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REVIEW

Transmitophagy in the heart: An overview of molecular mechanisms and implications for pathophysiology

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Transmitophagy

Abstract Mitochondria are essential for meeting cardiac metabolic demands and their dysfunction is associated with heart failure and is a key mediator of cardiac ischemia−reperfusion injury. Cardiomyocytes engage integrated mechanisms to maintain mitochondrial function; however, chronic stress or disease can overwhelm this capacity. The removal of damaged mitochondria is mediated by a process known as mitophagy, which, together with mitochondrial biogenesis, plays a key role in maintaining mitochondrial quality control. Maintenance of mitochondrial quality control was initially thought to be autonomously regulated within each cellular population with little exchange between cells. However, recently the phenomenon of transmitophagy has been identified in which damaged mitochondria are transferred to neighboring cells for degradation. This review discusses the current understanding of transmitophagy in the context of heart injury, aging and disease, with particular emphasis on exophers, migrasomes, and tunneling nanotubes as pathways mediating cell−cell communication between cardiomyocytes, macrophages and fibroblasts. We further discuss the potential of targeting transmitophagy for cardioprotection and highlight key unanswered questions and challenges. Addressing these gaps may reveal novel strategies to preserve mitochondrial homeostasis and improve the outcomes of patients with cardiovascular disease.

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1. Introduction

The human heart pumps approximately 2000 gallons of blood daily and consumes nearly 6 kg of ATP to sustain its contractile function[1]. This intense energy demand is met by mitochondria, which comprise 30% to 40% of cardiomyocyte volume[2] and produce 95% of the ATP needed for cardiac function through oxidative phosphorylation[3]. However, the heart's heavy reliance on mitochondria makes cardiomyocytes particularly vulnerable to mitochondrial dysfunction, which is associated with heart failure, ischemic injury, and cardiomyopathies[4,5]. Furthermore, heart failure affects more than 64 million people worldwide[6,7], and is associated with significantly reduced activities of mitochondrial complexes I and IV, as well as TCA (tricarboxylic acid) cycle enzymes, in end-stage failing human myocardium[8]. To preserve mitochondrial quality and sustain energy production, cardiomyocytes use mitophagy, the selective degradation of damaged mitochondria, coupled with biogenesis to produce new organelles.

While mitophagy and biogenesis preserve mitochondrial integrity under physiological conditions, these pathways can become overwhelmed during chronic stress or acute injury, leading to the accumulation of dysfunctional mitochondria. To provide more capacity for mitochondrial quality control cardiomyocytes use transmitophagy, a process through which damaged mitochondria are shuttled to neighboring cells (such as macrophages and fibroblasts) for degradation, providing a complementary clearance route. This review explores: (1) mechanisms and limitations of cell-autonomous mitophagy in cardiomyocytes; (2) mechanisms of transmitophagy; (3) cells involved in transmitophagy in the heart; (4) modulation of transmitophagy across development, aging, and disease; (5) therapeutic implications of transmitophagy; and (6) challenges in the field and future opportunities.

2. Mechanisms and limitations of cell-autonomous mitophagy in cardiomyocytes

The canonical PINK1/Parkin pathway is the best-characterized mitophagy mechanism, identifying dysfunctional mitochondria and tagging them for autophagic clearance[9−13] (Fig. 1). Specifically, when mitochondria lose their membrane potential, PINK1 evades protease cleavage and accumulates on the outer mitochondrial membrane. Subsequently, PINK1 phosphorylates ubiquitin and Parkin, and recruits Parkin translocation to the mitochondria, where it ubiquitinates outer mitochondrial membrane proteins. The ubiquitinated proteins are recognized by adaptor proteins such as p62 (SQSTM1), NDP52, and OPTN, linking damaged mitochondria to LC3 on the autophagosome to be sent to lysosomes for degradation[9−12]. In addition to the PINK1/Parkin pathway, cardiomyocytes utilize non-canonical mitophagy pathways[14]. These include mitochondrial-derived vesicles (∼70−150 nm) that bud from mitochondria and translocate to the lysosomes to be degraded[12,15−17], receptor-mediated mitophagy *via* proteins like BNIP3, Nix (BNIP3L), and FUNDC1, which are located on the mitochondria and interact with LC3 during hypoxia or ischemic stress[9−12,18−20], cardiolipin (a mitochondrial-resident lipid)-mediated clearance[21,22] and Rab9-mediated mitophagy[23].

Circadian rhythm and sex differences further modulate mitophagic activity in the heart. Our recent findings have shown circadian-dependent and sex-specific variations in cardiac mitophagy, with female and male hearts showing distinct temporal patterns of mitochondrial turnover[16]. Potential mechanisms include, but are not limited to: sex-dependent differences in mitochondrial composition, mitophagy signaling and mediating proteins, and hormonal or neurological regulation. These observations align with broader cardiac sex differences in signaling and remodeling that are shaped by sex hormones and chromosomes[24]. Because heart attack incidence is linked to time of day, and circadian dysregulation strongly impacts cardiac health, it is important to understand whether and how mitophagy is regulated in distinct cell types, whether by cell−autonomous mechanisms or by cell−cell communication, by time of the day and/or cardiac circadian clocks.

Despite having multiple mitophagy pathways, cardiomyocytes, which are post-mitotic cells with limited regenerative capacity[25,26], face significant challenges to the effective execution of the mitophagic process. Under conditions of chronic stress, aging, or ischemia−reperfusion injury, mitophagy efficiency declines, leading to the accumulation of defective mitochondria[27−32]. Mitochondrial dysfunction leads to excessive reactive oxygen species (ROS) production due to impaired electron transport chain efficiency, resulting in oxidative damage to mitochondrial DNA, lipids, and proteins[33−35]. This oxidative stress also activates pro-inflammatory signaling, including NF-κB and the NLRP3 inflammasome, promoting a chronic inflammatory state[36]. These processes can lead to impaired calcium handling, reduced ATP production, and eventually apoptosis, ultimately reducing myocardial contractility and driving the progression of heart failure[27].

As cell−autonomous mitophagy has limited capacity and is often insufficient under sustained or severe stress, leaving damaged mitochondria uncleared, transmitophagy, an intercellular process in which damaged mitochondria are exported to recipient cells for degradation[37], may provide a complementary process for maintaining mitochondrial quality.

3. Observations and mechanisms of transmitophagy

Transmitophagy was first discovered in the retina using both electron and fluorescent microscopy methods, where retinal ganglion cells shed mitochondria, which are then internalized and degraded by adjacent astrocytes[37]. This process is potentially biologically significant when damaged mitochondria are at the far end of the cells, away from degradative lysosomes, or when cell-autonomous mitophagy pathways are overwhelmed.

Transmitophagy relies on the ability of recipient cells to internalize and degrade foreign mitochondria, providing a compensatory route for mitochondrial clearance. Intercellular mitochondrial transfer may occur through several pathways:

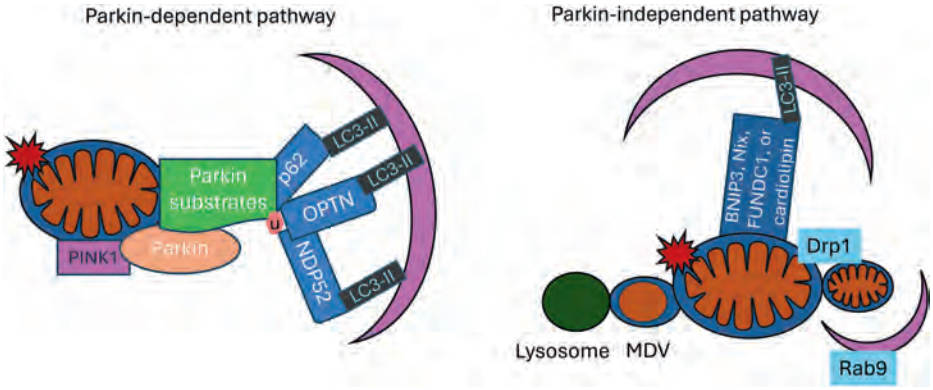

Figure 1 Mitophagy in cardiomyocytes—Parkin-dependent and Parkin-independent mechanisms. Mitophagy in cardiomyocytes involves both Parkin-dependent and Parkin-independent pathways for clearing damaged mitochondria. In the Parkin-dependent pathway, PINK1 accumulates on depolarized mitochondria, recruiting Parkin, which ubiquitinates mitochondrial proteins. These proteins are recognized by autophagy receptors (*e.g.*, p62, NDP52, OPTN), which then bind to LC3 on the autophagosome for degradation in lysosomes. In the Parkin-independent pathway, damaged mitochondria are cleared *via* Mitochondrial-Derived Vesicles (MDVs) and receptor-mediated mitophagy. BNIP3, Nix (BNIP3L), and FUNDC1 recruit LC3, facilitating autophagic degradation. Additionally, cardiolipin externalization marks damaged mitochondria for clearance by directly interacting with LC3. Furthermore, mitochondrial fission through Drp1 action enables Rab9-mediated mitophagy. MDVs bud off from mitochondria and can translocate and fuse with lysosomes to execute mitophagy.

exophers[38], migrasomes[39], tunneling nanotube transfer (TNTs)[40−42], extracellular vesicles (EVs)[43]. Tight or gap junctions can mediate small molecule exchange transfer mechanisms[44,45] (Fig. 2). Exophers are large vesicles (1−5 μm in diameter) that encapsulate damaged mitochondria and other cellular debris, which are then extruded and degraded by neighboring cells. Migrasomes are vesicles up to 3 μm in diameter released by migratory cells. TNTs (50−200 nm in diameter) are actin-based, membranous conduits that form dynamic, cytoplasmic connections between cells, enabling the transfer of mitochondria and other organelles. EVs are small (30−1000 nm in diameter) and can shuttle mitochondrial fragments to distant cells[46,47]. Tight junctions regulate paracellular permeability with the passage of ions or small molecules, and gap junction transfers are direct cell-to-cell transfer of ∼1−2 nm small molecules, through specialized channels[44,45]. Intercellular mitochondrial transfer can be beneficial in providing healthy mitochondria to recipient cells while allowing recipient cells to degrade damaged mitochondria from donors. However, it can also be detrimental, spreading dysfunctional mitochondria[48−53].

3.1. Exophers and transmitophagy

Exophers were first demonstrated in *C. elegans*, in which oxidized mitochondria and protein aggregates are expelled from neurons in exopher vesicles[54]. Exopher release increases in response to protein aggregation, inhibition of chaperone expression, autophagy, mitophagy, or proteasome activities[54]. Knockdown of pod-1 or emb-8 decreases exopher production. Mutations in ced-1/Megf10, ced-6/Gulp, and ced-7/ABC1 decrease exopher clearance. Intermediate filaments, adaptor proteins SQST-1/p62, HDA-6/HDAC6, and FTT-2/14-3-3 modulate exopher production[55]. Subsequently, it has been found that fasting, but not temperature or hypoxia, induces exophers through processes involving lipid synthesis, FGF/RAS/MAPK, and EGF/RAS/MAPK signaling[56]. Increased exopher formation in response to inhibition of neuronal early-acting autophagy genes is associated with extended lifespan, through a mechanism involving ATG-16[57]. Furthermore, although the initial report did not see phosphatidylserine (PS) on the exopher surface using annexin-V::GFP[54], a later study found that mutation of anoh-1, a homolog of TMEM16F required for PS exposure, decreased exopher production, implicating the involvement of PS[58] (Fig. 3). Compared to *C. elegans*, few studies have addressed the role of exophers in transmitophagy in mammalian systems.

In mammals, microscopy and biochemical analyses have identified exophers, 1−5 μm LC3-containing vesicles, that surround damaged mitochondria, protein aggregates, and other cell debris being taken up by macrophages surrounding cardiomyocytes[38]. Proteins involved in mitochondrial integrity, such as Opa1, Fis1, and Cytc are decreased in exophers compared to cardiac mitochondria, suggesting that the mitochondria in exophers are dysfunctional[38]. Supporting a role of macrophage in exopher clearance is the finding that two days of macrophage depletion using diphtheria toxin receptor under CD169/Siglec1 locus (that deplete cardiac resident macrophages that express sialoadhesin CD169) can lead to a doubling of exopher content in the heart[38]. Autophagy machinery plays a key role in the formation of exophers in cardiomyocytes, as mTOR inhibition increases their formation and Atg7 knockout decreases their formation[38]. Macrophage depletion increased mitochondrial number and size but reduced cristae and ATP production. This accompanied an increase in inflammasome formation, autophagy blockade, and impaired cardiac function, including decreased LV volume, E/A ratio, LV-ejection fraction, cardiac output, and both diastolic and systolic function as indicated by hemodynamic analyses[38].

In response to cardiac stress, such as isoproterenol (ISO)-induced adrenergic stress, exopher production is increased threefold[38]. Genetic deletion of Oma1, a metalloendopeptidase, has been shown to protect against mitochondrial damage and is cardioprotective in ISO, AngII and TAC-induced heart failure[59], and decreased exopher formation has been found associated with decreased mitochondrial damage in *Oma1*$^{-/-}$ mice[38]. These observations are consistent with exopher release being induced by mitochondrial dysfunction. *In vivo* imaging and quantification indicate that cardiac macrophages engulf and degrade over 70% of

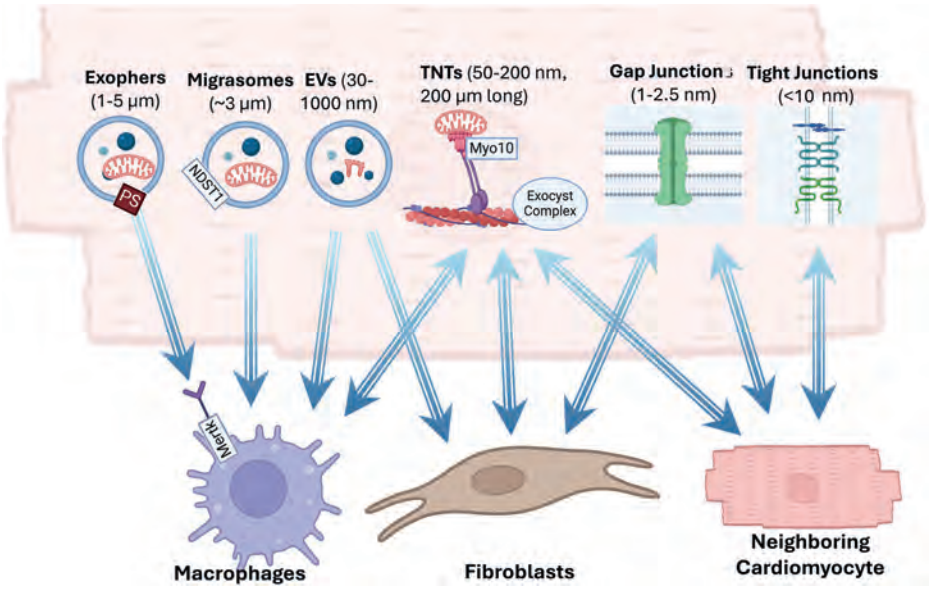

Figure 2 Intercellular mitochondrial transfer—pathways and molecular players. Mitochondria or fragments are transferred between cells by several mechanisms. Exophers (1−5 µm) encapsulate damaged mitochondria and other debris, which are extruded from cardiomyocytes and engulfed by macrophages through recognition of phosphatidylserine (PS) by the MerTK receptor. Migrasomes (∼3 µm), formed during cell migration, carry mitochondria and contain markers like TSPAN4 and NDST1, facilitating uptake by macrophages. Tunneling nanotubes (TNTs) (50−200 nm), up to 200 µm long, are actin-based conduits that connect cells, allowing direct mitochondrial transfer from cardiomyocytes to fibroblasts, macrophages, and neighboring cardiomyocytes, regulated by Myo10 (Myosin-X) and the Exocyst complex. Extracellular vesicles (EVs) (30−1000 nm) shuttle mitochondrial fragments to macrophages and fibroblasts. Tight and gap junctions facilitate the transfer of small molecules like ATP through specialized channels, with gap junctions allowing direct transfer of molecules through ∼1−2 nm channels. Figure generated in BioRender.

exophers released by ISO-stressed cardiomyocytes[38]. Furthermore, exophers express phosphatidylserine (PS) as an "eat-me" signal, recognized by MerTK tyrosine kinase in the macrophages. MerTK plays a key role in exopher clearance in the heart as MerTK knockout mice exhibit accumulation of extracellular mitochondria, activation of inflammasomes, blunted autophagy,

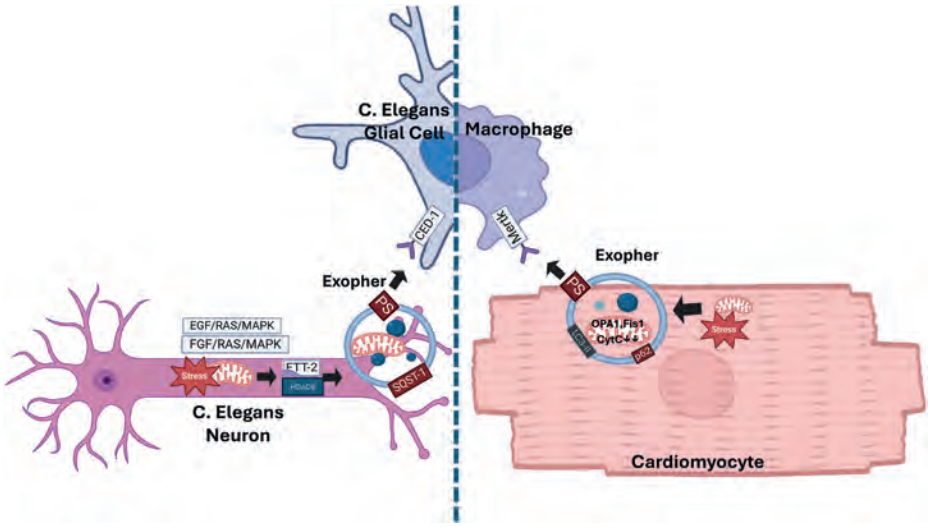

Figure 3 Exophers and transmitophagy. In *C. elegans* neurons, oxidative stress or proteasomal inhibition triggers the formation of exophers that encapsulate damaged mitochondria and protein aggregates, which are ejected and cleared by glial cells. This process involves intermediate filaments and autophagy adaptor p62 (SQST-1), with HDAC6 and FTT-2 modulating exopher production, and CED-1, CED-6 and CED-7 modulating exopher clearance. Fasting also induces exophers through pathways involving lipid synthesis, FGF/RAS/MAPK and EGF/RAS/MAPK signaling. In mammalian cardiomyocytes, mitochondrial dysfunction leads to exopher formation with mitochondria exhibiting decreased Opa1, Fis1 and Cytc. Exophers exhibit PS exposure on the membrane for recognition by MerTK receptors on macrophages. Figure generated in BioRender.

and reduced LV E/A ratio[38]. Since MerTK expression is higher in M2 macrophages compared to M1[60], it could modulate their efficacy in transmitophagy. Furthermore, a subpopulation of cardiac-resident macrophages which exhibit high TREM2 expression, actively take up cardiomyocyte-derived damaged mitochondria during sepsis-induced cardiomyopathy[61].

Neuron-derived exopher-like protrusions are phagocytosed by adjacent glia *in vivo* in mammalian models, with neuron−glia interactions modulating their production and removal[58,62]. In Alzheimer's disease (AD) human cortex and mouse models, exophers are found adjacent to neurons and Iba1^{+} microglia; with higher density in the hippocampus in AD compared to controls, supporting an inducible response to proteotoxic stress[62]. Together with cardiac data showing macrophage-dependent clearance of cardiomyocyte exophers *in vivo*[38], these observations point to a stress-responsive pathway that offloads damaged proteins and dysfunctional mitochondria to neighboring cells. Additional studies in the mammalian heart are urgently needed to gain a more comprehensive understanding of the role of exophers in the clearance of dysfunctional mitochondria in cardiomyocytes under physiologic and pathophysiological states.

3.2. *Migrasomes*

Migrasomes were first described in the extracellular space around normal rat kidney (NRK) cells in non-confluent culture, stimulated by increased migration and subsequently taken up by neighboring cells[39]. These structures contain tetraspanins, such as TSPAN4, and their formation depends on actin polymerization, as shown by the reduction of migrasomes when cells are treated with actin polymerization inhibitors[39]. Similar structures have also been observed in diverse cell types including primary macrophages, primary neurons, and embryonic stem cells, as well as *in vivo* in the eye, intestine, and the lung[39]. Subsequently, migrasome-specific protein markers (NDST1, PIGK, CPQ and EOGT) have been identified, which are absent in exosomes from normal rat kidney cultures[63]. These markers, together with electron microscopy, have enabled identification of migrasomes in diverse tissues and biofluids, consistent with an active role of migrasomes in cell-cell communication[63].

Damaged mitochondria located in the cell periphery can be disposed of through migrasomes in a process also called mitocytosis. In L929 cells, dynein knockdown promotes mitocytosis, while knockdown of KIF5B, Drp1 and Myosin19 suppresses this process. Enhanced mitocytosis preserves mitochondrial function, while inhibition suppresses it. *In vivo*, knockdown of mitocytosis decreases neutrophil viability in the circulation[64]. Notably, migrasomes not only dispose of damaged mitochondria but also aid intercellular transfer of mRNAs and proteins[65]. In the myocardial ischemia/reperfusion injury model, it has been shown that low-intensity pulsed ultrasound increased migrasome-dependent mitocytosis and alleviated mitochondrial dysfunction *in vitro*, and conferred cardioprotection in a Tspan-4 and RhoA dependent manner[66] (Fig. 4).

Migrasomes can also be derived from neutrophils and these migrasomes accumulate at injury site and trigger platelet activation and clotting[67]. Additional proteins have been identified associated with human neutrophil migrasomes, including coagulation factors, CD66b and CD16[67]. Migrasome associated long non-coding RNAs are a novel prognosis marker in kidney renal clear cell carcinoma[68]. In the context of cardiovascular diseases, machine learning studies have identified migrasome-related

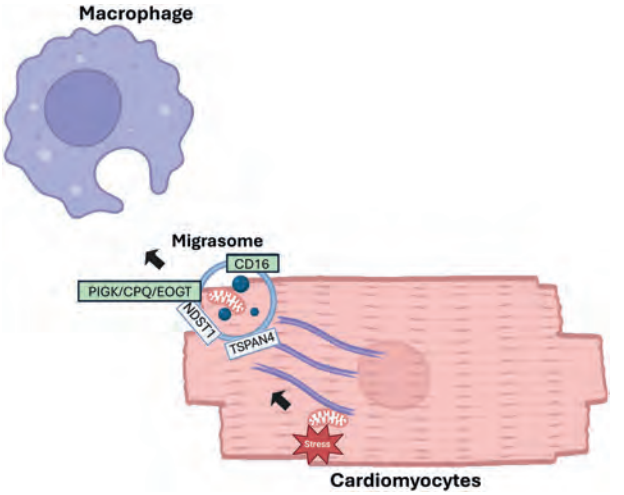

Figure 4 Migrasome formation and mitocytosis in mammalian cells. Migrasomes consist of NDST1, PIGK, CPQ, and EOGT. They form during cell migration or stress in migrating cells. Damaged mitochondria can be disposed of through migrasomes in a process also called mitocytosis, which has been shown to be associated with low-intensity pulsed ultrasound-induced cardioprotection in a TSPAN-4 dependent manner[66]. Figure generated in BioRender.

signatures linked to cardiac macrophage transformation between anti- and pro-inflammatory states, suggesting potential therapeutic targets for mitigating acute myocardial infarction[69]. Recent studies also have shown that *TSPAN4* mRNA is upregulated in macrophages in atherosclerosis human Gene Expression Omnibus database. Additionally, *TSPAN4* mRNA was found elevated in mouse model with HDL receptor +/− with ApoE$^{-/-}$, in response to Probucol, and in coronary artery ligation-induced mice[70]. The role of migrasomes in other diseases, including tumor, urology, obstetrics and gynecology, ophthalmology and neurology has been reviewed recently[71]. Despite these studies, the extent and significance of migrasome-mediated transmitophagy compared to other forms of cell-autonomous and *trans*-mitophagy pathways in diverse cardiovascular diseases are yet to be fully understood.

3.3. *Tunneling nanotubes (TNTs)*

TNTs are thin, membrane-like structures composed of F-actin, capable of extending distances of up to several hundred micrometers, creating a direct bridge between cells. They are regulated by proteins such as Myo10 (Myosin-X)[72], M-Sec (TNFαIP2)[73], and components of the exocyst complex, the organelle docking system for TNTs[74]. The exocyst complex, a protein assembly composed of subunits Sec3, Sec5, Sec6, Sec8, Sec10, and Sec15, which form the core of the complex, along with Exo70 and Exo84, which anchor TNTs to recipient cells and enable strong intercellular connections. Actin-regulating proteins such as Cofilin and Arp2/3 stabilize and reorganize the actin cytoskeleton to maintain TNT integrity during mechanical stress in the heart[75].

Rab GTPases, particularly Rab8a and Rab11 recycling, drive TNT formation. In macrophages Rho GTPase Cdc42 and Rac1 regulate Arp2/3-dependent actin polymerization and TNT biogenesis[76]. In macrophage-epithelial systems, TNTs have been shown to transfer functional mitochondria to stressed recipient cells, restoring mitochondrial membrane potential and reducing

ROS levels[41]. Mitochondrial Rho GTPase 1 (Miro1) facilitates the movement of mitochondria along cytoskeletal tracks to facilitate delivery[77]. Oxidative stress enhances TNT formation[75]. Furthermore, apoptotic cells with exposed phosphatidylserine ('eat-me' signal) use TNT-mediated transfer to neighboring cells[78].

Although not yet observed in cardiac ischemia/reperfusion (I/R) *in vivo*, TNT-mediated transfer has been documented during cardiac cell development[40], *in vitro* between cardiomyocytes under ischemia[79], and in other cell types such as retinal pigment epithelial cells[80], neurons-astrocytes[81], and bone marrow mesenchymal stem cells (BMSCs)-nucleus pulposus cells (NPCs)[41], highlighting the potential that TNT-mediated communication may play a role in maintaining cellular health (Fig. 5). However, not all TNT-mediated mitochondrial transfer is beneficial to recipient cells. Depending on cargo and context, TNTs can also propagate diseases and injury[75,82]. Recipient lung cancer cells exhibit mitochondrial-peroxisome dysfunction and caspase-independent oxidative cell-death, an observation which can be targeted therapeutically in cancer[82].

Insights from studies of TNT in the central nervous system have also demonstrated both protective and pathological cargo transfer. In neurodegenerative disease models, α-synuclein (α-Syn) aggregates move predominantly from neurons to microglia, and mitochondria travel in the reverse direction to support stressed neurons[83,84]. Live-cell confocal microscopy, fluorescent labeling of mitochondria and α-Syn fibrils, and 3D imaging have been used to visualize TNTs between neurons and microglia, revealing this polarity and showing that TNT formation increases in response to α-Syn exposure[83]. Most TNTs were actin-based, while a subset contained microtubules involved in long-range mitochondrial transport. These findings extend earlier work demonstrating TNT-mediated prion protein transfer between neurons, astrocytes, and dendritic cells, which contribute to pathologic spread[84,85]. These observations support the concept that TNT-mediated transfer can be advantageous or detrimental depending on context. Therapeutically, modulating TNT cargo specificity or formation conceivably can enhance beneficial mitochondrial transfer while limiting pathogenic protein propagation[83–85].

As mentioned above, transmitophagy may occur through several pathways: exophers[38], migrasomes[39], and tunneling nanotube transfer (TNTs)[40–42]. Likely, these pathways have different capacities, efficiency, and signaling mechanisms. Exophers have been shown to mediate transmitophagy between cardiomyocytes and macrophages. Thus, this mechanism may be in place when macrophages are stimulated. Migrasomes are vesicles released by migratory cells; thus, whether they are utilized to clear cardiomyocyte-derived mitochondria is unclear. TNTs are cytoplasmic connections between cells, thus needing cell–cell contact and active transport of organelles. One potential hypothesis is that damaged mitochondria send signals to the cytoskeleton to drive TNT formation. Collectively, exophers, migrasomes, and TNTs may provide complementary routes for intercellular mitochondrial clearance in the heart. The relative contributions of each pathway may vary depending on stress context, cell type, and signaling environment.

4. Cells involved in transmitophagy in the heart and their communications with cardiomyocytes

Transmitophagy relies on both the efficient transfer of mitochondria and the ability of recipient cells to degrade the damaged organelles. In the heart, cardiac macrophages, cardiac fibroblasts, and neighboring cardiomyocytes serve different roles in maintaining mitochondrial quality control (Fig. 2). Each of these cell types has specialized molecular adaptations that determine their ability to support transmitophagy. Understanding the roles of these recipient cells is essential for defining the intercellular dynamics of mitochondrial homeostasis in the heart.

4.1. Cardiac macrophages–cardiomyocyte interaction

Macrophages play essential roles in heart function by maintaining heart tissue homeostasis and responding to acute and chronic injuries and diseases[86,87]. The depletion of macrophages in

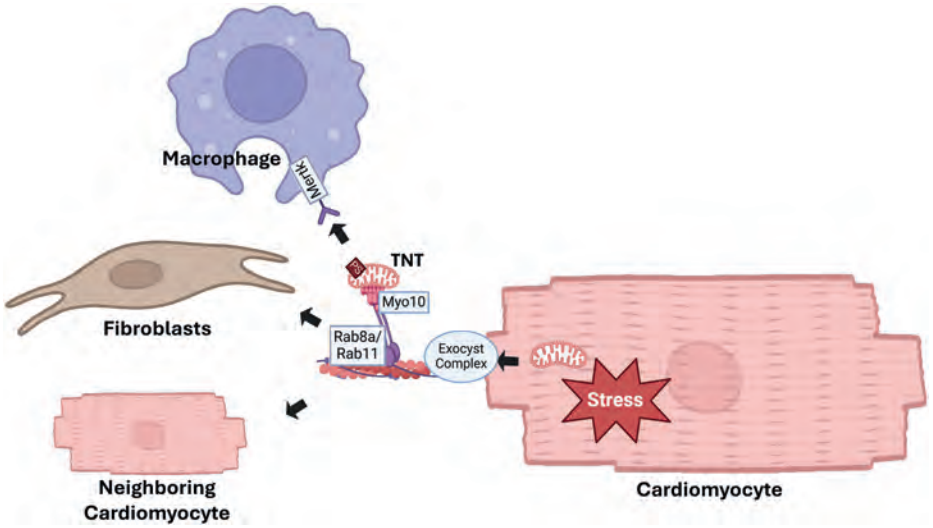

Figure 5 Tunneling nanotube (TNT)-mediated mitochondrial transfer. Dysfunctional mitochondria are transferred from cardiomyocytes to neighboring cells (macrophages, fibroblasts, and neighboring cardiomyocytes) *via* TNTs. TNT formation is driven by actin polymerization, with Myo10 and the Exocyst complex stabilizing the nanotube structure. Rab GTPases (Rab8a and Rab11) help regulate TNT formation. PS on apoptotic membrane can serve as a signal that promotes TNT-mediated interactions with recipient cells. Figure generated in BioRender.

experimental models leads to increased oxidative stress and mitochondrial damage in cardiomyocytes[38,88]. Macrophages also secrete anti-inflammatory cytokines such as interleukin-10 (IL-10), whose production and signaling can be impaired by mitochondrial dysfunction[89,90]. As discussed above, cardiac macrophages play an important role in cardiomyocyte mitochondrial quality control through exophers[38,61].

4.2. Cardiac fibroblasts–cardiomyocyte interaction

As the most abundant non-cardiomyocyte cells in the heart, cardiac fibroblasts play a key role in structural integrity and injury response. While their direct involvement in transmitophagy is understudied, cardiomyocyte-derived exosomes can activate fibroblasts and promote fibrosis[91]. As exosomes have been shown to be able to aid mitochondrial transfer between cells[49,50], it is conceivable that cardiomyocyte derived exosomes may be used to shuttle cardiomyocyte mitochondria to the fibroblasts for mitophagic degradation, an area that needs to be further investigated.

4.3. Cardiomyocyte–cardiomyocyte interaction

Adjacent cardiomyocytes are another potential recipient cell type in transmitophagy. Emerging work has shown that TNTs may drive intercellular communication in cardiomyocytes, particularly during stress or development. A recent study demonstrated the presence of TNTs mediating the transfer of extracellular vesicles between cardiomyocytes[40]. Another study showed that ischemia increases TNTs formed between cardiac cells, with mitochondria and lysosomes as contents[79]. Myocardial I/R injury also promotes migrasome-mediated mitocytosis, helping eliminate damaged mitochondria in neighboring cardiomyocytes[66].

5. Modulation of transmitophagy across development, aging, and disease

5.1. Development

The machinery capable of carrying out transmitophagy is active early in the heart. During cardiac development, cardiomyocytes form tunneling nanotubes that mediate the exchange of extracellular vesicles and cargo between neighboring cells, indicating a built-in intercellular trafficking program in the immature myocardium[40]. TNTs regulate dynamic interactions between the myocardium and the endocardium by cytoplasmic protein transfer[92]. Although currently uncertain, it is possible that mitochondria can be transferred through this mechanism as well. Furthermore, it is so far unclear whether resident cardiac macrophages establish a structural network around cardiomyocytes *in vivo* to sustain mitochondrial homeostasis and tissue fitness as they do in the adult heart[38]. Together, these data suggest that intercellular hand-off and clearance of organelles is available during development before adult-level mitophagy capacity is fully stressed.

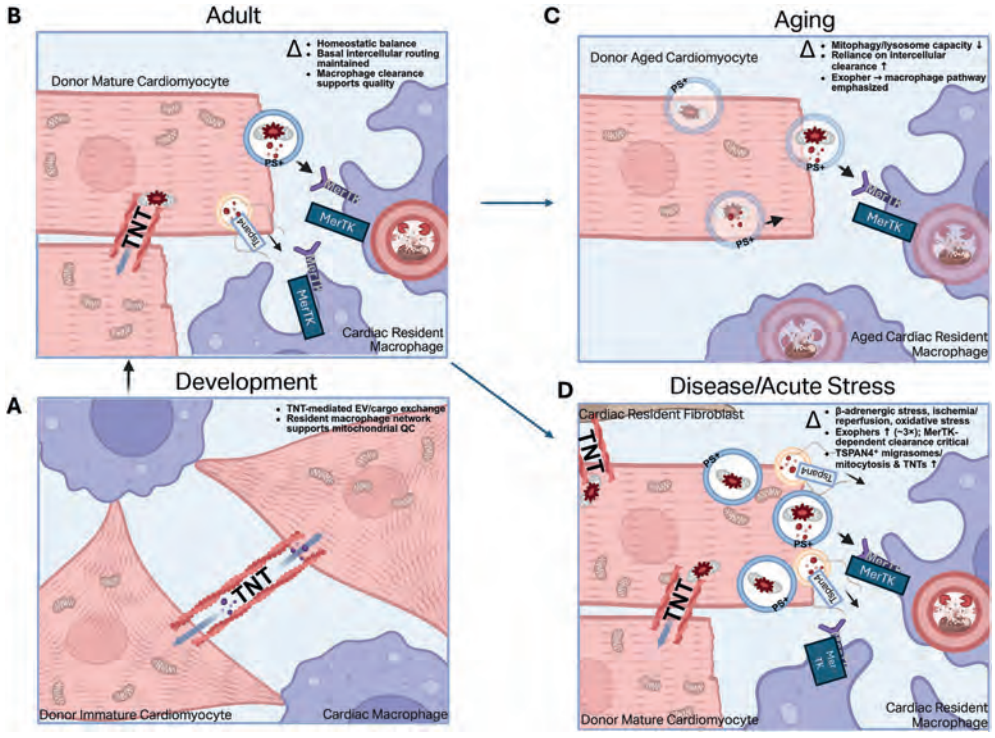

Figure 6 Transmitophagy in development, aging, and diseases in the heart. This schematic describes cell-autonomous mitophagy and transmitophagy in the developing, adult and aging heart. (A) There is evidence that during development, TNTs mediate exchange of extracellular vesicles and cargo between neighboring cells, and resident cardiac macrophages around cardiomyocytes support mitochondrial homeostasis. (B) In adult heart, cell-autonomous mitophagy and transmitophagy both can occur; the latter may be mediated by TNTs and exophers. (C) In aging heart, cell–autonomous mitophagy and lysosomal capacity are reduced. Whether there is elevation of transmitophagy pathways including those through TNT and exophers need further investigation. (D) β-Adrenergic stress, ischemia/reperfusion, and oxidative stress affect transmitophagy, through MerTK-dependent macrophage uptake, TSPAN4-mediated migrasomes/mitocytosis, and TNTs. Figure generated in BioRender.

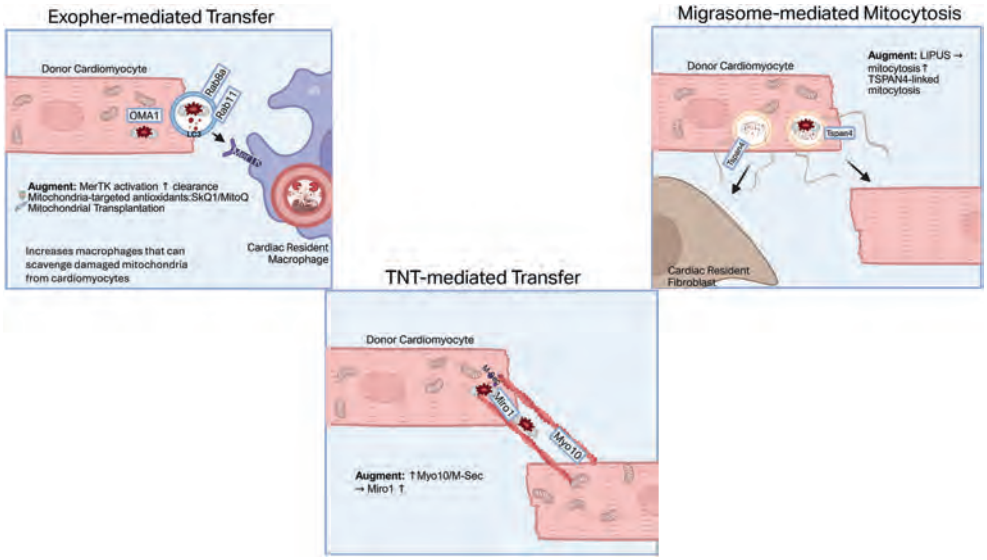

Figure 7 Therapeutic implications of transmitophagy. Graphical summary of potential therapeutic interventions targeting transmitophagy *via* exophers, migrasomes, and tunneling nanotubes (TNTs). Exopher pathway: damaged mitochondria are packaged into large vesicular exophers and cleared by MerTK-expressing macrophages. Potential therapeutic modulation includes MerTK activation of transmitophagy, complemented by healthy mitochondrial transplantation and mitochondria-targeted antioxidants (SkQ1, MitoQ) to improve mitochondrial quality. Another strategy is to increase macrophages that can scavenge damaged mitochondria from cardiomyocytes. Migrasome pathway: mitochondrial fragments are extruded along retraction fibers into TSPAN4-positive migrasomes, where they undergo mitocytosis and are degraded by neighboring cells. Potential targeting includes TSPAN4 activators to increase migrasome biogenesis, and complemented by low-intensity pulsed ultrasound (LIPUS) to increase mitocytosis. TNT pathway: F-actin—based TNTs, regulated by Myo10, Miro1, and actin polymerization dynamics, mediate direct transfer of mitochondria between cardiomyocytes and/or recipient macrophages or fibroblasts. Potential therapeutic targets include augmentation of Myo10/M-sec and Miro1. Figure generated in BioRender.

5.2. *Aging*

With age, mitochondrial quality control becomes less efficient: mitophagy signaling declines, and lysosomal degradative capacity is compromised[29–32]. In this setting, reliance on intercellular clearance likely increases. It remains to be investigated whether exopher, migrasome and TNT mediated intercellular transfers are elevated or downregulated in aging heart.

5.3. *Disease and acute stress*

Pathological stressors induce adaptive and maladaptive responses in cell-autonomous mitophagy and transmitophagy. In response to β-adrenergic stress, exopher-mediated transmitophagy is used to degrade cardiomyocyte mitochondria in the macrophages, and TNTs are also increased between bone marrow mesenchymal stem cells and cardiomyocytes[38,93]. During sepsis-induced cardiomyopathy, cardiac-resident macrophages that exhibit high TREM2 expression have been shown to scavenge cardiomyocyte-derived damaged mitochondria[61]. In response to I/R, migrasomes and mitocytosis are engaged and can be augmented by low-intensity pulsed ultrasound[66]. During *in vitro* ischemia, Langendorff heart perfusion, and in human hypertrophic hearts, TNTs form between cardiac cells with mitochondria observed within these bridges[79].

In total, exophers, migrasomes, and TNTs have been observed during acute and chronic cardiac stress, and whether they occur in the developing and aging heart still requires further investigation. Defining the mechanisms and regulation of these pathways is crucial for therapeutic development (Fig. 6).

6. Therapeutic implications of transmitophagy

Transmitophagy pathways, including exophers (large vesicles that expel damaged mitochondria), migrasomes (vesicles mediating mitocytosis), and tunneling nanotubes (TNTs, F-actin—based conduits) have been identified as routes for intercellular mitochondrial transfer. Despite these observations, targeting their therapeutic capabilities remains largely unexplored. Based on proteins involved in transmitophagy, for example, enhancing MerTK receptor levels may accelerate macrophage-mediated clearance of exopher-borne mitochondria and reduce inflammation[38]. Increasing TSPAN4-dependent migrasome formation may boost migrasome-mediated mitocytosis[66]. Upregulation of TNT scaffolding proteins, such as Myo10 and M-Sec, may strengthen TNT formation and support mitochondrial exchange in stress models[42,72]. However, while MerTK inhibitors have been used in cancer therapy (even though MerTK inhibition can be detrimental to the healthy tissues, in cancer therapy it aids the killing of cancer cells)[94], pharmacological activators of MerTK, Tspan4, or Myo10 have not been developed. There is still an urgent need for further studies to target transmitophagy as a cardiovascular protection strategy.

Additionally, intracellular mitochondrial transfer can be harmful. For example, as discussed above, TNTs are used to aid the spread of toxic proteins. Thus in such scenarios, inhibiting TNTs such as diminishing the levels of TNT scaffolding proteins, such as Myo10 and M-Sec, can be beneficial. Conceivably, MerTK, or TSPAN-4 inhibition may be beneficial to attenuate spreading of damaged mitochondria and proteins in certain pathological contexts.

Although genetic and pharmacological approaches have not been fully investigated, intrapericardial administration of a subpopulation of macrophages has been shown to scavenge damaged mitochondria from cardiomyocytes and attenuate sepsis-induced cardiomyopathy[61]. Cell-based therapies using autologous (patient-derived) and allogeneic (donor-derived) mitochondrial transplantation have shown cardioprotective effects from ischemia−reperfusion injury and improve contractile function[95,96]. Mitochondrial transplantation, involving the transfer of healthy mitochondria into damaged cardiomyocytes to restore bioenergetics, has shown promise in preclinical cardiac models[97−99]. This approach may complement or enhance endogenous transmitophagy by directly replenishing functional mitochondrial populations in at-risk hearts[100,101].

Furthermore, selective mitochondrial antioxidants (such as SkQ1 and MitoQ) stabilize donor organelles against oxidative damage, and PKCε activation confers additional protection during reperfusion injury[102,103]. Correction of pathogenic mtDNA mutations offers promise for inherited cardiomyopathies. Targeted mitochondrial DNA editing, using mitoTALENs to deplete mutant genomes and DdCBE base editors for precise mtDNA changes, has shown *in vivo* efficacy in the mouse heart, supporting future applications to inherited cardiomyopathies[104−106]. These approaches collectively can complement the modulation of transmitophagy in heart disease. Potential therapeutic intervention points along these pathways are summarized in Figure 7.

7. Challenges in the field and future opportunities

Recent studies have identified exopher-, migrasome-, and tunneling nanotube (TNT)-mediated mitochondrial transfer, providing valuable opportunities for understanding cardiovascular health, aging, and disease, as well as potential pathways for targeted therapeutic interventions to improve cardiac mitochondrial function and alleviate cardiac injuries and diseases.

Despite the identification of mitochondrial intercellular transfer pathways, several challenges remain in better understanding of mechanisms and regulation of these pathways *in vivo* in physiological and pathological conditions.

1. Studying mitochondrial intercellular transfer *in vivo* is technically challenging. TNTs are short-lived and fragile during fixation and sectioning, so under-detection is likely. Migrasomes are difficult to distinguish from other extracellular vesicles without a marker panel (TSPAN4 with NDST1, PIGK, CPQ, and EOGT) and correlative imaging. Exophers require size and cargo quantification to avoid distinguish from apoptotic bodies or large extracellular vesicles. Determining whether the transfer is uni-directional or bi-directional requires live-imaging. Finally, establishing whether these transfers are necessary and sufficient for tissue protection (or tissue damage) needs further functional manipulations to demonstrate causation.
2. **Regulation:** Whether transmitophagy is different between sexes, under circadian regulation, in response to fasting, and changes across the lifespan is still unclear. Furthermore, how to upregulate beneficial transmitophagy in aging and pathophysiological stress is still unclear. Given the sex- and circadian-dependent oscillations we and others observe in cardiac mitophagy, it will be important to test whether transmitophagy pathways (exopher release, migrasome/mitocytosis, TNT dynamics) are similarly regulated across time-of-day and sex, particularly under stress.
3. **Differential involvement of transmitophagy in various disease and injury models:** The mechanisms and roles of transmitophagy in the hearts of aging mice, as well as in different models of cardiovascular disease, remain poorly understood.
4. **Specific targeting:** Targeting transmitophagy without affecting other intracellular trafficking and intercellular communication remains a challenge. This may need identification and validation of specific modulators of transmitophagy.
5. **Mitochondrial homeostasis:** Further investigation is needed to understand how transmitophagy supports mitochondrial biogenesis and the propagation of healthy mitochondria.
6. **Potential risks of enhancing transmitophagy:** Intercellular transfer of mitochondria can be either beneficial or detrimental depending on the physiological/pathological contexts[107]. Damaged mitochondria transferred to recipient cells may overwhelm recipient cells and propagate cellular damage.

Table 1 Proteins involved in mitophagy and transmitophagy.

Protein name	Function
LC3	Mitophagy
PARKIN	Mitophagy
PINK1	Mitophagy
OPTN	Mitophagy
NDP52	Mitophagy
P62	Mitophagy
BNIP3	Mitophagy
BNIP3L (Nix)	Mitophagy
NBR1	Mitophagy
Rab9	Mitophagy
Drp1	Mitophagy
FUNDC1	Mitophagy
CED-1	Exopher
CED-6	Exopher
CED-7	Exopher
p62/SQSTM1	Exopher
HDAC6	Exopher
FTT-2/14-3-3	Exopher
EGF/RAS/MAPK	Exopher
anoh-1	Exopher
MerTK	Exopher
TSPAN4	Migrasome
NDST1	Migrasome
PIGK	Migrasome
CPQ	Migrasome
EOGT	Migrasome
KIF5B	Migrasome
Drp1	Migrasome
Myosin19	Migrasome
CD66b	Migrasome
CD16	Migrasome
F-actin	TNT
MYO10	TNT
M-Sec (TNFαIP2)	TNT
LST1	TNT
Rab8a and Rab11	TNT
Sec3, Sec5, Sec6, Sec8, Sec10, and Sec15	TNT
Exo70 and Exo84	TNT
Arp2/3	TNT
Miro1	TNT
Cdc42	TNT
Rac1	TNT

Furthermore, extracellular vesicles, exophers, or cell-free mtDNA may activate the immune system and induce inflammation.

8. Conclusions

Mitochondria can be transferred from cell to cell, and trans-mitophagy can serve as a complementary mechanism to cell-autonomous mitophagy for mitochondrial quality control in the heart. Mechanisms such as exophers, migrasomes and TNTs may facilitate this process (Table 1). The next pressing challenge will be to determine the temporal and spatial regulation (and specific regulatory proteins) involved in specific cardiac stresses, and to determine cardiovascular functional consequences of activation/inhibition of specific pathways in a time-controlled manner.

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Author contributions

Joshua Kramer, Eric Rohwer, and Jianhua Zhang wrote, edited and approved. Palaniappan Sethu, Min Xie, Timmy Lee, and Victor Darley-Usmar edited and approved.

Conflicts of interest

The authors declare no conflict of interest.

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