The Strength in Breakdown: Understanding Mitophagy and Its Implications in Cardiovascular Diseases

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Abstract

Mitophagy, the selective autophagy of mitochondria, plays a crucial role in maintaining cellular homeostasis by ensuring the quality and quantity of functional mitochondria. This process is essential for cellular health, as dysfunctional mitochondria can lead to severe pathological conditions, including cardiovascular disorders, cancer, and neurodegenerative diseases. Impaired mitophagy may result in abnormal mitochondrial morphology and DNA mutations, contributing to the progression of these ailments. Therefore, understanding the mechanisms regulating mitophagy and its implications in pathological contexts is of great importance. This review paper provides an in-depth exploration of the mechanisms of mitophagy and its role in maintaining mitochondrial quality. It summarizes the most recent findings in the field, particularly focusing on the implications of defective mitophagy in cardiovascular disorders. The study delves into the connections between impaired mitophagy and the development of atherosclerosis, ischemic heart disease, cardiomyopathies, hypertension, and peripheral vascular disease. Moreover, it discusses the various regulatory proteins and processes involved in mitophagy, presenting a comprehensive overview of the intricate network governing this crucial cellular process. By shedding light on the intricate mechanisms involved in mitophagy and its role in addressing cardiovascular disorders, this review paper paves the way for potential therapeutic targets aimed at mitigating mitochondrial dysfunction-related ailments. The identification of pathways and proteins associated with mitophagy provides valuable insights into potential interventions that could prevent or effectively treat these disorders. However, it also highlights the existing uncertainties and the need for further in-depth exploration to fully comprehend the complexity of mitophagy regulation and its broader implications in cellular health.

Keywords: mitophagy; mitochondria; atherosclerosis; CVD.

Significance | Understanding mitophagy's role in cardiovascular health offers potential therapeutic insights for related disorders.

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Editor Md Shamsuddin Sultan Khan, And accepted by the Editorial Board July 17, 2024 (received for review May 10, 2024)

Introduction

Mitophagy, a vital cellular process responsible for the selective degradation of dysfunctional or damaged mitochondria, plays a crucial role in maintaining mitochondrial quality and cellular homeostasis. The intricate balance between mitochondrial biogenesis and mitophagy is essential for ensuring the optimal functioning of these organelles, which are often referred to as the

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Please cite this article.
Anastasia V. Poznyak, Alexey V. Churov et al. (2024). The Strength in Breakdown: Understanding Mitophagy and Its Implications in Cardiovascular Diseases, Journal of Angiotherapy, 8(7), 1-14, 9718

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powerhouse of the cell due to their pivotal role in energy production, metabolic regulation, and cell survival.

Mitochondria are dynamic organelles with a high turnover rate, constantly undergoing fusion, fission, and turnover processes to maintain their functionality and integrity. When mitochondria become impaired due to various stressors such as oxidative damage, mitochondrial DNA mutations, or metabolic dysfunction, they can pose a threat to cellular health by generating excessive reactive oxygen species (ROS) and compromising energy production. To prevent the accumulation of dysfunctional mitochondria and mitigate the associated cellular damage, cells rely on mitophagy as a quality control mechanism to selectively remove damaged organelles while preserving the functional mitochondrial pool.

The dysregulation of mitophagy has been implicated in a wide range of pathological conditions, including neurodegenerative diseases, metabolic disorders, cancer, and cardiovascular diseases. Among these, cardiovascular disorders stand out as a major global health burden, contributing significantly to morbidity and mortality worldwide. The heart is a highly energy-demanding organ that relies heavily on mitochondrial function to meet its energy requirements for contraction and relaxation. Therefore, any disruption in mitochondrial quality control mechanisms, such as impaired mitophagy, can have deleterious effects on cardiac function and contribute to the development of various cardiovascular pathologies.

Studies have shown that dysregulated mitophagy is associated with the progression of heart failure, ischemic heart disease, cardiomyopathies, and other cardiovascular disorders. In the context of heart failure, impaired mitophagy can lead to the accumulation of damaged mitochondria, exacerbating oxidative stress, energy depletion, and myocardial dysfunction. Furthermore, in ischemic heart disease, where inadequate blood supply to the heart muscle results in tissue damage and impaired mitochondrial function, enhancing mitophagy has emerged as a promising therapeutic approach to limit cardiac injury and improve outcomes.

The implications of mitophagy in cardiovascular disorders extend beyond the realm of energy metabolism to encompass other critical processes such as apoptosis, inflammation, and oxidative stress. Mitochondria play a central role in regulating cell death pathways, and dysfunctional mitochondria can release pro-apoptotic factors that contribute to myocardial damage in conditions such as myocardial infarction and heart failure. By selectively removing damaged mitochondria through mitophagy, cells can mitigate apoptotic signaling and preserve cardiac function in the face of cellular stress.

Moreover, mitophagy has been linked to the modulation of inflammatory responses in the cardiovascular system, with dysfunctional mitochondria serving as a source of pro-inflammatory signals that exacerbate vascular inflammation and atherosclerosis. By promoting the clearance of damaged mitochondria through mitophagy, cells can attenuate inflammatory cascades and protect against the development of atherosclerotic plaques and vascular dysfunction.

In addition to its roles in apoptosis and inflammation, mitophagy plays a critical role in regulating oxidative stress levels in the cardiovascular system. Mitochondria are a major source of ROS production, and the accumulation of damaged mitochondria can lead to increased oxidative stress, DNA damage, and lipid peroxidation in cardiac cells. By eliminating dysfunctional mitochondria through mitophagy, cells can maintain redox homeostasis, reduce oxidative damage, and protect against oxidative stress-induced cardiomyocyte injury.

Overall, the intricate interplay between mitophagy, mitochondrial quality control, and cardiovascular health underscores the importance of further exploring the therapeutic potential of targeting mitophagy in mitigating cardiovascular diseases. By elucidating the mechanisms underlying mitophagy regulation and its impact on cardiac function, we can uncover novel therapeutic strategies aimed at preserving mitochondrial integrity, reducing cellular damage, and improving outcomes in patients with cardiovascular disorders. Understanding the nuances of mitophagy in the context of cardiovascular diseases holds significant promise for the development of precision therapies that target mitochondrial dysfunction at its core, offering new hope for patients facing these debilitating conditions.

In the following sections, we will delve deeper into the molecular mechanisms of mitophagy, its regulation in the context of cardiovascular disorders, and the current landscape of mitophagy-targeted therapeutic strategies in cardiovascular medicine. By exploring these aspects in detail, we aim to shed light on the potential of mitophagy modulation as a novel therapeutic approach for improving cardiovascular health and combating the burden of cardiovascular diseases on a global scale.

Mechanisms of mitophagy

Mitophagy, the selective removal of damaged mitochondria, is regulated by several mechanisms involving various proteins and processes.

PINK1/Parkin-Mediated Mitophagy (see Fig. 1):

PINK1- and Parkin- mediated mitophagy is among the most extensively researched mechanisms of mitochondrial biogenesis. This mechanism has received a lot of attention because PINK1 or Parkin (PARK2) loss-of-function mutations have been linked with the development of recessive juvenile parkinsonism (PD) (Jin and Youle, 2012). This pathway is activated due to a depolarization of the membrane as a result of mitochondrial injury. In case there is no impairment in the mitochondrial function, PINK1 kinase in mitochondria is dissolved by proteases and then degraded in the cytosol. Damaged mitochondria undergo depolarization resulting

in PINK1 retention on the outer membrane and causes ubiquitin phosphorylation, inducing the mobilization and stimulation of the E3 ubiquitin (Ub) ligase Parkin. Additionally, PINK1 phosphorylates Parkin at Ser65 within its Ub-like region. Then Parkin ubiquitinates various proteins within the membrane, and sets off the autophagy. These polyubiquitin chains are identified by autophagy adaptor proteins and serve as a ligand between mitochondria to autophagosomes (Meissner et al., 2015).

Due to the importance of normally functioning mitophagy for the cell, there are numerous pathways that regulate this process. Mitochondrial deubiquitinating enzymes (DUBs) control mitophagy by suppressing parkin-induced ubiquitination. For instance, Usp15 and Usp30 are DUBs that counteract ubiquitination in the outer membrane. Usp33 has been established as a DUB that opposes Parkin specifically (Park et al., 2021).

The mitochondrial ubiquitin ligase (MITOL) also prevents excessive mitophagy. For instance, it promotes Parkin ubiquitination, leading to its degradation by proteasomes. Therefore, ubiquitination control and regulation of Parkin levels are crucial elements in maintaining normal levels of mitophagy. Limitation of Parkin activity is especially critical since excess of Parkin can result in autophagy of almost all mitochondria. Mitophagy can also be regulated by PINK1 which triggers a non-canonical pathway involving mitochondrial Elongation Factor Tu (EF-Tu) by phosphorylating it at Ser222. This results in EF-Tu retention in the cytosol where it prevents ATG5-12 complex formation (Shiiba et al., 2021).

Other ubiquitin-mediated mitophagy mechanisms:

MUL1, ARIH1, and BNIP3/Nix (see Fig. 2are additional proteins involved in mitophagy regulation through ubiquitination).

Mitophagy is primarily regulated by ubiquitination. Not only Parkin, but also other ubiquitin ligases play a role in removing impaired organelles. Mitochondrial MUL1 E3 ubiquitin ligase is an E3 ubiquitin ligase that has two TM domains attached to the outer mitochondrial membrane and a RING finger domain oriented towards the cytoplasm. It has multiple mitochondrial proteins in common with Parkin, such as Mfn1 and 2, and Drp1. Studies on Drosophila and murine models have demonstrated that pathways involving this enzyme can replace the impaired or absent PINK1/Parkin mechanism. Trials in HeLa cells have shown that MUL1 can link to GABA Type A Receptor-Associated Protein through LIR-like sequences in the RING finger domain (Sun et al., 2022).

MUL1 not only functions as an E3 ubiquitin ligase but also acts as a mitochondrial receptor in the mitophagy process. MUL1 has recently been found to target ULK1 as a substrate. The mitophagy regulated by MUL1 is not dependent on Parkin or FUNDC1, but requires ATG5 as well as ULK1. Studies have shown that mitophagy can occur even in the absence of Parkin. Although tumor suppressors are believed to be primarily keeping mitophagy in check, the presence of ARIH1 ligase questions this theory (Fritsch et al., 2020). ARIH1 has been found to protect tumor cells from chemotherapy and is primarily released in stem cells and various cancer cells. It is a member of the RBR E3 ubiquitin ligase family which shares many common structural traits with Parkin. Both ARIH1 and Parkin interact with UBCH7, but they lack reactivity with lysine. Unlike Parkin, ARIH1 targets proteins other than Parkin substrates when setting off mitophagy (Villa et al., 2017).

Mitochondrial-derived vesicles (MDVs) are specific vesicles formed in the outer or inner mitochondrial membrane and are transported to other organelles carrying damaged or oxidized mitochondrial components which are to be degraded. This way MDVs clear injured mitochondria and restore homeostasis (Popov, 2022). MDVs have only been observed in a few cell types, including liver and heart cells. MDV amount is elevated in H9C2 cardiac myoblasts as a result of stress, and they have been shown to induce cardiac mitophagy. It is unclear if MDVs exist in all cell types (Vasam et al., 2021).

The B-cell lymphoma-2 (Bcl-2) protein family includes proteins that regulate programmed cell death, such as BNIPB3 and Nix (or BNIPB3L) proteins which can be found on the outer mitochondrial membrane and were initially believed to be responsible for cell apoptosis. Both proteins act as receptors and mediate mitophagy that does nor involve PRKN or PARK2. The C-terminal LIR domain is known to be a key element in triggering mitophagy by linking with Lc3 as a result of phosphorylation, as proved by recent trials in HeLa cells. Subsequently, removal of LIR suppresses mitophagy. Nevertheless, some studies suggest that Nix-regulated mitophagy is primarily dependent on the MER rather than LIR sequence. The deletion of MER in Nix cannot activate mitophagy (Klanova and Klener, 2020; Alam et al., 2021).

The TM sequence is responsible for the protein's location at the outer mitochondrial membrane and accelerates the formation of Nix homodimers via phosphorylation, a process vital for mitophagy. At the moment there is insufficient knowledge on the Nix-regulated mitophagy. The protein promotes BECN detachment from Bcl-BECN complex, resulting in a generation of an autophagosome (Marinković et al., 2021). Moreover, BNIP3 and Nix can attach to Rheb proteins to suppress mTOR mobilization via N-terminal, accelerating mitophagy. Nix depends on LIR to link to the Atg8 family proteins following phosphorylation and ubiquitination in hypoxic state. When there is enough Nix on the mitochondrial membrane, it will be depolarized and trigger mitophagy, although some scientists have questioned this theory, emphasizing that unlike the Parkin-mediated pathway, BNIP3-mediated mitophagy does not depend on the changes in membrane potential (Terešak et al., 2022). Further membrane depolarization was observed following mitophagy in cardiac progenitor cells even

without BNIP3. Studies have shown that Nix-dependent mitophagy is not necessarily induced by low oxygen. In colon carcinoma, hypoxia-related mitophagy is not associated with the availability of Nix but is triggered by 5' AMP-activated protein kinase. Thus, more research is required in order to investigate the connection between hypoxia and mitophagy involving BNIP3 as well as Nix-mediated mitophagy (Li et al., 2021).

FUNDC1-Mediated Mitophagy (see Fig.3):

Another mitophagy receptor localized on the outer membrane that has been excessively studied is FUNDC1, also known as FUN14 domain-containing protein 1. FUNDC1 contains three α-helical stretches with the C-terminal region located at the intermembrane and the N-terminal facing the cytoplasm in its LIR segment. Just like BNIP3 and Nix, FUNDC1 also links to Lc3-II through its LIR motif (Zhang, 2020). FUNDC1-mediated mitophagy is enhanced by hypoxia-related dephosphorylation, whereas other proteins with LIR sequences require phosphorylation to enhance their ability to link with Lc3. Additionally, FUNDC1 can bind to other members of this family, such as GABA Type A Receptor-Associated Protein, although their interaction is lower. Normally, Src and CK2 kinases phosphorylate Tyr 18 and Ser13 at the LIR domain in FUNDC1, suppressing its activity (Yoo and Jung, 2018). As a result of hypoxia or membrane potential loss, PGAM5 dephosphorylates FUNDC1 at Ser13. Studies indicate that mitophagy is primarily induced by Tyr18 and that Ser13 only supports this process. Tyr18 phosphorylation results in a marked decrease in the binding affinity to Lc3, while the changes in Ser13 have little impact. Additionally, ULK1 as well as UNC-51 are able to phosphorylate Ser17 in FUNDC1, increasing its binding affinity to Lc3, as observed in HeLa cells. This process promotes mitophagy to a much greater degree than the changes in Ser13 and Tyr18 under membrane depolarization or hypoxia. ULK1, in contrast with Parkin, moves to impaired mitochondria as a result of hypoxia. ULK1 substrates require further examination (Saito and Sadoshima, 2015).

MITOL has been observed to prevent unnecessary mitophagy by degrading FUNDC1. Just like Parkin, it ubiquitinates the outer membrane proteins. The ubiquitination of Lys19 in FUNDC1 by MITOL was observed to occur irrespective of phosphorylation. Furthermore, MITOL chockdown resulted in a suppression of FUNDC1 degradation and subsequent increase in mitochondria clearance (Li et al., 2021). Moreover, studies indicate that FUNDC1 mediates fusion and fission of mitochondria, thus having even more impact on mitophagy. MITOL was also reported to ubiquitinate other proteins involved in mitochondrial fusion processes, indicating its multifold involvement in mitophagy (Hall et al., 2014).

Lipid-Mediated Mitophagy (see Fig.4):

Certain lipids located in the outer mitochondrial membrane, such as cardiolipin and ceramide, stimulate mitophagy through their LIR motif. Ceramide is an important bioactive lipid of sphingolipid family catalyzed by ceramide synthases which comprise six groups, CerS1 to CerS6. Ceramides are synthesized in hepatic mitochondria by thioesterase and neutral ceramidase (Mullen et al., 2012). During endoplasmic reticulum stress, ceramides are moved from the ER to the OMM previous to mitophagy. Their cellular accumulation to a certain level, together with suppression of Akt phosphorylation and aggregation of Beclin-1, leads to the cellular death. Ceramides in the OMM interplay with the ceramide-binding domain of Lc3-II and discriminatingly delete impaired mitochondria (Choubey et al., 2021). In mitophagy, Lc3-II lipidation is essential for ceramide binding. CerS1 accelerates the preferential synthesis of C18-ceramides from stearic acids. Excessive expression of CerS1 or the addition of exogenous C18-ceramide can promote ceramide-induced mitophagy related to Drp1. Drp1 regulates the OMM localization of ceramides to affect autophagolysosomes. In tumor cells, Drp1 knockdown attenuates ceramide localization in OMM and autophagolysosomes recruiting. Mitochondrial fission is critical for ceramide-triggered mitophagy since Drp1 plays a major role in the regulation of mitochondrial division (Vos et al., 2021).

Furthermore, together with activated Bcl-2 Associated X-protein, ceramides create a ceramide channel in the lipid bilayer, which causes the release of cytochrome c and initiates apoptosis. Cardiolipin, generated by cardiolipin synthase, is a phospholipid that resembles ceramide. It is synthesized by mitochondria and accounts for around 25 mole percent of lipids in the mitochondrial membrane, which is also essential for mitochondrial division and various mitochondrial functions (Funai et al., 2020). The distribution of cardiolipin in normal mitochondria is asymmetric as regards IMM and OMM, with about 96.5 mole percent being restricted to IMM. A computational model suggests that N-terminal α-helices in Lc3 comprise the cardiolipin binding site. Normally, cardiolipin is located in IMM and interplays with OPA1 to stimulate IMM protein fusion and control mitochondrial networks. Under stress, another phospholipid, scramblase-3, transfers cardiolipin to OMM where it binds with Lc3-II.

PLS3 is a newly discovered protein in control of lipid transfer within cellular membranes (Kagan et al., 2014; Chu et al., 2013). Excessive expression of PLS3 in HEK293 cells causes cardiolipin aggregation in OMM and increases mitochondrial respiration and intracellular adenosine triphosphate. Cardiolipin transfer is also supported by nucleoside diphosphate kinase D, an oligomeric protein. Endogenous NDPK-D knockdown decreases cardiolipin on OMM triggered by CCCP in HeLa cells (Kagan et al., 2016).

Mitophagy impairments in cardiovascular disorders

Atherosclerosis

Atherosclerosis (ATH) is a chronic inflammatory condition prevalent in developed countries, characterized by the

accumulation of plaques within arterial walls due to interactions involving lipid accumulation, vascular smooth muscle cell (VSMC) growth, extracellular matrix turnover, calcium deposition, and inflammation. Recent research utilizing various techniques such as fluorescent and electron microscopy, as well as western blotting, has shed light on the role of autophagy, including mitophagy, in the development of atherosclerotic plaques in cell types like macrophages, VSMCs, and endothelial cells (Jaminon et al., 2019; Bennett et al., 2016).

Studies examining atherosclerotic human samples and animal models have revealed dysregulated or decreased autophagy levels, as evidenced by alterations in key autophagy proteins such as p62 and LC3-II within cells extracted from ATH plaques (Kim et al., 2021; Razani et al., 2012). Notably, individuals with unstable plaques exhibited a significant reduction in LC3-II expression compared to those with stable plaques, potentially leading to the accumulation of dead cells within arterial walls and plaque destabilization.

Furthermore, dysfunction in the autophagy process, such as the loss of autophagy-related genes like ATG7 in VSMCs or ATG5-null mice, has been associated with atheroma formation in atherosclerosis. In these cases, the failure to clear cholesterol crystals from plaques results in heightened interleukin secretion following macrophage inflammasome activation. While complete autophagy loss is incompatible with life in both humans and animals, partial autophagy decline may not always directly correlate with experimental atherosclerosis but could be linked to other serious dysfunctions, such as lysosomal disorders and p62 aggregation, impeding protein degradation processes (Pvo et al., 2013; Wang and Wang, 2015).

Although the understanding of mitophagy's role in atherosclerosis is still evolving, emerging evidence suggests that mitophagy, in concert with mitochondrial fission and fusion processes, plays a crucial role in maintaining mitochondrial quality by eliminating damaged mitochondria, thus influencing the overall health of the cellular mitochondrial population. Given the key roles of reactive oxygen species and inflammation in atherosclerosis progression, promoting mitophagy activation through stimuli like ox-LDLs and exogenous melatonin has shown promise in preventing ATH advancement by promoting plaque stabilization. Melatonin, for instance, has been shown to modulate mitophagy via SIRT3/FOXO3a/Parkin-mediated signaling pathways, thereby suppressing IL-1β expression and potentially mitigating atherosclerosis-related inflammation (Lin et al., 2022; Wan et al., 2022).

Ischemic Heart Disease

Ischemic heart disease, a condition often stemming from atherosclerosis, presents a significant challenge in myocardial function recovery due to severe mitochondrial damage incurred during periods of reduced blood flow. The alternation between ischemia and reperfusion in such conditions induces pH fluctuations, oxidative stress, and elevations in both mitochondrial and cytosolic calcium levels, culminating in the opening of the mitochondrial permeability transition pore (mPTP) and subsequent cardiac myocyte death (Su et al., 2022).

Autophagy, triggered by heightened cytosolic calcium levels, along with mitophagy, are recognized hallmarks of ischemia/reperfusion (I/R)-related disorders. Experiments conducted ex vivo on myocardial ischemia, such as those utilizing the Langendorff system, have significantly contributed to our understanding of known data. Noteworthy lysosomal changes were initially observed in perfused rabbit hearts in 1980, where the count of autophagosomes increased after 40 minutes of ischemia, peaking during reperfusion, indicating that both ischemia and reperfusion can instigate autophagy (Morciano et al., 2020). Similar results were later replicated in in vivo studies in mouse hearts, showcasing heightened autophagy levels characterized by increased expression of autophagy proteins, including LC3-II and Beclin1, which interact with the multifunctional Bcl-2-associated athanogene. Exposure to hypoxia and glucose deprivation followed by reperfusion in fetal mouse hearts further revealed an increase in autophagy, suggesting that autophagy may participate in repairing sublethal damage by limiting overall cellular damage. Interestingly, the suppression of autophagy by wortmannin hindered the induction of autophagy markers and mitigated cardioprotection in animal models (Gurusamy et al., 2009).

In response to ischemia and glucose deprivation, adenosine triphosphate levels in cardiac myocytes significantly decrease, coinciding with the activation of AMP-activated protein kinase (AMPK)-related autophagy and the suppression of the mammalian target of rapamycin (mTOR) pathway. Mice models overexpressing a dominant-negative form of AMPK exhibit reduced autophagy induction following ischemia. During the reperfusion phase, as physiological conditions are restored, AMPK activity diminishes, suggesting that autophagy proceeds through an AMPK-independent mechanism, potentially facilitated by Beclin1 overexpression as observed in some studies (Matsui et al., 2007).

Autophagy and mitophagy are commonly perceived as protective mechanisms; however, this view may oversimplify their roles. Autophagy may offer protective benefits during periods of cardiac energy deprivation, such as during ischemia, by fulfilling basic metabolic demands. Conversely, initiating autophagy under different circumstances, like during reperfusion, may prove deleterious. Studies have shown that the suppression of Beclin1 can safeguard cardiomyocytes from death in vivo. Additionally, Urocortin, a cardiac peptide known to mitigate I/R-induced myocyte death, can reduce Beclin1 expression by activating the PI3 kinase/Akt pathway (Marzetti et al., 2013).

The interplay between autophagy/mitophagy and the opening of the mPTP remains somewhat ambiguous and controversial. It is speculated that a feedback control loop exists between autophagy/mitophagy and mPTP activity, where each pathway regulates the other. Under moderate insults involving a few mitochondria, mPTP opening may activate an autophagy-related cellular repair mechanism; however, this process may be insufficient under conditions of massive damage that predispose cells to death (Calderón-Sánchez et al., 2021; Jin et al., 2018). Additionally, research suggests that BNIP3-mediated mitophagy in myocytes of adult failing hearts or under hypoxia may not rely on mPTP opening but instead necessitates the presence of ATG5, BNIP3, and constitutively expressed Beclin1 (Gustafsson, 2011).

Furthermore, endoplasmic reticulum stress and the unfolded protein response have been linked to the activation of autophagy/mitophagy during ischemia/reperfusion. Studies involving ventricular myocytes from cultured newborn rats and adult mice have demonstrated that both ER stress and the unfolded protein response become activated during ischemia/reperfusion. Hypoxia initiates the activation of the unfolded protein response in myocytes surviving in the border zones following myocardial infarction, indicating its involvement in the progression of ischemic heart disease in predisposed transgenic mouse models (Kny and Fielitz, 2022).

I/R-induced mitochondrial division leads to the emergence of two distinct mitochondrial populations with varying membrane potentials. Typically, depolarized mitochondria are unable to undergo fusion and become targets for mitophagy-mediated clearance. Mitochondrial fission is a prerequisite for mitophagy, as inhibiting this dynamic process, whether through dominant negative Drp1K38A activity or Fis1 RNA expression, disrupts mitophagy, leading to the accumulation of dysfunctional mitochondria (Hill et al., 2012). Mitochondria-associated membranes actively participate in determining fission sites, recruiting adaptors and proteins, and overseeing the completion of this process. Research on the inverted formin 2 protein, which regulates Drp1 upstream and plays multiple roles in mitochondrial fission, has provided further insights into these processes (Gao et al., 2020).

Additionally, evidence supporting the protective role of mitophagy in the heart has been reported. For example, in murine studies, FUNDC1, a mitophagy receptor that interacts with LC3, has been demonstrated to mediate mitophagy during hypoxia, regulating mitochondrial balance and protecting the heart from ischemia-reperfusion injury. When FUNDC1 phosphorylation by casein kinase 2α impedes its function, mitophagy is suppressed, resulting in significant tissue damage (Liu and Wu, 2022).

In a transgenic murine model experiencing acute myocardial infarction (MI) induced by left coronary artery ligation, autophagy is upregulated to maintain ATP levels and shield cardiac myocytes from coronary death. Administration of HMGB1, a highly mobile protein, can associate with mitophagy-dependent proteins upon exogenous delivery, potentially promoting the survival of heart myocytes in acute MI models (Schirone et al., 2022). Studies suggest that induced AMPK activation and mTORC1 suppression may mitigate apoptosis. Transgenic murine models with cardiomyocyte-specific HMGB1 overexpression have shown positive outcomes, including improved cardiac function, enhanced angiogenesis, and prolonged lifespan post-MI (Zhou et al., 2012). Notably, cardiac autophagy suppression akin to that induced by Mst1 stimulation in MI murine models has been linked to the formation of p62 aggregates, the loss of autophagosomes, and impaired heart function.

Maintaining cellular homeostasis during ischemia involves a delicate balance among mitochondrial quality control processes, where mitochondrial biogenesis plays a critical role in preserving cardiac energy production (Kaludercic et al., 2020)

Cardiomyopathies

Cardiomyopathies, including specific considerations such as diabetic cardiomyopathy (DCM), represent cardiac muscle disorders characterized by abnormal structure and function independent of co-existing cardiovascular diseases (CVDs) like uncontrolled hypertension, coronary artery disease, severe valvular issues, and genetic cardiac conditions. The prevalence of cardiomyopathy in the global population is approximately 3 percent but escalates to 12 percent in individuals with diabetes mellitus (DM), heightening their risk of heart failure and mortality (Sharma et al., 2017). Various factors contribute to the progression of cardiomyopathies, including elevated blood glucose levels, impaired insulin sensitivity, activation of the renin-angiotensin-aldosterone system, dysfunction of the sympathetic nervous system, increased free fatty acids, cardiac muscle inflammation, oxidative stress, myocardial fibrosis, and remodeling. However, the exact pathophysiological mechanisms remain to be fully elucidated (Tuleta and Frangogiannis, 2021).

In individuals with DM, there is a shift towards reduced glucose oxidation rates and heightened fatty acid oxidation rates within the heart. This metabolic alteration leads to oxidative stress, compromised oxidative phosphorylation, and eventual mitochondrial dysfunction. Increased fatty acid oxidation is energetically detrimental and is facilitated by the upregulation of the peroxisome proliferator-activated receptor. This metabolic stress-related mitochondrial dysfunction results in augmented reactive oxygen species production, calcium ion overload-induced mitochondrial permeability transition pore opening, and ultimately necrotic death of cardiac myocytes. Although substantial evidence points to the pivotal role of mitochondria in the pathophysiology and progression of cardiomyopathies, further investigations are

warranted to delineate the underlying mechanisms (Gollmer et al., 2020).

Mitophagy, the effective removal of dysfunctional mitochondria, plays a critical role in preserving cardiomyocyte survival by ensuring mitochondrial quality control. Dysregulation of mitophagy and autophagy has been implicated in the pathogenesis of various cardiomyopathies, including diabetic cardiomyopathy (DCM). Studies have shown that autophagy repression occurs in the hearts of mice with both type 1 and type 2 diabetes, suggesting that autophagy inhibition may contribute to the development of DCM (Fan et al., 2020).

Specific proteins such as Drp1, PINK1, and Parkin play key roles in mitochondrial quality control mechanisms. Lower levels of PINK1 and Parkin in the hearts of type 1 diabetic mice have been associated with reduced cardiac mitophagy, highlighting the significance of these proteins in maintaining mitochondrial health. The absence of these proteins leads to a decrease in the release of the small GTPase Rab9, involved in a noncanonical alternative selective autophagy mechanism, and results in mitochondrial degradation. Notably, Drp1, responsible for mitochondrial fission at the outer membrane, is essential for cardiac function and responds to energy stress. Removal of Drp1 in cardiomyocytes diminishes mitophagy and impairs heart function, increasing susceptibility to ischemia-reperfusion injury (Diao and Gustafsson, 2022).

Furthermore, a mutation in Drp1 (C452F) has been linked to the spontaneous development of monogenic dilated cardiomyopathy with associated mitochondrial defects, including impairments in mitophagy. This mutation acts as an activator of Drp1 GTPase, failing to promote protein disassembly following oligomerization, resulting in partial dysfunction. In the Python heart, alterations in mitochondrial Ca2+ uptake and an accumulation of inefficient mitochondria contribute to energetic failure and the onset of dilated cardiomyopathy. Additionally, disrupted mitochondrial fusion, as observed in the absence of both Mfn1 and Mfn2, accelerates the development of dilated cardiomyopathy (Cahill et al., 2015).

Numerous studies emphasize the critical role of mitophagy in cardiomyopathies. For example, mitophagy serves as a potential therapeutic target in cardiomyopathy associated with the transferrin receptor. Mice with impaired mitophagy due to Tfrc knockout develop severe cardiomyopathy. Insufficient digestion of mitochondrial DNA triggers inflammation in the myocardium and can lead to heart failure (Hsiao et al., 2021). High-fat diet-induced cardiac lipid accumulation inhibits mitophagy, while promoting mitophagy using specific strategies suppresses cardiomyopathy progression. Melatonin therapy enhances mitophagy and combats the negative effects of cardiomyopathy by regulating key cellular pathways. Additionally, sustained activation of AMP-activated protein kinase, normalization of autophagy, and inhibition of cardiomyocyte apoptosis by modulating specific signaling pathways contribute to cardioprotection in diabetic myocardium (Wang et al., 2022; Tong et al., 2019; Wang et al., 2018).

The role of the renin-angiotensin-aldosterone system (RAAS) in the pathogenesis of diabetes mellitus and hypertension is significant, with RAAS activation contributing to insulin resistance, oxidative stress, and cell death in the affected heart. Insulin signaling also plays a crucial role, particularly in suppressing autophagy during postnatal feeding (Zhang et al., 2017). Disruption of insulin receptor genes can lead to excessive organelle clearance and subsequent myocyte loss, culminating in heart failure. This collective evidence underscores the importance of autophagy and mitophagy in maintaining a functional mitochondrial network and highlights their cardioprotective functions (Underwood and Adler, 2013).

Hypertension

Arterial hypertension (AH) is a complex condition influenced by various factors and mechanisms that regulate blood pressure, as proposed by Dr. Irvine H. in his theory of the "mosaic of AH" in 1967. Effective management of AH is crucial as it remains a significant risk factor for cardiovascular diseases (Harrison, 2013). Limited research has addressed the activity of mitophagy in cardiac hypertension. In a study conducted in 2015 using young animals, it was discovered that the presence of AH combined with obesity exacerbates mitochondrial dysfunction, leading to a decline in ejection fraction and overall health outcomes (Tong et al., 2019; Brandt et al., 2019). Notably, the activation of the renin-angiotensin-aldosterone system serves a dual role: on one hand, it impedes mitochondrial biogenesis by reducing NRF1, TFAM, and PGC-1α, while on the other hand, it promotes excessive mitochondrial removal through mitophagy. These changes disrupt the equilibrium between mitochondrial fission and fusion processes, resulting in increased mitochondrial fragmentation due to OPA1 cleavage and MFN1 downregulation (Wolf, 2006). These significant alterations in mitochondrial turnover may exacerbate cellular damage. Overall, these findings suggest that mitophagy may play a role in the development of cardiac hypertension, warranting further investigation into these mechanisms. Substantial evidence was provided by a study involving a mouse model of AH induced by a high-salt diet. The administration of spermidine delayed the onset of AH in normal mice by promoting mitophagy and autophagy in cardiomyocytes. However, this beneficial effect of spermidine was not observed in ATG5 knockout mice, which exhibited elevated levels of p62/Sequestosome 1 (SQSTM1) and decreased levels of LC3-II (Picca et al., 2018).

Beyond malfunctions in mitochondrial quality control mechanisms, overall organelle dysfunction has been implicated in patients with AH. Capillary rarefaction at the microvasculature level is a significant clinical indicator that warrants assessment.

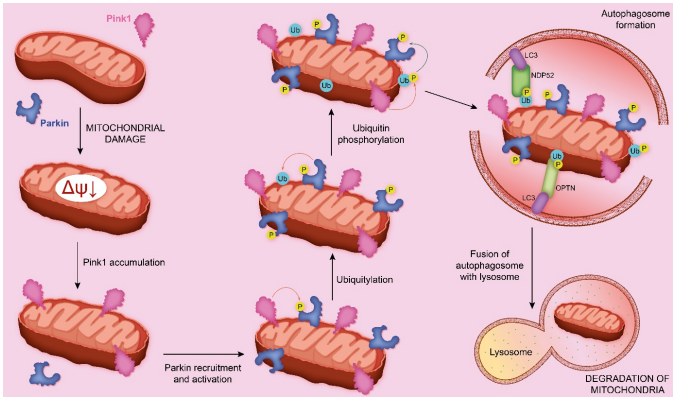

Figure 1. Mechanism of Pink1/Parkin-Mediated Mitophagy. Stress conditions may lead to mitochondrial damage, accompanied by depolarization and a decrease of the mitochondrial membrane potential (Δψ). Mitochondrial depolarization results in Pink1 accumulation at the outer mitochondrial membrane (OMM). Pink1 recruits and activates cytosolic Parkin. Pink1 phosphorylates Parkin at Ser65. Parkin ubiquitinates various proteins within the OMM. Pink1 also phosphorylates the Ub molecules attached to these OMM proteins, further enhancing Parkin's activity. Adaptor proteins (NDP52 and OPTN) bind both Ub and the autophagic protein LC3. They mediate the sequestration of mitochondria in an autophagosomal membrane. Subsequently, the autophagosome fuses with a lysosome, allowing for the degradation of its content by lysosomal hydrolases.

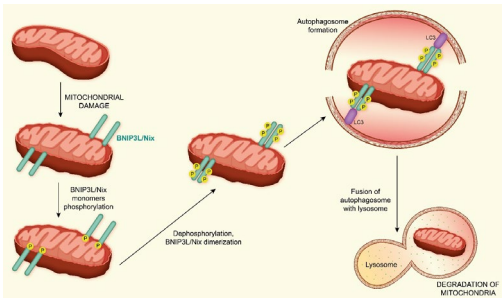

Figure 2. Mechanism of BNIP3L/Nix-mediated mitophagy. During the mitophagy induction, the monomers of BNIP3L/NIX, which are phosphorylated at Ser212, undergo dephosphorylation at their C-terminus to form more stable BNIP3L/NIX dimers. Simultaneously, double LIR motif phosphorylation at Ser34 and Ser35 enhances the recruitment of autophagosomes to mitochondria.

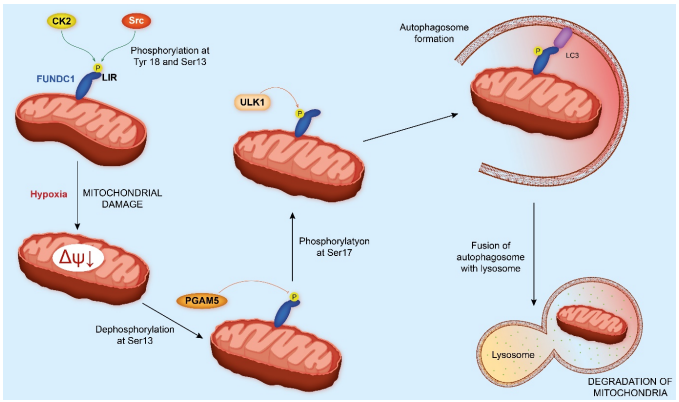

Figure 3. Mechanism of FUNDC1-mediated mitophagy. Mitophagy receptor FUNDC1 contains aLIR (LC3-interacting region) domain located at its N-terminus, which is exposed to the cytosol. Under normal conditions, FUNDC1 undergoes phosphorylation by CK2 and Src at Ser13 and Tyr18. During hypoxia, the activity of SRC and CK2 diminishes, and the mitochondrial phosphatase, PGAM5, dephosphorylates FUNDC1 at Ser13. The dephosphorylation of FUNDC1 at both Ser13 and Tyr18 enhances its interaction with LC3 and facilitates the activation of mitophagy. Additionally, ULK1 is able to phosphorylate FUNDC1 at Ser17, increasing its binding affinity to LC3.

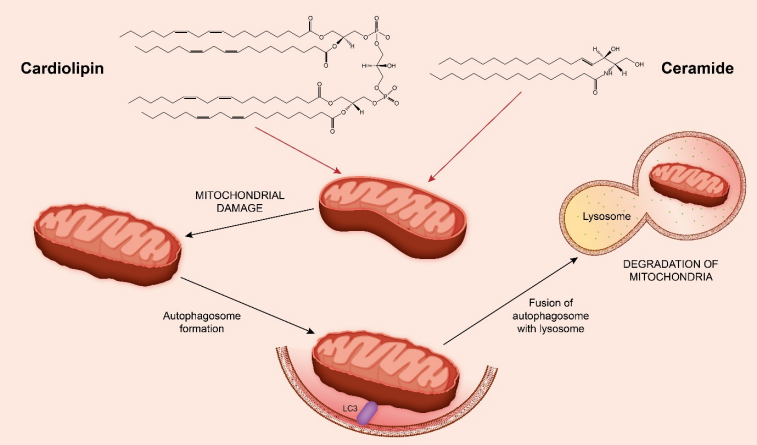

Figure 4. Mechanism of lipid-mediated mitophagy. Cardiolipin is transported from the inner mitochondrial membrane (IMM) to the outer mitochondrial membrane (OMM) and directly binds to LC3. This interaction triggers the initiation of mitophagy. Additionally, ceramide transported from the endoplasmic reticulum (ER) directly binds to the LC3 protein, which facilitates the recruitment of autophagosomes to damaged mitochondria. This recruitment process ultimately leads to lethal mitophagy.

Endothelial progenitor cells (EPCs), crucial for angiogenesis, may compensate for capillary rarefaction; however, mitochondrial dysfunction in these cells can disrupt microvascular resistance and impede the formation of new vasculature (Yu et al., 2019). The dysregulation of the CXCR4/JAK2/SIRT5 signaling pathway contributes to EPC dysfunction, exacerbating AH in affected individuals. Notably, the attenuation of CXCR4 in AH samples impedes SIRT5-mediated mitochondrial function through JAK2 phosphorylation (Yu et al., 2019).

Providing an overarching review of mitophagy/autophagy in hypertensive disorders is challenging due to conflicting evidence, particularly in pulmonary hypertension. Elevated levels of LC3-II have been observed in most disease models involving rodents and humans. The significance of this elevation remains a subject of debate, and the specific roles of the upstream and downstream processes are not definitively understood. In some instances, autophagy has been considered cardioprotective as it mitigated vessel remodeling, while in other experimental studies, autophagy elimination was associated with promoting angiogenesis and ameliorating heart failure and AH (Jiang et al., 2023).

Peripheral Vascular Disease

Peripheral vascular disease (PVD) is a condition that affects arteries and veins, resulting in pain and fatigue, typically during physical activity, without consistently impacting vessel structure. Vascular smooth muscle cells (VSMCs) are vital components of blood vessels, capable of transitioning into osteochondrogenic-like and macrophage-like cells, a process linked to damage within the peripheral vascular system, according to various studies (Haas et al., 2012). Factors such as cytokines, growth factors, oxidized LDLs, and oxidizing agents, known to stimulate autophagy, are believed to influence VSMCs in PVD cases (e.g., post-coronary angioplasty), triggering cell transformation into macrophage-like cells while inhibiting the osteochondrogenic type. Hence, autophagy appears to regulate the cellular response to damage (Checkouri et al., 2021). In deep venous thrombosis (DVT), a common type of PVD, ATG5 plays a crucial role in thrombus recanalization, primarily within the endothelium. Specifically, ATG5 promotes Akt phosphorylation, a process counteracted by the use of 3-methyladenine (3-MA), which hinders autophagy by reducing ATG5 levels, thereby impeding endothelial cell migration and tube formation (Li et al., 2022; Xie et al., 2020). Studies focusing on conditions involving significant tissue restructuring, such as cancer, have provided compelling evidence of autophagy's influence on angiogenesis, as evidenced by outcomes following pharmacological suppression of this pathway. For instance, elevated levels of cathepsin D and lysosome-associated membrane protein (LAMP) promote robust angiogenesis in hemangioma infants, while sustained ATG5 expression leads to cellular death (Prieto Huarcaya et al., 2022).

Individuals with peripheral artery disease often experience diminished physical activity not solely attributable to ischemia-induced complications or pain. Research comparing muscle fiber types and distribution in PVD versus non-PVD subjects has revealed heightened oxidative stress, reduced intermyofibrillar mitochondria, and impaired mitochondrial respiration (Schieber et al., 2017). Additionally, excessive mitophagy, coupled with the absence of compensatory mechanisms like PGC-1α overexpression, has been observed. This unregulated mitochondrial elimination, indicated by increased LC3-II levels within fibers, appears unrelated to age and necessitates further investigation to comprehensively understand its causes and implications. By leveraging existing data, future research endeavors can be steered towards developing innovative therapies for this class of disorders (Shi et al., 2014).

Limitations

While the studies discussed in this review shed light on the critical role of mitophagy in maintaining cellular homeostasis and its implications in various pathological conditions, there are several limitations that should be acknowledged:

Heterogeneity of Study Models: Many of the studies referenced in this review rely on animal models or cell culture systems to investigate the role of mitophagy in different diseases. While these models provide valuable insights, there may be limitations in extrapolating findings to human physiology due to inherent differences between species and cell types.

Limited Clinical Data: The translation of findings from preclinical studies to clinical applications is a crucial step in understanding the relevance of mitophagy in human disease. However, there is a scarcity of comprehensive clinical data linking mitophagy dysregulation to specific cardiovascular disorders, cancer types, or neurodegenerative diseases. Further clinical studies are needed to validate the significance of mitophagy in human pathology.

Mechanistic Complexity: Mitophagy is a multifaceted process regulated by a network of proteins and pathways. The interplay between different signaling cascades, mitochondrial dynamics, and cellular stress responses adds to the complexity of mitophagy regulation. Understanding the intricate mechanisms underlying mitophagy requires detailed mechanistic studies that can be challenging to conduct comprehensively.

Technical Challenges: Assessing mitophagy precisely and accurately presents technical challenges in terms of methodology. Techniques such as electron microscopy, immunofluorescence, and western blotting are commonly used to study mitophagy; however, these methods may have limitations in capturing dynamic changes in mitophagy flux or detecting specific molecular interactions involved in the process.

Variability in Mitophagy Assessment: Quantifying mitophagy levels and assessing its impact on cellular function can be challenging due to the lack of standardized assays and parameters

for measuring mitophagy. Variability in mitophagy assessment methods across studies can lead to inconsistencies in results and interpretations.

Context-Specific Effects: The role of mitophagy in different pathological conditions may vary depending on the cellular context, disease stage, and microenvironment. Mitophagy dysregulation may exert context-specific effects that are not fully understood and may require further investigation to elucidate the underlying mechanisms.

Interconnections with Other Cellular Processes: Mitophagy is closely intertwined with other cellular processes, such as apoptosis, inflammation, and oxidative stress. Dissecting the specific contributions of mitophagy to disease pathogenesis while considering its crosstalk with these interconnected pathways poses a challenge in attributing specific effects solely to mitophagy dysregulation.

Addressing these limitations through rigorous study designs, standardized methodologies, advanced imaging techniques, and interdisciplinary collaborations will be essential to deepen our understanding of mitophagy in disease pathogenesis and pave the way for innovative therapeutic strategies targeting mitochondrial dysfunction-related disorders.

Conclusion

The research conducted on mitophagy regulation has shed light on the intricate mechanisms involved in maintaining cellular homeostasis and addressing various diseases, particularly those related to cardiovascular disorders. The identified pathways and proteins associated with mitophagy provide valuable insights into potential therapeutic targets for mitigating mitochondrial dysfunction-related ailments.

However, despite the progress made in understanding mitophagy, there remain uncertainties and controversies that warrant further investigation. The contradictory results observed in some studies highlight the complexity of mitophagy regulation and the need for more in-depth exploration. Moreover, the interconnectedness of proteins involved in mitophagy with other physiological processes underscores the importance of comprehensive research to ensure that therapeutic interventions targeting mitophagy do not inadvertently disrupt essential cellular functions.

Future research in mitophagy should aim to address these gaps in knowledge, clarify conflicting findings, and explore the broader implications of modulating mitophagy in the context of overall cellular health. By advancing our understanding of mitophagy mechanisms and their implications, we can pave the way for more targeted and effective therapies for a range of mitochondrial dysfunction-related disorders.

Author contributions

A.V.P. prepared the original draft of the manuscript. V.N.S., A.V.C., A.A.L., D.F.B., I.N.L., and A.N.O. contributed to the review and editing of the manuscript.

Acknowledgment

Author was grateful to their department. This research was funded by Russian Science Foundation, grant number 24-15-00123.

Competing financial interests

The authors have no conflict of interest.

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