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Review

Harnessing Mitophagy for Therapeutic Advances in Aging and Chronic Neurodegenerative Diseases

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Abstract: Introduction: Mitophagy, the selective degradation of damaged mitochondria, is essential for maintaining cellular health and function, particularly in high-energy demanding post-mitotic cells like neurons and in microglial cells. Aging results in impaired mitophagy, leading to mitochondrial dysfunction, oxidative stress, the release of damage-associated proteins (DAMPs), and neuroinflammation, which contribute to neurodegenerative diseases such as Alzheimer's and Parkinson's. Mitochondrial dysfunction also contributes to the pathophysiology of depression by affecting synaptic plasticity, increasing neuroinflammation, and heightening oxidative stress. **Aim:** In this review, we summarize the recent developments on mechanisms of mitophagy, its therapeutic role in neuroprotection, and its implications in aging and neuroinflammation, complemented by future research requirements and implications. **Result/Discussion:** Therapeutic strategies that promote mitochondrial health, including enhancing mitophagy and mitochondrial biogenesis, show promise in treating neurodegenerative diseases and depression. Recent findings have emphasized therapeutic strategies to modulate mitophagy, such as pharmacological agents like urolithin A and rapamycin, genetic interventions such as PINK1/Parkin gene therapy, mitochondrial transplantation, and lifestyle and dietary interventions such as caloric restriction, exercise, and dietary supplements such as resveratrol and CoQ10. Key regulators of mitophagy, including the PINK1/Parkin pathway and various proteins like BNIP3, NIX, and FUNDC1, which facilitate the removal of damaged mitochondria, play a crucial role. **Conclusions:** These results highlight the importance of understanding the interplay between mitophagy and neuroinflammation and show that modulation of mitophagy can reduce oxidative stress and improve neuroinflammatory outcomes and depression in age-related neurodegenerative diseases. However, despite significant progress, challenges remain in understanding the underlying molecular mechanisms of mitophagy and its therapeutic regulation in aging disorders.

Keywords: mitophagy; neuroinflammation; oxidative stress; depression; aging; neurodegeneration

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1. Introduction

Mitophagy, the process by which cells selectively degrade damaged or superfluous mitochondria through autophagy, is essential for maintaining mitochondrial quality control. It plays a crucial role in preserving cellular health by eliminating dysfunctional mitochondria, which helps sustain cellular metabolism, reduce oxidative stress, and prevent apoptosis. This is especially important in post-mitotic cells like neurons [1,2].

As organisms age, they experience a gradual decline in cellular function and an increased susceptibility to stress and inflammation. Mitochondrial dysfunction is both a cause and an effect of aging, and it contributes to various age-related diseases, including neurodegenerative disorders like Alzheimer's, Parkinson's, and Huntington's disease, and multiple sclerosis [3]. In neurons, impaired mitophagy leads to the accumulation of damaged mitochondria, causing cellular dysfunction and toxicity. This is particularly