shown that following spinal cord injury, alterations in the local microenvironment, including inflammatory responses and oxidative stress, can aggravate copper metabolism disorders [15]. Both copper ion overload and deficiency can disrupt intracellular signaling pathways, such as the MAPK/ERK (Mitogen-Activated Protein Kinase/ Extracellular Signal-Regulated Kinase) and PI3K/Akt (Phosphoinositide 3-Kinase/Protein Kinase B) pathways, thereby affecting neuronal survival and regeneration [16]. The biological mechanism of copper-induced cell death indicates that copper overload can trigger intracellular lipid peroxidation and protein thiol oxidation, ultimately resulting in apoptosis or necrosis.

In animal models, selective knockout of the SLC31A1 or ATP7B gene can mimic copper metabolism disorders and allow observation of their effects on spinal cord injury progression. Gene expression analysis revealed that following spinal cord injury, the expression levels of SLC31A1 and ATP7B were significantly downregulated, further aggravating copper metabolism disorders. Correlation analysis demonstrated a positive association between the severity of copper metabolism disorders and spinal cord injury, indicating that copper metabolism disorders play a critical role in the progression of spinal cord injury.

Copper-induced cell death plays a prominent role during the progression of spinal cord injury. Observation under transmission electron microscopy revealed abundant copper ion deposition in the injured spinal cord tissue, along with hallmark morphological features of copper-induced cell death, including nuclear condensation of neurons and mitochondrial swelling. Further functional studies demonstrated that inhibiting copper ion uptake or promoting its excretion can significantly mitigate post-injury pathological alterations and improve neural functional recovery.

The interplay between copper metabolism disorders and copper-induced cell death is crucial in the progression of spinal cord injury. SLC31A1 and ATP7B, as key regulators of copper metabolism, have altered expression levels that directly influence intracellular copper distribution and the cytotoxic effects of copper ions. Further investigation into their regulatory mechanisms may provide novel targets and therapeutic strategies for spinal cord injury treatment.

4. Results

4.1 Impact of Copper Metabolism Disorders on Spinal Cord Injury

In this study, we established animal models of copper metabolism disorders to examine the role of copper-induced cell death during spinal cord injury progression [17]. The results demonstrated that copper metabolism disorders significantly exacerbated the pathological process of spinal cord injury. Histological staining revealed that spinal cord tissues in the copper metabolism disorder group exhibited more severe neuronal degeneration and necrosis, marked white matter demyelination, and extensive inflammatory cell infiltration. These pathological changes indicate that copper-induced cell death resulting from copper ion accumulation is a key contributor to spinal cord injury [18].

Further behavioral assessments demonstrated that animals in the copper metabolism disorder group had significantly impaired motor function recovery compared to the control group. Specifically, in both BBB (Basso, Beattie, Bresnahan) scoring and the inclined plane test, the copper metabolism disorder group scored significantly lower than the control group, reflecting severe motor deficits. These findings are consistent with histological observations and further corroborate the detrimental effect of copper metabolism disorders on spinal cord injury [19].

4.2 Features of Copper-Induced Cell Death During Spinal Cord Injury Progression

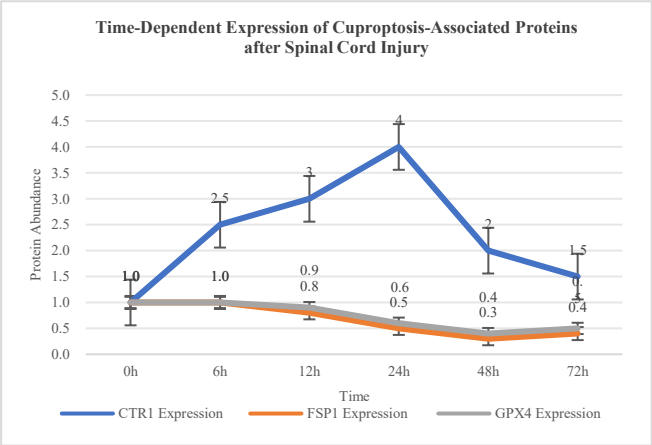

Figure 1: Temporal Profile of Copper-Induced Cell Death-Related Protein Expression following Spinal Cord Injury

In investigating the role of cuproptosis in spinal cord injury (SCI) progression, it is essential to delineate the temporal characteristics of cuproptosis following SCI [20]. In this experiment, Western blotting was performed to quantify proteins associated with copper metabolism in spinal cord tissues at different time points after SCI (0 h, 6 h, 12 h, 24 h, 48 h, and 72 h). The results demonstrated that the expression of the copper transporter (Copper Transporter 1, CTR1) was significantly upregulated at 6 h post-SCI, peaked at 24 h, and subsequently gradually declined. This pattern suggests that the early phase of SCI is characterized by a marked increase in copper ion (Cu^{2+}) influx, which may be related to the post-injury stress response.

Further analysis of key cuproptosis-related proteins, Ferroptosis Suppressing Protein 1 (FSP1) and its downstream effector Glutathione Peroxidase 4 (Gpx4), revealed that FSP1 was downregulated starting at 12 h post-SCI and reached its nadir at 48 h. Gpx4 expression decreased significantly after 24 h, mirroring the trend of FSP1 [21]. These findings suggest that oxidative stress induced by copper ion accumulation during SCI may inhibit the FSP1/Gpx4 pathway, thus facilitating cuproptosis.

Spinal cord tissue sections were stained using immunohistochemistry (IHC) to assess copper ion deposition in neurons following SCI. As shown in Figure 1, at 24 h post-SCI, neuronal copper ion deposition was markedly increased, accompanied by cell shrinkage and nuclear

condensation, consistent with the hallmark morphological features of cuproptosis.

The above experimental data suggest that copper ion accumulation resulting from copper metabolism disorders following SCI facilitates cuproptosis through inhibition of the FSP1/Gpx4 antioxidant pathway, thereby aggravating spinal cord injury. These findings provide a potential therapeutic target for SCI, indicating that modulation of copper metabolism and inhibition of cuproptosis may effectively mitigate post-injury pathological damage.

The manifestations of cuproptosis during SCI progression exhibit a time-dependent pattern and are mediated by copper ion accumulation and suppression of antioxidant pathways [22]. Future research should further explore therapeutic strategies targeting copper metabolism and cuproptosis - related proteins to potentially improve outcomes in SCI patients.

4.3 Roles of SLC31A1 and ATP7B in Copper Metabolism Disorders

In this study, we examined the expression changes of SLC31A1 and ATP7B and their impact on cellular function in copper metabolism disorders using gene functional analysis and experimental validation [23]. Experimental results demonstrated that in the spinal cord injury (SCI) model, SLC31A1 expression was significantly upregulated, whereas ATP7B expression was significantly downregulated. Such alterations in expression resulted in intracellular copper ion accumulation, consequently inducing cuproptosis.

Specifically, SLC31A1, the primary transporter for copper ion influx, is overexpressed, facilitating excessive copper ion entry into cells. Concurrently, ATP7B, a key protein responsible for copper ion efflux, is downregulated, resulting in impaired copper ion extrusion and further aggravating intracellular copper accumulation. Through Western blotting and quantitative PCR (qPCR) analyses, we validated these expression changes and found that they were positively associated with the severity of spinal cord injury.

Further functional experiments showed that copper ion accumulation led to the binding of lipoylated components in the tricarboxylic acid (TCA) cycle to copper ions, thereby causing the loss of iron-sulfur (Fe-S) cluster proteins. This event induced proteotoxic stress, culminating in cell death. Transmission electron microscopy (TEM) revealed mitochondrial structural disruption and a reduction in Fe-S cluster proteins, further corroborating this mechanism.

5. Discussion

5.1 Relationship Between Copper Metabolism Disorders and Cuproptosis

The mechanistic role of copper metabolism disorders in promoting cuproptosis during spinal cord injury (SCI) progression remains an area of active investigation [24]. Cuproptosis, a novel form of cell death, primarily involves the dysregulated expression of copper-transporting proteins, including solute carrier family 31 member 1 (SLC31A1) and copper-transporting P-type ATPase beta (ATP7B), resulting in intracellular copper ion (Cu^{2+}) overload [25]. This copper ion overload not only disrupts normal cellular function but also initiates a cascade of downstream events, ultimately culminating in cell death.

In the pathological process of spinal cord injury (SCI), the secondary injury phase plays a critical role and is characterized by mitochondrial dysfunction, inflammatory responses, and ionic imbalances [26]. Copper ion overload has been shown to exacerbate these pathological processes via multiple mechanisms. Excess copper ions bind to lipoylated components in the tricarboxylic acid (TCA) cycle, leading to the loss of iron-sulfur (Fe-S) cluster proteins, thereby inducing proteotoxic stress and perturbing intracellular protein homeostasis. Additionally, copper ion overload can directly impair mitochondrial function, resulting in energy metabolic deficits and further exacerbation of neurological dysfunction following SCI.

5.2 Role and Mechanisms of Cuproptosis in Spinal Cord Injury

Cuproptosis, a novel copper ion-dependent form of cell death, is of significant interest for elucidating its mechanisms in spinal cord injury (SCI) [27]. Distinct from conventional cell death pathways, the core mechanism of cuproptosis involves the dysregulated expression of copper-transporting proteins, including solute carrier family 31 member 1 (SLC31A1) and copper-transporting P-type ATPase beta (ATP7B), leading to excessive intracellular copper ion accumulation. This accumulation not only disrupts normal cellular physiological functions but also initiates a cascade of pathological events.

In the pathological progression of spinal cord injury (SCI), secondary injury is the main contributor to neurological dysfunction and is characterized by mitochondrial dysfunction, inflammatory responses, and ionic imbalances. Excess copper ions bind to lipoylated components in the tricarboxylic acid (TCA) cycle, thereby causing loss of iron-sulfur (Fe-S) cluster proteins. This process not only impairs mitochondrial function but also induces proteotoxic stress, culminating in cell death. For instance, experimental data demonstrated that in SCI models, SLC31A1 and ATP7B expression was significantly upregulated, accompanied by copper ion accumulation, decreased mitochondrial membrane potential, and increased rates of apoptosis.

Copper ion accumulation has been shown to further exacerbate inflammatory responses. Specifically, copper ions activate microglia, thereby promoting inflammatory cytokine release and exacerbating the local inflammatory milieu in the spinal cord injury region [28]. This inflammatory response not only directly damages neurons but also impairs repair and regeneration of surrounding tissues via downstream signaling cascades.

5.3 Mechanisms Regulating SLC31A1 and ATP7B

SLC31A1 and ATP7B, as key regulatory proteins in copper metabolism, are critical mediators in the mechanism of copper-induced cell death (CuCD) [29]. SLC31A1 (solute carrier family 31 member 1) serves as the primary transporter

for copper ion influx, whereas ATP7B (copper-transporting P-type ATPase beta) mediates copper ion efflux and regulates copper homeostasis within the endoplasmic reticulum. In conditions of copper metabolism disorder, overexpression of SLC31A1 leads to intracellular copper accumulation, and loss of ATP7B function further exacerbates this accumulation, thereby triggering CuCD.

Within the context of the gene regulatory network (GRN), SLC31A1 and ATP7B expression is modulated by various transcription factors and signaling pathways [30]. For instance, the metal response element (MRE) is upregulated in response to elevated copper ion concentrations, thereby increasing SLC31A1 expression, whereas ATP7B expression is regulated by hepatocyte nuclear factor 4α (HNF4α) [31]. Dysregulation of these mechanisms not only disrupts copper metabolic homeostasis but also directly participates in the initiation of cuproptosis.

6. Conclusions

This study investigated in depth the mechanisms by which copper metabolism disorders and the resulting copper-induced cell death influence the progression of spinal cord injury (SCI). By integrating a comprehensive literature review with experimental data analysis, it revealed how dysregulated expression of key copper-transporting proteins, including SLC31A1 and ATP7B, leads to intracellular copper accumulation, thereby compromising the survival and functional integrity of spinal cord neurons. The study demonstrated that copper ion overload disrupts the tricarboxylic acid (TCA) cycle, causes loss of iron-sulfur (Fe-S) cluster proteins, induces proteotoxic stress, and culminates in cell death. This process is closely linked to secondary injury following SCI, including pathological events such as mitochondrial dysfunction, inflammatory responses, and ionic imbalances.

This study established an animal model of copper metabolism disorder to investigate the detrimental effects of copper metabolism disruption on spinal cord injury progression. Experimental results demonstrated that animals in the copper metabolism disorder group displayed pronounced neuronal degeneration and necrosis, demyelination in the white matter, and extensive inflammatory cell infiltration. Behavioral assessments further showed a significant delay in motor function recovery in the copper metabolism disorder group relative to controls. These findings offer critical experimental evidence elucidating the role of copper-induced cell death in spinal cord injury.

This study further elucidated the expression dynamics of SLC31A1 and ATP7B in copper metabolism disorder and their functional consequences via gene functional analysis combined with experimental validation. Experimental results demonstrated that in spinal cord injury models, SLC31A1 expression was significantly upregulated, whereas ATP7B expression was markedly downregulated. This altered expression pattern resulted in intracellular copper accumulation, subsequently inducing copper-induced cell death (CuCD). Further functional assays showed that copper accumulation led lipoylated components in the tricarboxylic acid (TCA) cycle to interact with copper ions, causing the loss of iron-sulfur (Fe-S) cluster proteins. This process triggered proteotoxic stress, culminating in cell death.

Copper metabolism disorder markedly accelerates the pathological progression of spinal cord injury through the facilitation of copper-induced cell death (CuCD). This finding provides a novel perspective for elucidating the mechanisms underlying spinal cord injury and offers a theoretical foundation for the development of future clinical interventions. Modulating the expression of proteins involved in copper ion metabolism may provide novel therapeutic avenues for the management of SCI.

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