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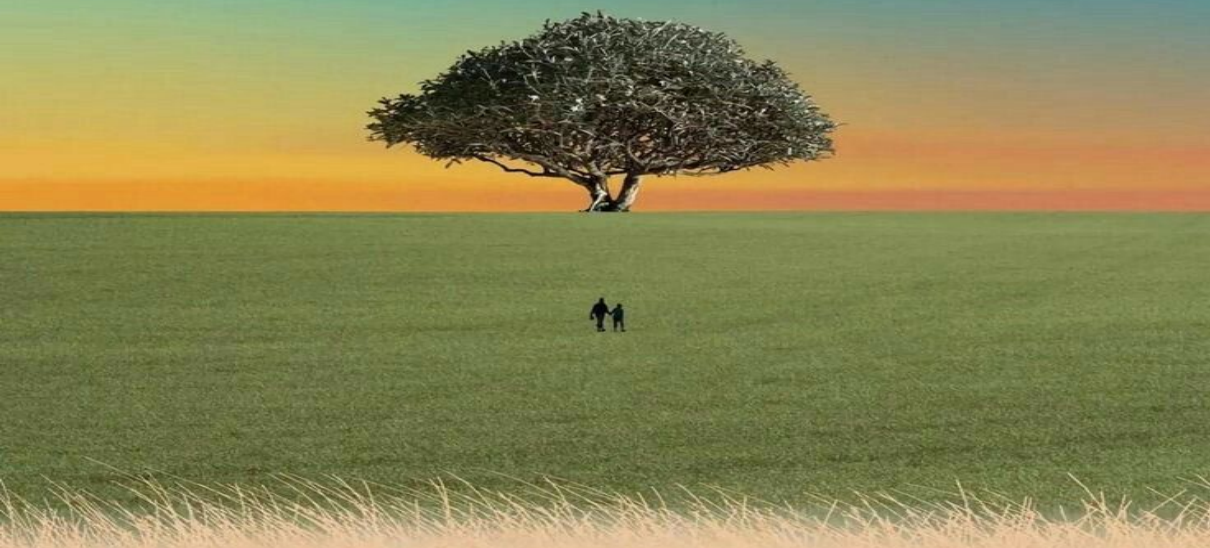

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İÇİNDEKİLER

MITOPHAGY MECHANISM AND ITS RELATIONSHIP WITH DISEASES

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1. INTRODUCTION

Mitochondria, essential organelles that serve as the cellular energy centers in all eukaryotic cells, are responsible for aerobic respiration and the production of adenosine triphosphate (ATP) through oxidative phosphorylation (Nunnari & Suomalainen, 2012; Özsan, 2023). In addition to being the primary organelles for reactive oxygen species (ROS) production during the electron transport chain, mitochondria are also exposed to oxidative stress under conditions of structural and functional impairment (Özsan, 2023; Wong & Holzbaur, 2014).

Mitophagy functions as a specific and selective type of autophagy. It involves the transport and degradation of damaged cytotoxic mitochondria into lysosomes via a selective autophagic mechanism. At the same time, it preserves mitochondrial structural and functional integrity as well as intracellular homeostasis by maintaining the balance of mitochondrial quality and quantity necessary for normal cell physiology and tissue development (Bravo-San Pedro et al., 2017). This process plays a critical role in maintaining

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mitochondrial homeostasis, ensuring cellular health, and regulating various physiological processes. Mitophagy is activated by stressors such as nutrient deficiency, hypoxia, DNA damage, inflammation, and mitochondrial membrane depolarization that disrupt mitochondrial homeostasis. However, the failure to eliminate defective mitochondria and the suppression of the mitophagy mechanism may lead to increased ROS production, inflammation, and apoptosis, resulting in a wide range of pathological outcomes such as diabetes mellitus, neurodegenerative diseases, and cancer. Recent studies have shown that impaired mitophagy is a significant factor in the pathogenesis of many human diseases, including neurodegenerative disorders, cancer, cardiovascular diseases, and metabolic disorders (Palikaras et al., 2017).

This review aims to provide a general overview of the regulatory effects of mitophagy-associated factors and proteins, focusing on their roles in cellular homeostasis, physiological function, and disease development.

2. MITOCHONDRIAL DYNAMICS

Fusion and fission are fundamental processes that govern mitochondrial dynamics, ensuring proper mitochondrial shape, distribution, and function. These dynamic events are controlled by guanosine triphosphatases (GTPases), particularly those belonging to the dynamin superfamily. Dynamin-related protein 1 (DRP1) is a cytosolic GTPase that translocates to mitochondria to facilitate fission. In contrast, the mitofusin proteins MFN1 and MFN2 are crucial mediators of outer mitochondrial membrane fusion. OPA1, another GTPase situated within the inner mitochondrial membrane and intermembrane space, is essential for modulating both the fusion and fission of the inner membrane. Notably, mutations in OPA1,

along with heightened cellular vulnerability to apoptosis, have been associated with the development of optic atrophy (Cipolat et al., 2004; Ferguson & De Camilli, 2012; Youle & Van Der Bliek, 2012).

Healthy mitochondria contribute to the exchange of genetic material and the preservation of mitochondrial morphology and function through the fusion and fission mechanisms involved in mitochondrial dynamics. The dynamics of mitochondrial fusion and fission are regulated by DRP1, MFN1, MFN2, and OPA1 proteins. Mitochondrial fission contributes to mitochondrial apoptosis and is necessary for the initiation of mitophagy, whereas mitochondrial fusion has an enhancing effect on mitochondrial metabolism. Under cellular stress, damaged mitochondria undergo fission from the mitochondrial network or are isolated due to DRP1 activation or mitochondrial membrane potential dysfunction in the autophagy system (Montava-Garriga & Ganley, 2020). As a result of mitochondrial imbalance, fusion and fission processes are disrupted, and the mitophagy mechanism is activated to degrade fragmented mitochondria (Shirihai et al., 2015). Consequently, the isolated mitochondria can be cleared through different mitophagy pathways involving both ubiquitin-dependent and ubiquitin-independent mitophagy receptors.

3. MITOPHAGY MECHANISM

The most prominent mechanism of mitochondrial turnover is autophagy. Defined in Greek as “self-eating,” autophagy is a catabolic process that allows eukaryotic cells to degrade cytoplasmic components, recover vital metabolites, and protect against toxicity caused by damaged organelles or harmful aggregates. Three main types of autophagy have been

identified in eukaryotic cells: macroautophagy, chaperone-mediated autophagy, and microautophagy (Boya et al., 2013).

One of the macroautophagy subtypes, mitochondrial autophagy (mitophagy), was first described by Lemasters in 2005 as a selective intracellular degradation mechanism targeting dysfunctional mitochondria. Mitophagy plays an important role in maintaining the homeostasis of the intracellular mitochondrial quality control system and regulating mitochondrial energy metabolism (Ajoolabady et al., 2022). Cells support mitophagy mechanisms through various stimuli and signaling cascades with the help of numerous regulators. In the regulation of mitophagy, both ubiquitin-dependent and ubiquitin-independent pathways operate (Khaminets et al., 2016).

3.1. Ubiquitin-Dependent Pathways

3.1.1. PINK1-Parkin Mediated Mitophagy

The ubiquitin-dependent pathway supports complex processes involving proteins anchored to the mitochondrial surface in order to promote mitophagy. The PTEN-induced putative kinase 1 (PINK1)-Parkin pathway acts as a sensor that detects cellular stress and removes damaged mitochondria, serving as a key regulator of ubiquitin-dependent mitophagy (Sekine & Youle, 2018).

Under normal physiological conditions, PINK1 is imported from the cytosol into the inner mitochondrial membrane by interacting with the translocase complex located on the outer mitochondrial membrane. Within the intermembrane space, it undergoes proteolytic cleavage by the presenilin-associated rhomboid-like protease (PARL), after which the truncated PINK1 is released back into the cytosol and targeted for degradation via the ubiquitin-proteasome system (UPS) (Vives-Bauza et al., 2010; Yamano & Youle, 2013). In

contrast, when mitochondria experience depolarization and lose their membrane potential, this import and cleavage process is disrupted. Consequently, PINK1 accumulates on the outer mitochondrial membrane instead of reaching the inner membrane. This accumulation acts as a signal, recruiting the cytosolic E3 ubiquitin ligase Parkin to the mitochondria in a PINK1-dependent manner (Fiesel et al., 2023). These sequential molecular events facilitate the delivery of dysfunctional mitochondria to autophagosomes, where they are subsequently degraded in autolysosomes, thereby concluding the mitophagy process (Uoselis et al., 2023).The PINK1–Parkin pathway mediates mitochondrial quality control mechanisms such as mitochondrial-derived vesicles and mitochondrial dynamics to maintain energy homeostasis. PINK1 indirectly stimulates dynamin-related protein 1 (DRP1) activation, inducing the fission of damaged Mitochondria (Pryde et al., 2016). On the other hand, Parkin-dependent degradation of abnormal and misfolded mitofusins (MFNs) disrupts mitochondrial fusion, thereby isolating defective organelles from the healthy mitochondrial network and preserving mitochondrial homeostasis (Tanaka et al., 2010). Additionally, PINK1 phosphorylates MFN2 and triggers mitochondrial separation, promoting the removal of damaged organelles in cooperation with Parkin (Y. Chen & Dorn, 2013).

3.2. Ubiquitin-Independent Pathways

Mitophagy is induced by various cellular stress signals and structural changes. Dysfunction of mitochondrial membrane potential is a strong stimulus for mitophagy (Elmore et al., 2001). Unlike the PINK1/Parkin pathway, mitophagy receptors primarily contribute to the remodeling of the mitochondrial network in response to peripheral stress, cellular reprogramming, or differentiation (J. Zhang & Ney, 2009).

Ubiquitin-independent mitophagy is primarily regulated by two major classes of receptors that facilitate mitochondrial clearance under both normal and stress conditions. One group comprises BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and its homolog NIX, while the other includes FUN14 domain-containing protein 1 (FUNDC1). NIX, an outer mitochondrial membrane protein, plays a pivotal role in the targeted elimination of dysfunctional mitochondria, particularly during the maturation of reticulocytes when mitochondria are removed from developing erythrocytes (Church & Margolis, 2024). Both BNIP3 and NIX are known to enhance mitophagy in response to hypoxic conditions through the stabilization of hypoxia-inducible factor-1α (HIF-1α), which promotes mitochondrial turnover (Jung et al., 2019). Under hypoxic stress, BNIP3 expression increases and localizes to the outer mitochondrial membrane via its C-terminal transmembrane domain. Mutations in BNIP3 that impair its ability to homodimerize—without affecting mitochondrial targeting—lead to mitophagy dysfunction, highlighting its essential role as an initiator of mitochondrial degradation (Hanna et al., 2012; Zhu et al., 2013). As with other mitophagy receptors, BNIP3 harbors an LC3-interacting region (LIR) motif in its N-terminal segment. This motif enables direct binding to LC3, independent of ubiquitin tagging, thus allowing the damaged mitochondria to be sequestered into autophagosomes for selective degradation via the autophagic pathway (Bai et al., 2023).

FUNDC1, another outer mitochondrial membrane protein, functions as a receptor for hypoxia-related mitophagy (Liu et al., 2012). Like BNIP3, FUNDC1 supports mitochondrial fission in response to stress by recruiting DRP1 to mitochondria (Chen et al., 2016; Landes et al., 2010).

4. THE EFFECT OF MITOPHAGY ON DİSEASES

4.1. Metabolic Diseases

Chronic hyperglycemia and insulin resistance, which are among the major symptoms of type 2 diabetes mellitus (T2DM), are associated with mitochondrial damage (Özsan & Ceylan, 2023). High glucose concentrations lead to mitochondrial dysfunction by increasing oxidative stress, which results in elevated mitochondrial ROS production and tissue damage (Rovira-Llopis et al., 2017). Therefore, the preservation of mitochondrial quality through mitophagy is vital for preventing disease progression.

Persistently high glucose levels promote mitochondrial fission, which ensures mitochondrial dynamics, while decreasing mitochondrial fusion due to DRP1 recruitment and impairment of OPA1/MFN function (Rovira-Llopis et al., 2017). Compared to healthy controls, mitophagy flux is reported to be impaired in T2DM patients, whose mitochondria are smaller in size (Bhansali et al., 2017). Expressions of mitophagy-related proteins, including NIX, PINK1, and Parkin, have been shown to increase in prediabetic individuals with mild hyperglycemia but decrease in patients with T2DM (Scheele et al., 2007). Thus, elevated ROS levels associated with T2DM may contribute to the suppression of mitophagy and the accumulation of dysfunctional mitochondria.

Obesity, which significantly increases the risk of developing T2DM, shares several common mechanisms involving mitophagy. In obesity, mitochondrial quality in adipose tissue is impaired, and disruption of the balance between mitochondrial fission and fusion leads to mitochondrial damage, resulting in a reduced mitophagic response (Greene et al., 2015).

4.2. Cardiovascular Diseases

The heart muscle is a vital organ that primarily generates adenosine triphosphate (ATP) through oxidative phosphorylation. Mitochondria occupy approximately 30% of the cardiac muscle volume and produce about 6 kg of ATP daily to support the pumping power of the heart. This high demand of the heart is directly associated with the function of myocardial cells and mitochondrial quality control (Han et al., 2017; Sciarretta et al., 2018). Dysfunctional mitophagy correlates strongly with mitochondrial damage and reactive oxygen species (ROS) formation, both of which contribute to the pathogenesis of cardiovascular diseases (Lu et al., 2023). Dysfunctional mitochondria produce less ATP and excessive ROS. Increased sensitivity of cardiac muscle to oxidative stress and excessive ROS accumulation can lead to chronic damage processes such as increased ischemia/reperfusion injury (IRI), heart failure, apoptosis, and fibrosis, ultimately resulting in cardiac dysfunction and cardiomyocyte death (Whelan et al., 2010).

Studies have shown that dysfunctional mitophagy in cardiac tissue is associated with increased susceptibility to stress and the development of heart failure. Parkin expression in the heart increases rapidly in response to mitochondrial damage, suggesting an adaptive response of the heart to cellular stress. In experimental mice deficient in Parkin, an accumulation of dysfunctional mitochondria, increased ventricular remodeling, and progression to heart failure were observed after myocardial infarction (Han et al., 2017; Ikeda et al., 2015; Kubli et al., 2013). Indeed, alterations in mitophagy regulators in mouse models result in various forms of cardiac dysfunction. Furthermore, mice deficient in PINK1, BNIP3, NIX, and ATG5 develop various cardiac defects, including cardiomyopathy, cardiac hypertrophy, and accumulation of dysfunctional Mitochondria (Billia et al., 2011; Dorn, 2010).

4.3. Neurodegenerative Diseases

Mitophagy, a mitochondrial quality control process, regulates mitochondrial function to preserve neuronal health (Dias et al., 2013; Rugarli & Langer, 2012). Mitochondrial damage and impaired mitophagy play key roles in the pathogenesis of many neurodegenerative diseases, including Parkinson's and Alzheimer's diseases (Özsan et al., 2025).

Parkinson's disease is a common neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of mutated α-synuclein aggregates (Dauer William & Przedborski Serge, 2003; Kısadere et al., 2021). PINK1 is highly expressed in organs and tissues with high energy demand, including the brain, heart, and muscles (Suen et al., 2010). Loss of PINK1 or Parkin activity impairs mitophagy by reducing the recruitment of ubiquitin-binding proteins and promoting excessive mitochondrial fusion through accumulation of MFN1 and MFN2 (Burté et al., 2015). Mutations in PINK1 and Parkin are involved in the pathogenesis of Parkinson's disease and suppress the formation of mitophagy (Pickrell & Youle, 2015).

Alzheimer's disease is an age-related neurodegenerative disorder characterized by neuronal cell death in the cerebral cortex, leading to severe memory loss and cognitive decline (Kısadere et al., 2019; Özsan et al., 2025). Accumulation of damaged mitochondria, synaptic degeneration, amyloid-β oligomers derived from amyloid precursor protein, and intracellular neurofibrillary tangles are all implicated in the pathogenesis of Alzheimer's disease (Cen et al., 2021). In Alzheimer's disease, the levels of DRP1 involved in mitochondrial fission and OPA1 involved in mitochondrial fusion are reported to be decreased. These changes lead to neuronal abnormalities, mitochondrial dysfunction, and

excessive accumulation of amyloid-β, ultimately suppressing mitophagy and resulting in neuronal death (Li et al., 2016; Song et al., 2021).

4.4. Cancer

Cancer adversely affects human health through the abnormal proliferation and differentiation of local tissue cells caused by various factors that lead to genetic damage and tumor formation (Panigrahi et al., 2020a).

Mitophagy is a key regulator in determining whether a cell survives or undergoes programmed death. While its excessive activation may result in mitochondrial depletion, leading to inadequate ATP production and eventual cell demise, a balanced mitophagic response is crucial for maintaining intracellular homeostasis and promoting cell viability. In the context of malignant neoplasms, mitophagy has been shown to contribute to the dysregulated growth and persistence of cancer cells, functioning in a dual capacity as both a promoter of tumorigenesis and a potential tumor suppressor (Chang et al., 2017a). The interplay between these opposing roles is pivotal in influencing whether a tumor progresses or regresses through apoptotic mechanisms.

Mitophagy appears to be functionally important in tumor suppression through the removal of damaged mitochondria that may contribute to carcinogenesis (Vara-Perez et al., 2019). Lauren et al. (2017) reported that mitophagy inhibits tumor growth by eliminating damaged mitochondria; otherwise, dysfunctional mitochondria alter cell structure and may directly or indirectly trigger tumor formation (Drake et al., 2017). Accordingly, different levels of mitophagy have been observed in various cancers, including rectal, lung, and breast cancer, compared to normal conditions (Ferro et al., 2020).

Although cell proliferation is associated with metabolic reprogramming that inhibits oxidative phosphorylation and enhances glycolytic flux, cancer cells typically exhibit decreased oxidative phosphorylation and increased glycolysis. During cancer progression, some cancer cells shift mitochondrial aerobic respiration to glycolysis to meet their energy demands—a phenomenon known as the Warburg effect. The Warburg effect is characterized by abnormal mitochondrial quality control, increased ROS production, altered redox regulation, and deficient apoptotic signaling (Panigrahi et al., 2020b). In the mitophagy process, Parkin suppresses the Warburg effect by enhancing oxidative metabolism (Zhang et al., 2011). Therefore, Parkin can be considered to exhibit tumor-suppressive activity.

The PINK1/Parkin pathway serves as a central mediator of mitophagy. Parkin dysfunction can lead to mitophagy inhibition and promote carcinogenesis in various cancer types. Mutations in these two proteins have been detected in numerous tumors, including lung cancer, ovarian cancer, glioblastoma/glioma, colorectal cancer, and breast cancer (Chang et al., 2017b). Inhibition of mitophagy during cancer development can significantly impair the function of cellular systems (cells, tissues, organs) and lead to increased ROS levels (Fujiwara et al., 2008; Youle & Narendra, 2011). Indeed, elevated ROS can cause DNA damage and promote gene expression dysfunction, ultimately contributing to cancer progression (Um & Yun, 2017).

When exposed to hypoxia or cellular stress, mitochondria undergo a decline in membrane potential, initiating the autophagic clearance of dysfunctional organelles. This depolarization mechanism plays a significant role in shaping the malignant characteristics of tumor cells (Ferro et al., 2020; Panigrahi et al., 2020c). In this context, the outer mitochondrial membrane proteins BNIP3 and its paralog NIX

act as pivotal regulators of mitophagy activation under hypoxic conditions. Hypoxia-inducible factor 1 (HIF-1) enhances the expression of both NIX and BNIP3 in tumor environments, and NIX-driven mitophagy has been implicated in the progression of glioblastoma (Sowter et al., 2001). Notably, suppression of the NIX receptor disrupts the survival of cancer stem cells by promoting reactive oxygen species (ROS) clearance and triggering apoptosis in tumor populations (Jung et al., 2019).

5. CONCLUSION

The multifaceted role of mitochondria in cellular energy production, metabolic regulation, and redox balance has attracted increasing scientific interest, particularly in the context of how these functions intersect with the maintenance of cellular homeostasis and the regulation of mitophagy under pathological conditions. The recognition and degradation of damaged mitochondria through autophagosomes are achieved via the coordinated action of various mitophagic mechanisms. Mitophagy is a homeostatic process that plays a critical role in both the preservation of cellular health and the pathogenesis of numerous diseases. Functional impairments in different mitophagy pathways directly contribute to the onset and progression of various disorders. Therefore, comprehensive research is required to understand how diseases are influenced by mitophagy and to identify potential mitophagy-regulating factors that play a central role in these processes.

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