ER-Mitochondria Crosstalk in Mitophagy Failure: Implication for Neurodegenerative Disorders

Vaishnavi V. Sur, Himanshu B. Tapase, Aaditi D. Deo, Dr. Pankaj M. Pimpalshende,

Prajwali V. Shende*

Hi-Tech College of Pharmacy, Chandrapur - 442406

Corresponding author: prajwalishende25@gmail.com
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Abstract

The critical association between mitochondria-associated membranes (MAMs), which are endoplasmic reticulum (ER)-mitochondria contact sites, and mitophagy failure in neurodegenerative diseases is the subject of this review. Because of the high energy demands and restricted regeneration of neurons, they rely on specific mechanisms of mitochondrial quality control (MQC) including biogenesis, dynamics, and mitophagy to counteract ROS damage, bioenergetic deficits or collapse of proteostasis. By activating PINK1-Parkin-dependent ubiquitination of outer mitochondrial membrane proteins or receptor-mediated pathways, mitochondria degrades dysfunctional mitochondria through mitophagy, while its impairment damages toxic organelles, exacerbating diseases like PD, AD and amyotrophic lateral sclerosis (ALS). Additionally, MAMs function as active centers for Ca2+ mechanistic interactions. How does this explain the development of Parkinson's disease? Despite the maintenance of optimal 10-65 nm spacing by tethering proteins like MFN2, VAPB-PTPIP51, and PDZD8, disruptions such as MNF2 mutations in Charcot-MarieTooth disease or TDP-43 aggregates on ALS cause wide gaps, blunt signaling, (via PINK1/Parkin recruitment) or stall binding to LC3 adaptors. In this state, disease-specific insults converge as: -synuclein overloads MAM in PD, A/tau disrupts Ca2+ flux in AD, mutant SOD1/VAPB impairs contacts in the ALS, and mHTT blocks HD mitophagy blockade, ROS surges, inflammation (NLRP3 at MAFs), and neuronal death. By discussing mitophagy pathways, MAM architecture and crosstalk functions as well as failure mechanisms and disorder links, this synthesis concludes: "MAM stabilizers (e.g, the anti-tumor P-like pridopidine), with or without food coke, inducer[M] and ER stress modulators (4-PBA] are therapeutically effective in returning homeostasis to normal cells.". In the future, super-resolution imaging, CRISPR screens and biomarkers will be used for precision interventions balancing clearance with biogenesis.

Keywords: Mitochondria, Endoplasmic Reticulum, Mitophagy, mitochondria-associated membranes, Neurodegeneration.

1. Introduction:

The neurons are specialized and have exceptional metabolic demands and limited regenerative abilities, which make them susceptible to disruptions in cellular homeostasis. Within the organism, mitochondria are essential for neuronal function, serving as a source of energy through oxidative cohesion (ATP transport), calcium regulation within cells, redox regulation, and cellular signal activation. It is difficult to maintain a healthy mitochondrial population due to the long lifespan and polarized morphology of neurons[1]. The hallmark features of neurodegenerative disorders are mitochondrial damage or dysfunction, which results in ROS generation, impaired bioenergetics, synaptic failure, and neuronal death. To maintain mitochondrial integrity, neurons use a closely monitored mitochondrialism controlled by mitochondria (MQC), including biogenesis, dynamics (fission and fusion), selective removal of damaged mitochondria, and mitophagy. By preventing the accumulation of oxidative stress and maintaining neuronal homeostasis, mitophagy is an essential component of autophagic autopsies that efficiently eliminate dysfunctional mitochondria. The significance of defective mitophagy in the development of

neurodegenerative diseases like Parkinson's disease, Alzheimer'S, amyotrophic lateral sclerosis, and Huntington's is highlighted. Additionally, it plays a crucial role as innate immunity.[2,3]

Recently, it has been discovered that mitophagy is not a self-contained process but relies on communication between organelles. The ER can be smooth or rough in structure and plays a role in controlling important cellular functions, such as protein synthesis, folding, and transport. Besides supplying proteins, the ER is involved in the metabolism of lipids, carbohydrates, and drugs, as well as being a significant storage site for Ca2+. Specimen-associated ER membranes (MAMs) are where functional and physical connections between the er and mitochondria take place. These domain(s). The coordination of calcium transfer, lipid exchange, mitochondrial dynamics, and autophagosome formation processes by these contact sites is crucial for mitophagy.[4]

This ER–mitochondrial crosstalk regulates mitochondrial fission, which is necessary for the segregation of damaged segments in the mitophagus.[A]. Furthermore, the recruitment of autophagy machinery and mitochondrial membrane potential are influenced by calcium signaling and lipid supply from the ER. These finely tuned processes are compromised by the disruption of ER–mitochondrial contacts, leading to defective mitophagy. Damage to mitophagy signaling pathways, altered calcium homeostasis due to chronic ER stress and destabilization of er–mitochondrial tethering proteins, can result in the accumulation of dysfunctional mitochondria within neurons. Neurodegenerative diseases can be caused by a converging pathogenic mechanism, such as the failure of ER-mitochondria-mediated mitophagy. The accumulation of chronic mitochondrial damage intensifies oxidative stress, neuroinflammation, and proteostatic imbalance, leading to increased neuronal dysfunction and degeneration. We present a summary of current knowledge regarding molecular crosstalk between the endoplasmic reticulum and mitochondria, with emphasis on the structural and functional proteins responsible for controlling contact sites between ER and mitochondrials. We cite the inter-organelle communication that governs important cellular processes such as calcium signaling, dynamics of mitochondria and mitophagy."[M]. Determining the molecular basis of ER-mitochondrial interactions and their role in regulation of mitophagy is crucial for understanding the causes of neurodegenerative diseases and finding new therapeutic options that aim to restore mitochondrial homeostasis.[5–7]

2. Mitophagy Pathway

2.1 Overview of Mitophagy

It aims to remove damaged mitochondria by using autophagosomes, which then join with lysosomes to break down and recycle the parts. This process helps keep mitochondria in good condition and stops cell damage caused by the buildup of broken organelles. Mitophagy can also help reduce the amount of ROS produced and stop important nutrients like oxygen from being used up unnecessarily, which allows cells to live through various unhealthy conditions.[6]

The process starts when the mitochondria's membrane potential, called ΔΨm, decreases, which usually happens because of harm from things like oxidative stress, toxins, or lack of oxygen. This causes PINK1 kinase to build up on the outer part of the mitochondria, which then adds a phosphate group to ubiquitin and brings in the E3 ubiquitin ligase called Parkin. Parkin adds ubiquitin to proteins on the outer membrane of mitochondria, like MFN1 and MFN2, which tags the mitochondria so that autophagy proteins such as p62/SQSTM1 can recognize them. These proteins then connect the tagged mitochondria to LC3, which is part of the structure that forms autophagosomes.[5,6]

Mitophagy helps protect against neurodegenerative diseases by removing broken mitochondria, but when this process doesn't work properly, it causes harmful mitochondria to build up, leads to low energy, increases harmful Chemicals in the Body, And Results in the Death of Nerve Cells.

2.2 Pathways and Mechanism of Mitophagy

Mitophagy is a process where the cell removes damaged mitochondria, helping to keep the cell healthy. This happens mainly through two main ways:

• PINK1/Parkin dependent

• PINK1/Parkin independent

2.2.1 PINK1-Parkin-mediated mitophagy

The PARK6 gene codes for a kinase known as Serine/threonine PTEN-induced putative kinase 1, or PINK1, and the PARK2 gene codes for an E3 ubiquitin ligase called Parkin. Changes in the PINK1 and Parkin genes are the first genetic changes linked to neurodegenerative diseases. Parkin works as part of the process that happens after PINK1 in the signaling for mitophagy. It is important to build ubiquitin chains in the mitochondria as part of the PINK1-Parkin pathway that controls mitophagy. The three key parts of this setup are PINK1, which senses damage in the mitochondria, Parkin, which helps strengthen the signal, and ubiquitin chains, which carry out the signal's effect.

PINK1 as a mitochondrial damage sensor:

PINK1 works as a careful detector of damage to mitochondria by checking how well the organelle can take in proteins, mainly because it is very responsive to the electrical charge across the mitochondrial membrane, called ΔΨm. In healthy mitochondria, new PINK1 protein is made and moves through the outer membrane, which is handled by the TOM complex, and then through the inner membrane, which is managed by the TIM23 complex. This movement is guided by the N-terminal part of PINK1 called the presequence and the membrane potential known as ΔΨm. Matrix processing peptidase (MPP) cuts off the presequence, then PARL, an inner membrane protease, trims it further. This releases PINK1 into the cytosol, where it gets broken down by the proteasome through the N-end rule pathway, which helps keep its levels in check.Damage Detection Mechanism Mitochondrial stressors (e.g., uncouplers like CCCP, ROS, unfolded proteins) dissipate ΔΨm, stalling PINK1 import at the TOM-TIM23 transition; it accumulates as full-length form on the outer mitochondrial membrane (OMM) in a TOM-TIM23 supercomplex. This accumulation, rather than direct damage detection, signals dysfunction—PINK1 "probes" import integrity, as even TIM23 disruption stabilizes it without full ΔΨm loss.[8–10]

Parkin as a signal amplifier:

Parkin consists of ubiquitin-like (Ubl), repressor element of Parkin (REP), in-between-RING (IBR). resulting in the release of RING2 and exposure of the E2 interaction surface in RING1. RING2 accepts ubiquitin from E2 enzyme through a thioester bond and subsequently transfers it to substrates. Parkin transforms from a self-inhibiting dormant enzyme to an active E3 to ubiquitinate a number of OMM proteins, such as mitofusins1 (MFN1), mitofusins2 (MFN2), mitochondrial Rho-GTPase 1 (Miro1), and voltage-dependent anion channel 1 (VDAC1). Later phosphorylation of ubiquinated proteins which draws more parkin to the mitochondria, thereby generating more ubiquitin chains. Parkin is spatially selective for depolarized mitochondria. This unique selectivity appears to be the key to Parkin’s efficient and rapid ubiquitylation of dysfunctional mitochondria.[11]

Ubiquitin chains as a signal effector:

Ubiquitin chains act as important signals in the process of mitophagy, which is when damaged mitochondria are removed. These chains serve as signals that mark the damaged mitochondria, telling the cell to remove them. They help bring in the machinery needed for autophagy so that the damaged mitochondria can be properly broken down and removed. Chain Formation Parkin creates a mix of K63 and K48 types of polyubiquitin chains on proteins in the outer mitochondrial membrane, such as MFN1, MFN2, MIRO, and VDAC, following the activation of PINK1. These chains get more numerous because of a process called phospho-ubiquitin feedback. Short chains of ubiquitin are enough to start mitophagy, even if the whole proteasome system isn't working, as seen in experiments where they focused on adding ubiquitin to the outer mitochondrial membrane.

Adaptor Recruitment: Chains connect autophagy adaptors like OPTN, which is modified by TBK1 to have a stronger bond, NDP52, p62/SQSTM1, and TAX1BP1. These adaptors help move tagged cargo to the LC3/GABARAP proteins on autophagosomes. The interaction between OPTN and ATG9A helps the membrane grow larger. USP30 counters this by cutting chains, which acts as a brake on mitophagy. Downstream effects include damage to OMM proteins, breaking up mitochondria through DRP1 activity, and stopping mitochondrial movement by removing MIRO, which helps the lysosomes clear waste while keeping the cytosol safe from harmful ROS and inflammation[9].

Mechanism of PINK1-Parkin-mediated mitophagy

In the standard PINK1–Parkin pathway, when the mitochondria lose their membrane potential, it starts the main process that turns a normally inactive quality-control system into a strong signal for mitophagy. Under normal conditions, PINK1 is constantly brought into the mitochondria through the TOM/TIM23 complexes. Once inside,

it is cut by two enzymes, MPP and PARL, and then sent back to the cytosol where it is quickly broken down by the proteasome. Because of this process, the amount of PINK1 found on the outer part of the mitochondria stays very low. When the electrochemical gradient across the inner membrane goes away, like when uncouplers such as CCCP or too much reactive oxygen species are present, the import of PINK1 through TIM23 stops. This lets the full-length kinase build up on the outer mitochondrial membrane. There, PINK1 gets a phosphate group added to itself and also adds a phosphate to ubiquitin at the Ser65 spot on the existing ubiquitin molecules attached to proteins in the outer mitochondrial membrane. This creates small groups of phospho-ubiquitin that act as markers showing where damage has happened. These signals made of phospho-ubiquitin are important for starting Parkin's action. They attach to Parkin and, along with the help of PINK1 making a specific part of Parkin, called the N-terminal ubiquitin-like domain, more active at a spot called Ser65, they change the shape of Parkin so it stops blocking itself. This allows Parkin to move from inside the cell to the damaged mitochondria. This process starts a cycle where more ubiquitination happens, which makes more targets for PINK1 to work on. Once it starts working, Parkin acts like an RBR E3 ligase that adds mainly K63- and K48-linked chains of ubiquitin to several proteins on the outer mitochondrial membrane, such as mitofusins (MFN1 and MFN2), MIRO1 and MIRO2, VDAC, and TOM20. This process helps break down fusion and movement proteins like MFNs and MIRO, encourages fission of the mitochondria through DRP1, stops damaged parts from moving, and marks the outer membrane with strong “eat-me” signals of ubiquitin. These special coatings made of ubiquitin are noticed by certain proteins called autophagy receptors like p62/SQSTM1, NDP52, OPTN, and TAX1BP1. These proteins come together on the surface of mitochondria and connect with LC3/GABARAP proteins on early autophagic membranes through specific areas that interact with LC3. This process links the tagged mitochondria to the growing autophagosome. When TBK1 adds a phosphate group to OPTN and similar proteins, it makes them stick better to ubiquitin and LC3. However, enzymes called deubiquitinases, such as USP30, reduce the activity of Parkin, helping to control when mitophagy happens. When mitochondria are damaged, they are wrapped up in special bags called autophagosomes. These bags then join with lysosomes, which are like recycling centers inside the cell. The lysosomes break down the damaged parts of the mitochondria and reuse their building blocks. Besides getting rid of whole bad mitochondria, this process involving PINK1 and Parkin also helps remove specific parts of the mitochondria that are not working right. This allows the cell to carefully manage the quality and balance of proteins in the mitochondria without having to completely remove the whole organelle.[8,12]

2.2.2 PINK1-Parkin-independent mitophagy

Some ways to get rid of damaged mitochondria don't rely on PINK1 or Parkin. These methods usually involve receptors and don't need ubiquitin. They often happen when there's less oxygen, during growth, or because of other types of stress.

OMM receptors attach directly to LC3/GABARAP family proteins found on autophagosomes.

BNIP3: Hypoxia-Driven HomodimerizationBNIP3 (Bcl2/adenovirus E1B 19kDa-interacting protein 3), a HIF-1α target, localizes to OMM via C-terminal transmembrane domain under normoxia but remains monomeric/inactive; hypoxia induces disulfide-linked homodimerization, exposing N-terminal LIR (WTHL) for high-affinity LC3 binding (KD ~2 μM), clustering mitochondria for macro-autophagosome formation. Key regulators: AMPK adds a phosphate group to Ser17/24, which is near the LIR region, to help LC3 attach better; ERK1/2 helps the protein pair up; and calpain cuts the protein, releasing a part that goes to TFEB and turns it on. Cardiac ischemia-reperfusion reduces the amount of ROS and the size of the heart attack, and helps the heart resist a type of cell damage called ferroptosis. When BNIP3 is not present (KO), it stops the process of removing damaged mitochondria under low oxygen conditions (hypoxia mitophagy), but it does not stop the normal process of mitochondria turnover that happens without low oxygen.

NIX (BNIP3L): Developmental Clearance

NIX has about 56% similarity to BNIP3, and they both have a similar sequence called LIR (WQVL); it's important for the final stage of red blood cell development—when NIX is missing, mice keep their mitochondria in immature red blood cells, which stops them from maturing properly.

The process starts with transcriptional activation through GATA1 and BACH1, then involves inserting into the outer mitochondrial membrane. After serine phosphorylation at positions 17 and 24 by ERK, the protein becomes exposed to LIR. This mechanism helps remove damaged mitochondria in neurons, heart muscle cells, and cancer cells, and it works without needing Parkin. Redundancy: When both BNIP3 and NIX are missing in MEFs,

hypoxia-induced mitophagy doesn't happen anymore; NIX helps meiotic oocytes and CPC differentiation by working together with FUNDC1.

FUNDC1: Phosphorylation ToggleFUNDC1 (FUN14 domain-containing 1) spans OMM constitutively; normoxia features inhibitory phosphorylation (Ser13 by CK2, Tyr18 by SRC), masking LIR (WVEL); hypoxia triggers PGAM5 phosphatase dephosphorylation (Ser13) and ULK1/AMPK kinase activity (Ser17, LIR activation), achieving ~10-fold LC3 affinity increase. It interacts with OPA1 to help maintain the cristae in mitochondria; it's especially important in skeletal and heart muscles, as shown by the fact that removing FUNDC1 (FUNDC1 KO) makes it harder for muscles to adapt during exercise. It also has roles that don't depend on low oxygen levels, and in mice without Parkin, this interaction helps restore function through ULK1.

BCL2L13 and FKBP8: Niche RolesBCL2L13 localizes to mitochondria-ER contact sites (MAMs) via C-terminal tail; exposes LIR (WRVL) constitutively for LC3 binding, driving fission-independent mitophagy in HeLa/cancer cells under starvation; insensitive to hypoxia/CCCPFKBP8 (peptidyl-prolyl isomerase) uses N-terminal CARD-linked LIR (WxxL) for LC3 recruitment; induces basal mitophagy during apoptosis, DRP1-independent; overexpressed in glioblastoma

Mechanism of receptor mediated pathway

Receptor-mediated mitophagy uses certain proteins on the outer mitochondrial membrane that work as markers to help the cell specifically wrap up damaged mitochondria into autophagosomes, without needing ubiquitin-based systems to help with the process. These receptors have areas called LIRs, which are similar to the pattern W/F/YxxL/I, and they directly connect to proteins in the LC3/GABARAP family. This helps link mitochondria to the forming phagophores. Under normal conditions, many of these receptors are either not active because their genes are turned off, covered up after they're made, or being broken down and removed. For example, BNIP3 and NIX (also known as BNIP3L) are present in small amounts under normal oxygen conditions, because a process called SCF^FBXL4-dependent ubiquitination helps break them down through the proteasome, and their ability to interact with Rb and Bcl-2 can block their BH3 domains. When there is not enough oxygen or when red blood cells are developing, certain proteins like HIF-1α and GATA1 increase the production of BNIP3 and NIX. These proteins then move into the outer membrane of mitochondria through their transmembrane parts. They also form pairs connected by a special sulfur bond at a specific amino acid called Cys64, which helps group these proteins together on the mitochondria. This grouping makes the proteins more stable and ready for their role. At the same time, changes in the LIR area, like adding phosphate groups to certain spots (such as Ser17 and Ser24 by AMPK, JNK1/2 or ERK, and Ser60/Thr66 by JNK), make BNIP3/NIX better at connecting with LC3. This turns them into receptors that help start mitophagy. Other processes, like cutting the protein with calpain, can create smaller pieces that affect how lysosomes are made through TFEB. FUNDC1 is another example of how receptors can be controlled to start mitophagy. In normal oxygen conditions, casein kinase 2 (CK2) and SRC family kinases add phosphate groups to FUNDC1 at specific spots, Ser13 and Tyr18. This changes the shape of FUNDC1, hiding its LIR region and preventing it from connecting with LC3. Additionally, the mitochondrial E3 ligase MARCH5 adds another layer of control by adding ubiquitin molecules to FUNDC1, which stops it from working properly. However, the deubiquitinase USP19 helps reverse this effect to some extent. When there is not enough oxygen or other stressful conditions, the phosphatase called PGAM5, which is near MIC60 at the places where mitochondria touch each other, removes a phosphate group from Ser13. At the same time, other proteins like ULK1 or SIK2 add a phosphate group to Ser17. Together, these changes make the LIR motif visible and help it connect better with LC3. Other things, like the NLRX1–RRBP1 groups, help in making sure that LC3 gets lipids added locally, which helps form mitophagosomes around mitochondria that have FUNDC1 on them. Other receptors, like BCL2L13 and FKBP8, seem to work in a more constant way. Their N-terminal myristoylation and transmembrane parts help keep them attached to the OMM. Also, regions that look similar to BH3 or CARD help show their LIRs to LC3 or GABARAP. FKBP8's ability to change the shape of certain proteins can also help activate BECN1 and the class III PI3K complex. This connects the activation of receptors to the early steps of autophagy signaling. When these receptors become active, they often gather damaged or unnecessary mitochondria at specific places where autophagosomes start to form, like near the ER/MAM areas or the Golgi. This process helps link the cargoes to the autophagy system.,including ULK1/ATG13 (to a limited extent for BNIP3/NIX), the VPS34–BECN1 complex that generates phosphatidylinositol-3-phosphate (PI3P), and downstream PI3P effectors such as WIPI proteins and ATG2 that drive membrane expansion. ATG9A-positive vesicles add more membrane, and the way BNIP3/NIX interacts with WIPI proteins shows that, in some cases, mitophagy can happen even if ULK1 is not as important. Breaking up mitochondrial networks using proteins like DRP1, FIS1, MFF, and other fission factors

helps separate mitochondria that have receptors on them. Proteins like NLRX1 and NIPSNAP1/2 might help keep these mitochondria connected to the autophagic process. As the phagophore grows longer, LC3/GABARAP molecules attached to phosphatidylethanolamine build up on the growing membrane, ultimately closing around the mitochondrion that has a receptor mark. After the initial steps, the process continues with the help of certain small GTPases like RAB7 and SNARE proteins such as SYNTAXIN17. These proteins work together to bring mitophagosomes close to lysosomes, enabling the lysosomes to break down and reuse the parts of the damaged mitochondria through an enzyme called cathepsin. Even though ubiquitin isn't the main part of the first step in this process, enzymes that change ubiquitin, like USP30 and MARCH5, still help control how stable the receptors are and how much protein is removed from the outer mitochondrial membrane. They act like brakes or controls that influence how much mitophagy happens. It's important to note that even if key receptors like BNIP3, NIX, and FUNDC1 are genetically disrupted, receptor-mediated mitophagy doesn't completely stop, because other receptors such as BCL2L13 can take over partially. This shows that there's a backup system of signals on the outer mitochondrial membrane, called "eat-me" signals, which work together to keep mitochondrial recycling strong in different body conditions and during stress.

3. Architecture of Er-Mitochondrial Contacts

ER-mitochondria contact sites, also called mitochondria-associated membranes, are special areas where the endoplasmic reticulum touches the mitochondria. There's a very small space, about 10 to 65 nanometers wide, between them. This space helps the ER and mitochondria talk to each other in both directions. These contacts, which cover about 20% of the mitochondrial surface, use different proteins that physically link the membranes together. These proteins help keep the membranes close and allow important functions to happen, like moving calcium ions, swapping phospholipids, and working together to handle stress in the cell, such as removing damaged mitochondria through a process called mitophagy. Physical tethers need to follow certain rules: each part has to be connected to a separate organelle, if the connections are disturbed, like when there's more space between them, it affects how things work, and this can lead to problems like reduced movement or function.[13]

3.1 Core Tethering Complexes

IP3R–VDAC1–GRP75 Triad: The inositol 1,4,5-trisphosphate receptor (IP3R, isoforms 1–3) on the ER spans six transmembrane domains with a large cytoplasmic N-terminus forming the Ca2+ pore, while voltage-dependent anion channel 1 (VDAC1), the dominant OMM porin, creates a β-barrel conduit. These connections happen through a helper protein called GRP75, also known as Mortalin or mtHSP70. This protein attaches to the end of the IP3R and a part of VDAC1 that faces the inside of the cell. This helps keep a typical distance of about 30 to 65 nanometers between these structures, which is what you see when the rough endoplasmic reticulum transitions into the smooth endoplasmic reticulum. Parkinson's-related DJ-1 helps control this process, making it easier for calcium to flow into the mitochondria, which supports the enzymes in the Krebs cycle. When the IP3R is removed, the mitochondria can't take in enough calcium, which separates the energy production process from the rest of the cell's functions.

Mitofusin-Based Tethers (MFN2–MFN2/MFN1): Mitofusin 2 (MFN2), which is a type of dynamin-like GTPase, is found in two places: about 20 to 30% of it is attached to the ER through a tail anchor, and it can connect with itself (MFN2–MFN2) or with MFN1 on the outer mitochondrial membrane (OMM) in a different way (MFN2–MFN1). Unlike the mitochondrial fusion proteins MFN1 and MFN2 that help bring membranes together, the MFN2 links between the ER and outer mitochondrial membrane stop fusion and help shape the ER into tube-like structures. These links also limit the space between the ER and mitochondrial membranes to about 100 nanometers, break up ER fragments, and reduce the uptake of materials between them. Changes in the MFN2 gene related to Charcot–Marie–Tooth disease type 2A affect a process called neuronal MERCS, which is connected to problems in the nerves.

VAPB–RMDN3 (PTPIP51): The ER protein VAPB has a part that sticks out on the outside called the MSP domain, which attaches to the FFAT motif on RMDN3/PTPIP51, which is a part that helps control microtubule movement. This attachment happens along with a nearby twisted section of the protein, which helps make the connection stronger. This results in very close contacts between the two proteins, about 10 to 30 nanometers apart. This pair helps move phospholipids around—ORP5 and ORP8 use RMDN3 to pull PI(4)P from the cell membrane and bring it to mitochondria where it interacts with phosphatidylserine (PS). They also affect how IP3R controls calcium release. ALS mutations in the VAPB gene, like P56S, or TDP-43 clumps make it harder for proteins to

stick together, which changes the shape of synaptic spines and dendrites. When RMDN3 is missing, it increases the splitting of mitochondria through Drp1.[14]

3.2 Additional Specialized Tether

RRBP1, which is a protein found in the endoplasmic reticulum (ER) and has regions called RRM and transmembrane helices, connects with SYNJ2BP, a protein in the outer mitochondrial membrane. SYNJ2BP has a domain called PDZ that helps RRBP1 wrap around the mitochondria. This wrapping brings the ER close to the mitochondria, which helps with making new proteins and storing fats. When mitophagy happens, Parkin adds a tag called ubiquitin to SYNJ2BP, which stops the ER from wrapping around the mitochondria.

BAP31, which is also called ER B-cell receptor-associated protein 31, connects to FIS1, a protein that helps split the outer membrane of the endoplasmic reticulum. This connection allows signals for cell death to travel through a protein called procaspase-8. Even though losing FIS1 doesn't change the amount of MERCS much, it helps bring in Drp1 at the places where the membrane is about to split, linking how the ER changes shape to where it is attached to other structures.

PDZD8: ER PDZ domain-containing 8 harbors a lipid-transfer SMP barrel, self-tethering or partnering OMM proteins to form tripartite hubs with endosomes; depletion widens gaps, blocks PS/PC exchange, and impairs hypoxia-induced mitophagy via PINK1 stabilization[14]

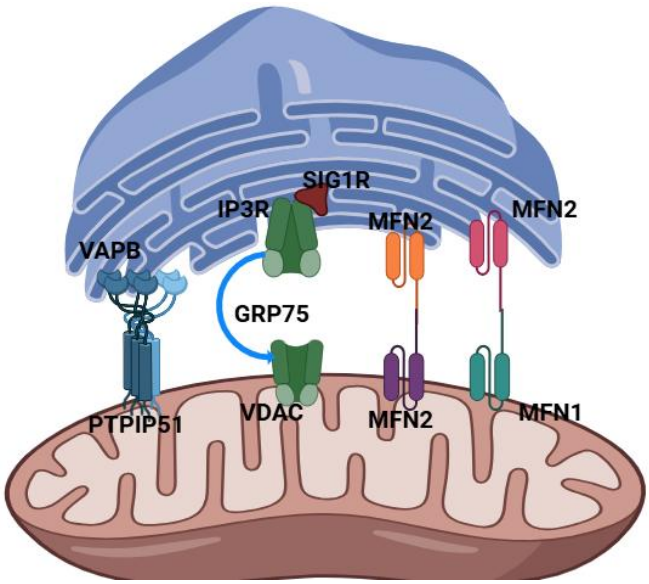

Fig.1. ER-Mitochondrial tethering proteins

4. ER–mitochondria crosstalk functionalities

The endoplasmic reticulum and mitochondria connect through special areas called mitochondria-associated membranes. These tethers help control important cell functions like calcium signaling, how cells handle fats, the movement of mitochondria, the process of cleaning out old cell parts, and the body's response to inflammation.

4.1 Ca^{2+} Homeostasis

Calcium ions play a key role in sending signals between nerve cells and in the activity of synapses. The ER acts as the main place inside the cell where calcium ions are stored, with a concentration of about 1 millimolar. At the same time, the calcium levels in the cell's fluid are kept very stable, around 100 nanomolar. Calcium ions move from the ER to the mitochondria at the MAMs, and this movement is powered by the electrical difference across the mitochondrial membrane, which is about –180 mV.

The main parts are the SERCA pumps, which move calcium from the cytosol into the ER, IP_3 receptors and ryanodine receptors located on the ER, and VDAC1 found on the outer part of the mitochondrial membrane. The IP_3R–GRP75–VDAC1 complex creates a working Ca^{2+} bridge, and SIG1R helps keep the ER–mitochondrial Ca^{2+}

signaling stable. Keeping a proper space between the ER and mitochondria, about 15 nanometers, helps improve the efficiency of calcium transfer. The flow of calcium ions supports the energy production in mitochondria, but when this process goes wrong, it causes too much calcium inside the mitochondria, leads to harmful free radicals, and can result in neurological disorders.

4.2 Lipid Homeostasis

MAMs have enzymes that help break down and use fats, which control the making of phospholipids and sterols. Phosphatidylserine is made in the ER and then sent to the mitochondria, where it turns into phosphatidylethanolamine. This phosphatidylethanolamine goes back to the ER, where it gets methylated to become phosphatidylcholine. This PS transfer via MAMs is rate-limiting.

Certain proteins linked to the MAM, like StAR, ATAD3, ERMES, EMC, and LTC1/LAM6, help move phospholipids and sterols, including cholesterol, into the mitochondria to support the production of steroids. The makeup of lipid rafts at MAMs affects where proteins go and how calcium signals work. Mitochondrial fusion and fission are also involved.

4.2 Mitochondrial fusion and fission

ER–mitochondria contacts define sites of mitochondrial fission. ER tubules physically squeeze mitochondria, which allows DRP1, a GTPase that causes fission, to come in and work. Fusion and fission help keep the shape and working of mitochondria normal.

The main regulators involved are DRP1, MiD51, inverted formin-2, and the mitofusins called MFN1 and MFN2. MFN2 plays a key role in connecting the ER with mitochondria, and its function is controlled by the mitochondrial ubiquitin ligase MITOL.

4.3 Autophagy

ER–mitochondria connections act as places where autophagosomes are made. When there is no food, certain proteins linked to autophagy, like ATG14, DFCP1, and ATG5, move to MAMs. This begins the process of forming phagophores. MFN2-dependent tethering is necessary for correct autophagosome formation. Mitophagy is a process where the body removes damaged mitochondria, and it happens through signals like PINK1/Parkin and NIX. Rab32 also helps control the structure of MAMs and the growth of autophagosomes, showing how communication between the ER and mitochondria is very important for keeping autophagy working properly.

4.5 Inflammation

MAMs play an important role in activating the NLRP3 inflammasome, which is the only inflammasome that is directly connected to the contacts between the endoplasmic reticulum and mitochondria. NLRP3 activation happens when there is too much calcium, too many reactive oxygen species, problems with the mitochondria, and changes in ion movement.

When it becomes active, NLRP3 and ASC move from the ER and cytosol to the MAMs, placing the inflammasome in a position to detect mitochondrial ROS and danger signals. ER–mitochondria proximity thus spatially organizes inflammatory signaling.[15,16]

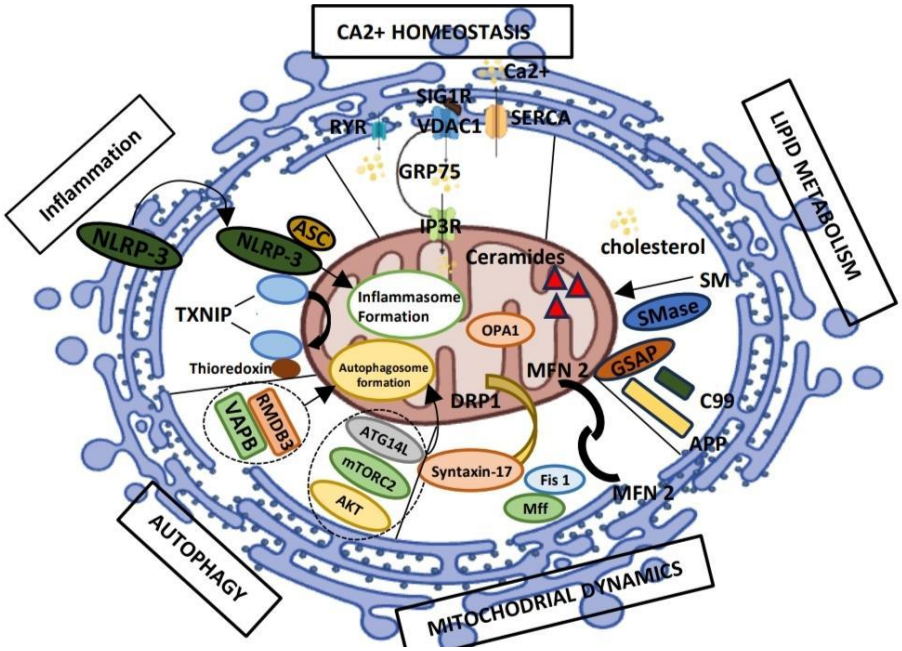

Fig.2. integration of complex ER-Mitochondrial functions: Ca2+ homeostasis, inflammation, autophagy, mitochondrial dynamics, and lipid metabolism.

5. Mechanisms Underlying Mitophagy Failure Due to ER–Mitochondrial Dysfunction

When the endoplasmic reticulum and mitochondria don't work properly, it causes mitophagy to fail. This happens because the structure and signals from the mitochondria-associated ER membranes (MAMs) get disrupted. These MAMs usually help control the quality of mitochondria in a well-organized way. In healthy cells, different systems that connect parts of the cell—like MFN2-dependent bridges between the ER and mitochondria, VAPB–PTPIP51 groups, PACS2, PDZD8, and ERMES/EMC in simpler organisms—help keep the spaces and positions between cell parts clear and organized. This setup supports important processes like moving calcium around, exchanging lipids, and setting up the right places for cell division and the formation of autophagosomes. At these points where the ER meets mitochondria, the ER tubes wrap around the mitochondria and bring in the machinery needed for splitting mitochondria (DRP1, MiD51, MFN1/MFN2, MITOL). This helps separate damaged parts of mitochondria so they can be removed by a process called mitophagy. At the same time, proteins like PINK1, Parkin, BECLIN-1, Rab32, and key autophagy proteins such as ATG14, ATG5, and DFCP1 gather temporarily at MAMs to start and grow the cup-like structures (phagophores) that surround and engulf damaged organelles. When the way cells connect is weakened or changes abnormally—like when there's not enough MFN2, PACS2 is missing, or the VAPB–PTPIP51 groups are broken apart by proteins linked to ALS such as TDP-43 or FUS—the part of the cell called the ER and the mitochondria stop being closely connected. This causes less calcium and lipid groups to form, the body can't properly bring in proteins that help remove damaged mitochondria, and autophagosomes (which are like garbage bags for the cell) don't form correctly or in the right place.[17,18] As a result, damaged mitochondria stay inside the cell instead of being removed. When calcium signaling isn't working properly at these damaged areas, it makes mitophagy even worse. The connection between parts that handle calcium is weaker, so less calcium gets into the mitochondria through these pathways. This lowers the amount of energy the mitochondria can make and stops the process that helps autophagy work properly. At the same time, too much or too long calcium moving into the mitochondria causes them to leak, releasing harmful chemicals like cytochrome c, which triggers cell death through a process called apoptosis. This overshadows the body’s natural protective process of removing damaged mitochondria through mitophagy. In addition, changes in how lipids are moved through the MAM—especially the cycle involving phosphatidylserine, phosphatidylethanolamine, and phosphatidylcholine, which is controlled by PSS1/2, mitochondrial decarboxylase, and PEMT2—along with the processing of triacylglycerol and sterols by DGAT2, ACAT1/SOAT1, and FACL4—can change the makeup of the mitochondrial membrane. This affects the supply of membrane material and the signals that help shape the membrane, which are needed for LC3 lipidation, expansion of the phagophore, and the proper wrapping of damaged mitochondria. Parkinson’s disease, ALS/FTD, Alzheimer’s disease, Huntington’s disease, and cerebral ischemia all show these same patterns. These conditions show that changes in the structure of the MAM, problems

with calcium levels, or issues with lipid balance can lead to a gradual breakdown of mitophagy. This causes the build-up of unhealthy mitochondria, long-term stress in the ER, activation of inflammasomes, and eventually, the death of neurons.[19–21]

6. ER–MITOCHONDRIAL CROSSTALK AND NEURODEGENERATIVE DISORDERS

When the communication between the endoplasmic reticulum and mitochondria at their contact sites is disrupted, it greatly affects the balance of neurons. This disruption contributes to the development of neurodegenerative diseases by causing problems with calcium handling, abnormal lipid levels, faulty removal of damaged mitochondria, and an increase in harmful reactive oxygen species. These defects show up clearly in different diseases, usually by causing problems with tether proteins that make the gaps between cell parts bigger, stop the cell from checking quality, and lead to a chain reaction of neuron damage.

6.1 Parkinson's Disease (PD)

Parkinson’s disease involves problems with the mitochondria's ability to maintain quality control and also affects the connection between the endoplasmic reticulum and mitochondria at the membranes where they meet. Changes in the PINK1 and Parkin genes, which are important in causing Parkinson's disease, stop a process called mitophagy. This process helps remove unhealthy mitochondria from cells. Normally, PINK1 attaches to mitochondria that have lost their charge, then adds phosphate groups to ubiquitin and Parkin, and starts the process of breaking down these proteins through ubiquitin.[22] Both move to MAMs, which help control calcium levels, move lipids around, and start the process of forming early mitophagosomes. Patient fibroblasts show problems with the connections between the endoplasmic reticulum and mitochondria, and they also have issues with calcium levels. These issues are connected to stress in neurons. In dopamine-producing neurons, the PINK1/Parkin pathway also helps control how materials are moved through the cell using a protein called Miro GTPase. When PINK1 is activated and Parkin starts to mark proteins, Miro comes off the damaged mitochondria, which stops the mitochondria from moving and allows them to be cleared away. Mutations keep Miro active, letting broken organelles move improperly and clump together, which makes energy and calcium problems worse. Sporadic Parkinson's disease includes α-synuclein (α-Syn), which is found at MAMs and affects lipids and how they connect. Physiologic levels help with transporting proteins, but too much, like extra copies of the SNCA gene, weakens the connections, reduces the ability to control calcium levels, and increases calcium in the cytosol and mitochondria—leading to excitotoxicity. Aggregates also block other pathways that help remove damaged parts of cells, such as chaperone-mediated autophagy, which slows down the process of clearing mitochondria. When PINK1 and Parkin are missing, along with too much alpha-synuclein, it causes problems at the MAMs.[23] This leads to poor mitophagy, weak connections between the mitochondria and the rest of the cell, and issues with the lysosomes. As a result, mitochondria pile up, there's more harmful free radicals, and the communication between nerve cells in the dopamine pathways breaks down. Therapies that help improve mitophagy, keep the MAM structure stable, or reduce α-Syn levels may offer hope.[24,25]

6.2 Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) affects how different parts of the cell communicate, especially at the points where the endoplasmic reticulum meets the mitochondria. These areas are called mitochondria-associated membranes (MAMs), and communication at these sites is disrupted in ALS. Proteins connected to ALS, such as TDP-43, mutated SOD1, and VAPB, affect these connections, which mess up calcium movement, energy production, and the body's ability to keep mitochondria working properly—things that are really important for the high-energy needs of motor neurons. Cytoplasmic TDP-43 clumps, which are often found in both sporadic and inherited ALS, lower the closeness between the ER and mitochondria by breaking the connection made by the VAPB-PTPIP51 link. This structure helps keep connections stable, allowing calcium to move efficiently from the ER to the mitochondria to make ATP. [26]TDP-43 disruption makes it harder for cells to take in nutrients, reduces energy levels, and worsens problems in long-axon motor neurons. ALS tissue samples and models show changes in VAPB/PTPIP51, and VAPB mutants copy these changes in calcium balance. Increasing VAPB or PTPIP51 helps fix the connection and function of synapses in TDP-43 models, showing that these could be useful for treatment. Mutant SOD1, which is linked to inherited ALS, clumps together on the outer membranes of mitochondria. It attaches to VDAC1, which reduces the flow of ions and ADP through the membrane. This makes it harder for the body to get enough oxygen and energy, because removing VDAC1 makes the symptoms of SOD1 mice worse. VDAC1 helps connect how SOD1 affects the IP3R-GRP75-VDAC1 calcium pathway, which leads to problems in the MAM, making TDP-43 and VAPB issues worse. Together, TDP-43, SOD1, and VAPB all

affect how MAMs are connected and work, leading to ongoing problems with calcium and ATP, nerve cell membrane changes, increased harmful chemicals, failure of the cell's waste removal process for mitochondria, and loss of connections between nerve cells—this all leads to the death of motor neurons. MAM restoration strategies seem to work well when combined with efforts to prevent aggregation[27,28].

6.3 Alzheimer's Disease (AD)

Alzheimer's disease goes beyond just the buildup of amyloid-beta plaques and tangled tau proteins to affect the whole nervous system, especially the points where the endoplasmic reticulum and mitochondria connect. These junctions handle calcium exchange, lipid production, movement, and the start of autophagosomes—important for keeping neurons strong and healthy. MAM changes cause stress in the mitochondria, poor removal of damaged mitochondria, and early loss of synapses. Aβ is made at MAMs through APP-secretase complexes, which increases the amount produced locally. Aβ then messes up the calcium and lipid signals in the MAM area: more movement of IP3R to VDAC leads to too much stress on the mitochondria, changing from short bursts of energy to a sudden increase in harmful chemicals, changes in membrane leaks, and signals that lead to cell death. [29]Lipid issues make membranes worse, which starts a bad cycle involving Aβ and MAM. Tau proteins become overly phosphorylated, which makes things worse by attaching to mitochondria, reducing their energy potential, disrupting how they split and merge, and hindering the transport along nerve fibers. Tau stops PINK1 from staying stable and prevents Parkin from coming in, which reduces mitophagy and lets harmful organelles that make too much ROS keep around. Aβ and tau target MAMs to disrupt mitophagy sites, which are needed for forming autophagosomes[30]. When signals get messed up and the PINK1-Parkin pathway isn't working right, mitochondria build up in the dendrites and synapses. This causes proteins to become damaged, messes up how vesicles move around, and makes calcium levels unstable. These changes lead to loss of dendritic spines and memory problems before the neuron actually dies. Therapeutically, normalizing MAM, using mitophagy boosters like PINK1-Parkin or receptor-targeted approaches, and enhancing lysosomal function all target this key area, providing a comprehensive approach to fight against the Aβ/tau processes.[31,32]

6.4 Huntington's Disease (HD)

Huntington's disease is a type of brain disorder that is passed down in a dominant way. It happens when there are too many CAG repeats in a gene called HTT, which leads to a harmful version of a protein called huntingtin. This harmful protein has a long stretch of the amino acid glutamine, which is toxic to brain cells. In addition to the usual problems with movement, thinking, and mental health, mitochondrial issues start appearing early on as a major problem, even before a lot of brain cells are lost . The mutant huntingtin protein harms mitochondria by changing how genes are expressed in the nucleus, by interacting directly with the mitochondria's membrane, and by causing problems with how mitochondria move, function, and are maintained. These changes damage the ability to make ATP, disrupt the balance of calcium, and worsen the control of reactive oxygen species (ROS), making striatal medium spiny neurons more at risk. A key problem is the failure to properly remove damaged mitochondria. Neurons use mitophagy to get rid of old and broken parts inside their mitochondria, but Huntington's disease makes this process fail. The harmful protein mHTT goes into the space between mitochondrial membranes and sticks strongly to the TIM23 complex, which stops other important proteins from entering the mitochondria. This messes up the mitochondrial protein mix, reducing important enzymes and helper proteins that the cell needs to handle stress and repair itself. As a result, the signals for fission, fusion, and mitophagy don't work properly, which lets damaged mitochondria build up in the nerve cell branches.[33]

mHTT further derails dynamics and transport. In high-definition models and patient tissue, it attaches to the fission GTPase Drp1, increases its activity, and leads to too much fragmentation. Broken mitochondria have trouble producing energy and moving properly along nerve cells, which leaves synapses without healthy mitochondria and keeps damaged ones stuck in areas of the brain that need a lot of energy. Although breaking up mitochondria helps in the process of removing damaged ones, too much breaking up along with problems in moving parts and failing to bring in necessary materials overloads the cleanup systems. Also, issues with calcium levels make the situation worse. HD mitochondria don't handle calcium well, they lose their charge and become leaky when there's too much excitotoxic stress. This creates stressed organelles that are ready for mitophagy, but when the import process, movement, and lysosomal function are not working properly, these organelles stay, leading to more ROS, signals that cause cell death, DNA damage, and problems with synapses. These processes are similar to those seen in polyglutamine diseases, where faulty proteins damage mitochondrial health. Fixing important proteins, such as those involved in breathing or cell movement, often helps improve problems, which shows that these proteins are really causing the issues. In high definition, mHTT's multiple attacks on TIM23 import, Drp1 fission, axonal

transport, and stress responses cause the body to fail in clearing harmful proteins, which worsens energy failure, increases damage from harmful substances, and leads to the loss of nerve cells. This positions mitochondrial-targeted therapies as promising interventions.[34,35]

7. Therapeutic Targeting of Er-Mitochondrial Crosstalk

Targeting the communication between the endoplasmic reticulum and mitochondria at the mitochondria-associated membrane (MAM) shows potential for treating conditions like Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, cancer, and metabolic disorders. This approach can help by keeping the connections between MAMs strong, improving the removal of damaged mitochondria through mitophagy, and controlling stress in the endoplasmic reticulum. [36]

Small molecules and protein–protein interaction (PPI) regulators help adjust connections like VAPB–PTPIP51, IP3R–Grp75–VDAC, Mfn2, Miro, Sig-1R, and SYNJ2BP–RRBP1. Stabilizers, such as Sig-1R agonists like fluvoxamine or pridopidine, and synthetic linkers, help keep the normal flow of calcium and lipids, maintain ATP production, and support neuron survival, which helps improve movement in fruit flies with Parkinson's disease. Disruptors like IP3R antagonists [2-APB], oligomycin analogs, and Grp75/IP3R–VDAC inhibitors stop hyper-tethering, calcium overload, and cell death in models of ALS and AD.[37]

7.1 Mitophagy Enhancer

Some substances that help activate PINK1 and Parkin, like kinetin riboside, CCCP, and optochemical tools, keep PINK1 on the damaged mitochondria. This allows Parkin to attach to proteins on the outer mitochondrial membrane, such as Mfn1, Mfn2, and VDAC1. It also helps bring in OPTN and NDP52 along with LC3, which are important for forming autophagosomes. Using inhibitors of DUB enzymes increases the process that is affected in Parkinson's disease. Natural compounds like urolithin A from pomegranates, resveratrol, curcumin, and actinonin help improve pathways that don't rely on PINK1, such as BNIP3/NIX and FUNDC1, and also help reduce levels of harmful oxygen molecules called ROS. Protectants like SS-31 and substances that increase PGC-1α through exercise or supplements, along with pridopidine, help keep MAMs and respiration functioning in Huntington's disease.[38]

7.2 ER Stress Modulators

Chemical chaperones like 4-phenylbutyrate and TUDCA help proteins fold correctly and reduce problems with amyloid-β and MAM causing calcium imbalance. UPR tuners, like PERK inhibitors (GSK2606414, salubrinal), IRE1/ATF6 modulators, and Sig-1R activators, help balance the body's responses, keep the IP3R and IRE1 stable, increase Nrf2 activity, and connect ER stress through RRBP1–NLRX1–LC3 to mitophagy without causing cell death. These treatments work well in models of Parkinson's disease, ALS, and diabetes.[39]

8. Future Perspective

Mitophagy is the process where the cell removes damaged mitochondria through a specific type of cell cleaning called autophagy. This process is important for keeping the cell healthy and balanced, and it closely connects with the membranes that link the endoplasmic reticulum to the mitochondria. MAMs help move calcium, exchange lipids, and send signals between different cell parts, and mitophagy helps keep mitochondria healthy and working properly. Problems in both can lead to brain disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease. New studies show that focusing on these pathways could be a promising new treatment approach, combining a deeper understanding of how they work, recent technology improvements, and real-world patient applications.

8.1 Mechanistic Insights and Research Directions

Future research will look into different mitophagy pathways, including the PINK1-Parkin pathway, receptor-based pathways like BNIP3, NIX, FUNDC1, and PHB2, and pathways controlled by deubiquitinase enzymes. The goal is to either increase or reduce these specific pathways without affecting the whole autophagy process. Using combinatorial approaches that combine mitophagy with mitochondrial biogenesis through the PGC-1α-NRF1/2-TFAM pathway can help repair and restore the whole mitochondrial network, instead of just removing damaged mitochondria.

For MAMs, detailed study of tether proteins such as MFN2, VAPB, PTPIP51, and the IP_3R-GRP75-VDAC complexes will help understand how these components interact with each other over time. Some questions that are still not fully answered include what exactly PINK1 and Parkin target, how other pathways can make up for their loss when they're missing, and how mitophagy can act in different ways depending on the situation, like helping or harming the cell under low oxygen or poor nutrition conditions. Some substances that boost PGC-1α, which is like what happens when you exercise or eat less, might help reduce fragmentation in different health conditions.

Longitudinal studies show that changes in MAM and mitophagy are early signs of disease; for example, measurements in cerebrospinal fluid can predict the progression of Alzheimer's disease several years in advance.[40]

8.2 Technological Advances

Super-resolution microscopy and optogenetics will allow for real-time observation of MAM changes and mitophagy in cells made from patients' skin or blood samples. AI-powered proteomics and CRISPR methods are used to study groups of proteins like IP_3R-Grp75-VDAC-DJ-1, which are involved in Parkinson's and ALS. These tools help find molecules that can stabilize these protein groups, such as modulators of VPS13D. New ways to measure mitophagy include non-invasive markers like special reporters that track metabolic changes, parts of mitochondria found in the blood, and imaging tools like PET tracers. These methods aim to make testing for mitophagy more standard and reliable. AUTAC chimeras and gene therapies, like improved BNIP3/NIX, allow for exact targeting and breakdown of certain mitochondrial parts that are linked to diseases..

8.3 Therapeutic Targets and Applications

8.3.1 MAM Modulation

Stabilizing the connections between IP_3R, GRP75, and VDAC helps regulate calcium flow in Alzheimer's and Parkinson's diseases, which lowers the buildup of harmful proteins like Aβ and tau and reduces calcium overload. Stopping too much attachment, like in PS2 mutants, reduces the making of Aβ. Certain drugs called SIG1R agonists, such as pridopidine, are being tested in advanced stages of clinical trials for conditions like Huntington's disease and amyotrophic lateral sclerosis. These drugs are also being studied for Parkinson's disease. They help improve the flow of substances within cells and reduce the clumping of a protein called alpha-synuclein. Synthetic tethers that block MFN2/VAPB and PACS-2 improve the balance of fats in the body and help clear damaged mitochondria in ALS and ischemia conditions.

8.3.2 Mitophagy Tuning

Some medicines that target specific pathways can help in early stages of Parkinson's, Alzheimer's, or ADHD by either increasing PINK1-Parkin activity or reducing USP30. Other pathways, like NAD^+, SIRT1, and AMPK, are linked to improving overall health and longevity. A "tunable set-point" stops too much or not enough (like in neurons) by using inducers along with biogenesis agents.

By 2030, experiments might use chaperones, inhibitors that stop MCU, and CRISPR technology, like targeting mutant huntingtin's MAM binding, to reduce ROS and cell death.

8.3.3 Clinical Translation and Challenges

MAM/mitophagy treatments might change neurodegenerative diseases into conditions that are easier to handle, thanks to nanodelivery systems that help get drugs past the blood-brain barrier and iPSC models that make sure the treatments target the right cells. Pridopidine has helped slow down the worsening movement problems in Huntington's disease, showing improvement since 2021.

The challenges involve differences between cell types and specific protein forms, finding the right level of activity, and keeping the balance between removing substances and making new ones. Disease-focused uses include helping protect the heart and metabolism by boosting mitophagy after an injury and fighting cancer by reducing the ability of tumors to grow and survive. This connection shows that MAMs and mitophagy work together as key tools for personalized medicine in brain and nervous system conditions.[41,42]

9. Conlusion

The complex communication between the endoplasmic reticulum and mitochondria, which happens at the mitochondria-associated membranes, plays a key role in mitophagy. This process helps keep the quality of mitochondria in neurons stable, especially when there is stress from neurodegenerative diseases. This review explains how groups of proteins like IP3R-GRP75-VDAC1, MFN2 bridges, and VAPB-PTPIP51 help move calcium, transfer fats, and create places where damaged parts of cells can be removed. These processes help PINK1 and Parkin mark damaged parts for removal, or trigger the cell's own cleaning system to get rid of them. Pathological disruptions, from PINK1/Parkin mutations in Parkinson's disease and TDP-43/VAPB severance in ALS to Aβ/tau hyperactivation in Alzheimer's and mHTT import blockade in Huntington's, converge on MAM destabilization, yielding mitophagy stasis, ROS surges, bioenergetic collapse, and synaptic failure. These shared flaws show that MAMs are leading the way in treatment. Some medicines, like SIG1R agonists (such as pridopidine) and MFN2 modulators, help restore the connections between mitochondria. At the same time, other drugs such as urolithin A and USP30 inhibitors help boost mitophagy. These are used together with drugs that reduce ER stress, like 4-PBA and PERK blockers, to improve the flow of cellular processes without causing too much autophagy, as shown in studies using disease models. PGC-1α activators show promise in balancing cell energy production, helping to slow the progression of Huntington's disease in early research studies. Looking ahead, using high-resolution imaging to study iPSC neurons and MAM markers like phospho-ubiquitin and proximity measurements will help identify specific conditions and thresholds in different contexts. Looking at neurodegeneration as a disruption caused by MAM issues opens the door to new, targeted treatments. These treatments can fix the balance between different cell parts, stop the faulty process of mitophagy, and strengthen nerve cells. This marks a big change in how we approach brain disorders.

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