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Role of Ferroptosis in Brain Disease

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Abstract

Ferroptosis, a recently identified form of regulated cell death characterized by iron-dependent lipid peroxidation, has emerged as a critical player in the pathophysiology of various brain diseases. In neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, dysregulation of iron homeostasis and increased oxidative stress contribute to neuronal damage and cell death. Ferroptosis-related markers have been identified in post-mortem brains of individuals with these conditions, suggesting a potential involvement of ferroptosis in the progression of these diseases. Additionally, ischemic stroke and Traumatic Brain Injury (TBI) are associated with a surge in oxidative stress, leading to lipid peroxidation and neuronal death. Ferroptosis has been implicated as a mediator of secondary brain injury in these cases, presenting a novel target for therapeutic intervention. This abstract provides a comprehensive overview of the action of ferroptosis in brain disorders, highlighting its molecular mechanisms, key regulators, and potential therapeutic implications.

Keywords: Lipid peroxidation; Neurodegenerative diseases; Ischemic stroke; Traumatic brain injury

Introduction

Ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation, has emerged as a distinctive and consequential player in the landscape of brain diseases. Unlike classical forms of cell death such as apoptosis or necrosis, ferroptosis is driven by the relentless accumulation of lipid peroxides within cellular membranes. The brain, with its intricate and delicate architecture, is particularly susceptible to oxidative stress, making the study of ferroptosis in neurological contexts a matter of critical importance. With an increasing body of evidence linking ferroptosis to neurodegenerative disorders, ischemic events, traumatic injuries, and even psychiatric conditions, unravelling the molecular intricacies of this unique cell death pathway promises to offer novel insights into the pathogenesis of diverse neurological ailments. As researchers delve into the complexities of ferroptosis in the brain, the potential for targeted therapeutic interventions is becoming increasingly apparent, holding promise for a paradigm shift in the management of these debilitating disorders. This introduction sets the stage for an in-depth exploration of ferroptosis in brain diseases, emphasizing its significance and potential as a focal point for future research and therapeutic development.

Role of ferroptosis in brain degeneration

The role of ferroptosis in brain degeneration has garnered significant attention in recent years, as researchers uncover the intricate interplay between oxidative stress, lipid peroxidation, and neurodegenerative disorders. Here, we explore the pivotal involvement of ferroptosis in brain degeneration, focusing on its mechanisms and contributions to conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) [1,2].

Accumulation of lipid peroxidation in neurodegenerative diseases

Ferroptosis is characterized by the iron-dependent accumulation of lipid peroxides within cellular membranes. In the context of brain degeneration, this phenomenon is particularly pronounced. Studies have identified elevated levels of lipid peroxidation markers in the brains of individuals with neurodegenerative disorders, suggesting a connection between ferroptosis and the pathological processes underlying these conditions [3].

Dysregulation of iron homeostasis

Iron, a key player in ferroptosis, is tightly regulated in healthy cells. However, in neurodegenerative diseases, disrupted iron homeostasis has been observed. Excessive iron levels contribute to the initiation of ferroptotic cascades by promoting the Fenton reaction, generating Reactive Oxygen Species (ROS) and triggering lipid peroxidation [4,5].

Altered glutathione metabolism

Glutathione, a crucial antioxidant, plays a protective role against ferroptosis by scavenging lipid peroxides. In brain degeneration, alterations in glutathione metabolism have been reported, compromising the cellular defense mechanisms against oxidative stress and rendering neurons more susceptible to ferroptotic damage [6]. Understanding the role of ferroptosis in brain degeneration provides a novel perspective on the common pathways that contribute to neuronal loss across diverse neurodegenerative diseases. Targeting ferroptosis may offer innovative therapeutic strategies to mitigate the progression of these debilitating conditions, presenting a new frontier in the quest for effective treatments for brain degeneration [7,8].

Mechanism of ferroptosis in brain degeneration

The mechanism of ferroptosis in brain degeneration involves a complex interplay of biochemical processes that ultimately lead to iron-dependent lipid peroxidation and subsequent cell death. While the exact mechanisms may vary between different neurodegenerative diseases, there are common underlying pathways associated with ferroptosis in the context of brain degeneration. Here, we outline the key molecular events involved in the mechanism of ferroptosis in the brain:

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Iron accumulation: Dysregulation of iron homeostasis is a central event in ferroptosis. In brain degeneration, an abnormal buildup of iron occurs, potentially triggered by factors such as oxidative stress, inflammation, or genetic mutations. The excess iron becomes a catalyst for the Fenton reaction, leading to the generation of highly reactive and toxic hydroxyl radicals (•OH) [9].

Fenton reaction and Reactive Oxygen Species (ROS) generation: The Fenton reaction involves the reaction between iron and Hydrogen Peroxide (H2O2), resulting in the formation of hydroxyl radicals. These ROS contribute to oxidative stress, damaging cellular components such as lipids, proteins, and DNA. In ferroptosis, the primary focus is on lipid peroxidation, a process initiated by ROS attacking polyunsaturated fatty acids in the cell membrane [9].

Lipid peroxidation: Polyunsaturated Fatty Acids (PUFAs) in the cell membrane are particularly vulnerable to attack by ROS. In ferroptosis, lipid peroxides are formed as a result of the oxidation of PUFAs. These lipid peroxides disrupt the integrity of the lipid bilayer, leading to membrane destabilization and functional impairment [10].

Glutathione depletion: Glutathione, a critical antioxidant, plays a crucial role in protecting cells from oxidative damage. In ferroptosis, there is a depletion of cellular glutathione levels. Reduced glutathione is responsible for scavenging lipid peroxides, and its diminished availability contributes to the accumulation of lipid peroxides in the cell membrane [10].

Conclusion

In conclusion, the intricate interplay of iron-dependent lipid peroxidation, oxidative stress, and cell death, collectively known as ferroptosis, has emerged as a critical mechanism in the pathogenesis of neurodegenerative disorders. The extensive body of research exploring ferroptosis in the context of neurodegeneration, including Alzheimer's disease, Parkinson's disease, and Huntington's disease, underscores its significant contribution to the progressive loss of neurons observed in these debilitating conditions. The dysregulation of iron homeostasis, the Fenton reaction-mediated generation of reactive oxygen species, and the subsequent lipid peroxidation form a cascade of events that compromise cellular integrity, particularly in the vulnerable environment of the brain. Glutathione depletion and inactivation of the protective enzyme GPX4 further amplify the susceptibility of neurons to ferroptosis cell death. Mitochondrial dysfunction adds another layer to the complexity, linking ferroptosis to broader cellular processes. In summary, the burgeoning field of ferroptosis in neurodegeneration not only deepens our understanding of the molecular mechanisms underpinning these diseases but also opens new avenues for therapeutic development. As research progresses, unraveling the complexities of ferroptosis in the brain may pave the way for innovative and targeted treatments, offering hope for slowing or halting the progression of neurodegenerative disorders.

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