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The Aging-Mitochondria-Cuproptosis Axis Promotes Neurodegenerative and Cardiovascular Diseases: Mechanisms and Potential Therapeutic Strategies

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Abstract. As leading global causes of mortality and disability, the incidence of neurodegenerative and cardiovascular diseases rises significantly with advancing age. Neurons and myocardial cells that are terminal - differentiated cells relying on mitochondrial energy supply are quite sensitive to the mitochondrial dysfunction caused by aging.As an emerging regulated form of cell death different from the classical pathway, cuproptosis shows a close connection between mitochondrial metabolism and copper homeostasis imbalance, thus offering a new perspective for understanding the common pathological mechanisms of the two diseases. This article not only systematically expounds the key pathological pathway of "aging-mitochondrial dysfunction-copper homeostasis imbalance-cuproptosis" but also concentrates on analyzing how aging causes the decrease of mitochondrial ATP production, the excessive generation of reactive oxygen species (ROS) and the imbalance of mitochondrial quality control.This article explores how these factors cooperate along with the imbalance of copper homeostasis to prompt cuproptosis, finally leading to irreversible damage to neurons and cardiomyocytes.However, in neurodegenerative diseases, this pathway is in fact closely related to pathological protein aggregation.In the cardiovascular diseases this pathway has been significantly involved in the formation of ischemia-reperfusion injury. The therapeutic strategies targeting this pathway such as copper chelators cuproptosis-related protein inhibitors as well as the promotion of mitochondrial autophagy have already demonstrated great effectiveness in preclinical studies.This common pathological axis is a common one, which not only provides a unified framework for understanding the common pathogenesis of neurodegenerative diseases and cardiovascular diseases, but also generates new directions for the advancement of future combined treatment strategies.

Keywords: aging, mitochondrial dysfunction, cuproptosis, neurodegenerative diseases, cardiovascular diseases.

1. Introduction

Neurodegenerative diseases (such as Parkinson's disease and Alzheimer's disease) and cardiovascular diseases (such as heart failure and myocardial infarction) are the major age-related

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diseases that cause death and disability worldwide. Their incidence rate increases significantly with age [1,2]. According to epidemiological studies, there is an indication that these two types of diseases that often occur together have a common pathological basis behind them [2]. The neurons and myocardial cells damaged by these two diseases have a very high energy requirement, and they especially depend on mitochondrial energy supply to perform normal functions [3]. The dysfunction of mitochondria is not only a typical feature of aging but also a key link related to these two types of diseases [1]. In neurodegenerative diseases the malfunction of mitochondria will make the aggregation of pathological proteins more serious; in cardiovascular diseases it directly brings about the energy crisis of myocardial cells [3,4].

Recent investigations have revealed that beyond mitochondrial dysfunction, the dysregulation of copper ion homeostasis plays a vital driving part in the pathogenesis and development processes of neurodegenerative diseases and cardiovascular diseases [4]. The newly discovered cuproptosis mechanism connects mitochondrial metabolism and copper ion balance at the molecular level, which provides a new perspective for uncovering the common pathological mechanisms of these two types of diseases.Cuproptosis which is mediated by copper ions has a selective effect on the acylated proteins in the tricarboxylic acid (TCA) cycle to exert its cytotoxicity, causing protein aggregation as well as metabolic disorders, and finally leading to programmed cell death [5].

This review, based on the most recent research advancements, intends to systematically expound the core role of the "aging - mitochondrial dysfunction - copper homeostasis imbalance - cuproptosis" axis.It integrates existing evidence to analyze the axis of this molecular mechanism, exploring new therapeutic strategies for this axis, and providing a unified framework to understand the commonalities between neurodegenerative diseases and cardiovascular diseases.

2. The aging-mitochondria-cuproptosis axis: common pathological mechanisms and therapeutic strategies for neurodegenerative and cardiovascular diseases

2.1. Aging-induced mitochondrial dysfunction: a shared pathological hub for neurodegenerative and cardiovascular diseases

Aging leads to the decline of cell function. These processes collectively drive neuronal injury in neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease) and vascular impairment in cardiovascular conditions (e.g., atherosclerosis) via multiple mechanisms, including genomic instability, mitochondrial dysfunction, cellular senescence, and chronic inflammation [1].

For example, the survival of neurons and cardiomyocytes is going to be affected at the same time by mitochondrial dysfunction and oxidative stress, while the senescence - associated secretory phenotype (SASP) will set off chronic inflammation and speed up the development of these two diseases [1].

There are three main manifestations of mitochondrial dysfunction that is caused by aging: (1) the reduction of the mitochondrial energy production.This process stems from the reduced activity of the electron transport chain (ETC) complex and the decreased efficiency of oxidative phosphorylation (OXPHOS), thereby leading to insufficient production of ATP. In neurodegenerative diseases, this is also closely associated with mitochondrial DNA damage and bioenergetic defects as well [6]. (2) Excessive production of reactive oxygen species (ROS). This mechanism is brought about by the electron leakage of the electron transport chain and the weakening of the antioxidant defense system like superoxide dismutase, thereby triggering a series of oxidative stress reactions.This is related to the mitochondrial oxidative stress and metabolic disorders in cardiovascular diseases [6,7].

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(3) The failure of mitochondrial quality control mechanisms. This process involves disorders in the mitochondrial autophagy pathway (such as PINK1 Parkin signal dysregulation) and mitochondrial dynamics imbalance (abnormal expression of fusion/fission proteins), resulting in the buildup of impaired mitochondria and perturbation of protein homeostasis [6].

In neurodegenerative diseases, these mechanisms can cause neuronal energy depletion, synaptic dysfunction, and abnormal protein aggregation (such as Aβ and α-synuclein), accelerating the pathological progression of Parkinson's disease and Alzheimer's disease [6]. In cardiovascular diseases, these mechanisms lead to apoptosis of vascular endothelial cells, increased inflammatory response and formation of atherosclerotic plaque, which promote the progression of hypertension and heart failure [7].

2.2. Aging-induced mitochondrial-lysosomal dysfunction synergy drives the pathological cascade from copper homeostasis imbalance to cuproptosis

In aging and disease states, dysfunction of lysosomes and their mediated cellular quality control systems lead to an imbalance in copper ion homeostasis. The lysosome which is the core organelle in cells for degrading macromolecular substances and maintaining ion balance when its functions get reduced will directly disrupt the regulation pathway of copper ions [8]. During the aging process the stability of lysosomal membranes decreases which causes issues with the function of the hydrogen ion pump (V - ATPase) and then the pH value inside lysosomes goes up. This further suppresses the activity of metal ion chaperones (such as metal chaperones) and the localization and function of metal transporters (like CTR1 and ATP7A/B) eventually resulting in abnormal accumulation of copper ions in the cytoplasm. Meanwhile when lysosomes have problems the mTORC1 signaling pathway that gets activated will suppress the autophagy flow and also decrease the cleaning of damaged proteins and organelles. The abnormal aggregation of copper - binding proteins (such as those like SOD1 and ATOX1) will intensify the situation of chelation failure and also bring about the situation of copper ion toxicity release.Additionally, the dysregulation of mitochondrial - lysosomal crosstalk can result in the excessive production of reactive oxygen species (ROS), which then further impairs the structure and function of copper chaperone proteins under oxidative stress, thus forming a vicious cycle in copper ion metabolism [8].

An excessive accumulation of copper ions and mitochondrial dysfunction can trigger a novel copper-dependent cell death mechanism that is called cuproptosis.Copper ions specifically bind to the acylated sites of key proteins in the tricarboxylic acid cycle (such as FDX1, LIAS and so on), and through direct interactions cause abnormal oligomerization and functional inactivation of these proteins [9]. FDX1, as a key regulatory factor of copper reductase and lipid acylation modification, not only promotes the lipid acylation modification of tricarboxylic acid cycle enzymes such as dihydrolipoamide transacetylase (DLAT) by binding to copper ions, but also triggers large-scale aggregation and precipitation of these enzymes.This process directly disrupts the integrity and the function of the tricarboxylic acid cycle, resulting in a sharp reduction in ATP production, an imbalance of the reducing equivalents in the cells, and finally causing a collapse of the energy metabolism and the termination of the cell life activities [9].Moreover, the above-mentioned abnormal aggregation processes of those proteins can trigger severe protein toxicity stress, thus causing the imbalance of mitochondrial protein homeostasis and the formation of abnormal protein aggregates.These aggregations result in unique types of cell death, and eventually bring about the initiation of the irreversible cell death program [5].

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2.3. Pathological features and mechanistic differences of cuproptosis in neurodegenerative and cardiovascular diseases

In neurodegenerative diseases the abnormal combination of copper ions and the acylated proteins in the mitochondrial tricarboxylic acid cycle leads to cuproptosis.This binding causes these proteins to come together, iron - sulfur cluster proteins to be consumed, and protein toxicity stress to occur, and finally results in cell death [3]. In Alzheimer's disease (AD), the improper copper balance causes the abnormal accumulation of β - amyloid and tau proteins within neurons.Copper ions also strengthen the neuroinflammatory response through oxidative stress, thereby causing the apoptosis and functional loss of neurons.The interaction between cuproptosis brought about by copper overload and mitochondrial dysfunction gives rise to issues in energy metabolism and also causes an increase in oxidative stress.These comprehensive actions that accelerate the neurodegenerative process, which are manifested as cognitive problems and motor function reduction, occur in accordance with [3].

In cardiovascular diseases, cuproptosis, which is a kind of cell death brought about by the imbalance of copper homeostasis, is fairly noticeable in various pathological situations.Within atherosclerosis, stroke, heart failure injury, and ischemia-reperfusion, cuproptosis can activate specific cell death pathways, resulting in myocardial cell loss and also leading to the deterioration of cardiac function, thus promoting disease progression [4]. Cuproptosis is not only related to mitochondrial dysfunction and oxidative stress responses caused by copper ion accumulation, but it may also interact with other cell death mechanisms such as inflammatory pathways, etc., thereby exacerbating tissue damage and cardiac remodeling.Moreover, in the process of getting old, a situation of dysregulation in the mitochondrial quality control mechanism occurs, for example.Please make it clear about the specific content.For example, the impaired mitophagy and the impaired protein degradation may further intensify the pathological effects related to cuproptosis. These accumulated effects will disrupt the quality control of mitochondria in myocardial cells, thus leading to the accumulation of mitochondria with abnormal functions, which are characterized by impaired oxidative phosphorylation, increased production of reactive oxygen species (ROS) and decreased ATP synthesis.These changes, which by intensifying the loss of myocardial cells, promoting myocardial fibrosis and impairing the contractile function, further accelerate the development process of heart failure [4].The pathological mechanisms of cuproptosis in neurodegenerative diseases have both similarities and differences (see Table 1).

Table 1. Differences and similarities of cuproptosis in Neurodegenerative Diseases (NDs) and Cardiovascular Diseases (CVDs)

Compare dimensions	Similarities	Differences	
		Neurodegenerative diseases	Cardiovascular diseases
Core triggers	Mitochondrial dysfunction associated with aging [5], intracellular copper homeostasis imbalance (elevated free copper ion levels) [3, 4], Increased oxidative stress [3, 4]	Pathological protein aggregation (Aβ, tau, αsyn) [3]	Ischemia/reperfusion injury, hemodynamic stress [4]
Consequence of Cuproptosis	Metabolic collapse, protein toxicity stress, key functional cell death [3, 4]	Neuronal loss, cognitive/motor dysfunction [3]	Myocardial remodeling, reduced cardiac contractile function [4]
Mainly affects cell types	Terminal differentiating and highly metabolizing cells	Neurons and astrocytes	Myocardial cells and vascular endothelial cells
Disease progression	Irreversible organ failure	Chronic, progressive (years to decades)	Acute starts or chronic worsening (from several hours to several years)

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2.4. Therapeutic strategies targeting the cuproptosis pathway: from copper homeostasis regulation to mitochondrial function repair

In neurodegenerative and cardiovascular diseases, copper homeostasis imbalance can exacerbate pathological processes, therefore targeting the cuproptosis pathway is a potential therapeutic strategy: (1) application of copper chelators, (2) inhibition of cuproptosis core protein function, (3) improvement of mitochondrial function to achieve upstream regulation

The copper chelator combines with excess copper ions in order to reduce the copper content inside cells, thereby inhibiting the occurrence of cuproptosis.For example, studies indicate that copper chelators such as tetrathiomolybdate or penicillamine can be employed to reduce the toxic accumulation of copper. These copper chelators, which keep copper in balance by regulating genes related to copper metabolism (like ATP7A and ATP7B), show protective effects in models of cancer and cardiovascular diseases [9]. In the neurodegenerative diseases, the copper chelators which have the potential to delay the progression of the diseases by alleviating the copper-induced oxidative stress and mitochondrial damage.

FDX1 which is a key regulatory protein of cuproptosis when excessively activated will cause the aggregation of copper-dependent tricarboxylic acid cycle enzymes.Targeting FDX1 through small - molecule inhibitors or gene silencing techniques can block the copper death pathway [9]. In respect of cardiovascular diseases, intervening in FDX1 may relieve copper - induced toxicity in vascular endothelial cells and smooth muscle cells, thereby enabling the improvement of atherosclerotic and related pathological conditions.

The upstream regulation that is achieved by enhancing mitochondrial function can indirectly suppress copper death.An excessive quantity of copper can cause mitochondrial protein aggregation and functional disorders, therefore the improvement of mitochondrial health status (such as through antioxidants or mitochondrial autophagy inducers) can decrease the toxic effects resulted from copper accumulation. It has been researched that the improvement of mitochondrial metabolism and the reduction of oxidative stress can effectively relieve the cell death triggered by copper.For example, in the models of neurodegenerative diseases, mitochondrial protectants like coenzyme Q10 or NAD+ precursors can also enhance the cell's tolerance as well [10]. This strategy is also effective in the cardiovascular system with the maintenance of intact mitochondria to prevent the copper-related vascular aging process.

Current research shows that copper homeostasis imbalance directly leads to mitochondrial dysfunction and cuproptosis, but existing intervention methods (such as copper chelators) lack tissue specificity and may interfere with physiological copper metabolism [10]. Therefore, in the future, the targeted intervention programs for precisely regulating copper homeostasis and mitochondrial function need to be made more perfect.

At present, in the aspect of clinically evaluating the progression or treatment effect of copper death-related diseases, there is still a lack of specific biomarkers.In the future, what one has to do is to explore those biomarkers which can be used for early diagnosis and monitoring of treatment response. Besides, it is necessary to promote the cooperation among basic science, pharmacology and clinical medicine in order to develop and verify the drugs which can treat both neurodegenerative diseases and cardiovascular diseases.

3. Conclusion

The pathological pathway of "aging - mitochondrial dysfunction - copper homeostasis imbalance - cuproptosis" has brought about a significant breakthrough in understanding the common

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pathological mechanisms of neurodegenerative diseases and cardiovascular diseases.Cuproptosis connects the seemingly different categories of neurodegenerative diseases and cardiovascular diseases through the common molecular pathway of mitochondrial damage and copper homeostasis imbalance, thus providing a unified explanation for the common comorbidities in clinical practice. It has opened up new perspectives for interpreting the internal connections among the age-related systemic diseases.This review shows that scholars should adopt an overall research approach that goes beyond the boundaries of traditional diseases.Through interdisciplinary cooperation, this approach can come up with the complicated interaction mechanisms among the aging, metal homeostasis and cell death.

In the domain of treatment, targeting the cuproptosis pathway has indeed brought about a quite significant paradigm shift.Through the regulation of the copper-related mechanism it is expected that the new intervention methods can simultaneously alter the progression of neurodegenerative diseases and cardiovascular diseases. However to apply these research findings to clinical practice it is necessary to rely on the strict verification of the mechanism research and the carefully designed clinical trials to ensure the effectiveness and safety. This highlights the necessity of combining basic research insights with the strictness of clinical transformation.

In the days to come, the research work ought to center on enhancing the targeted intervention programs so that the copper homeostasis and mitochondrial function can be precisely regulated.An in - depth dissection of the mechanisms of cuproptosis at the molecular and cellular levels is carried out with the aim of finding biomarkers for early diagnosis and monitoring of treatment response, promoting interdisciplinary drug research and development as well as clinical translation, striving to create a collaborative framework connecting laboratory findings and clinical applications, and also making efforts to redefine the treatment landscape of age - related comorbidities through innovative biological insights.

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