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REVIEW

Role of Mitochondrial Dysfunctions in Neurodegenerative Disorders: Advances in Mitochondrial Biology

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Abstract

Mitochondria, essential organelles responsible for cellular energy production, emerge as a key factor in the pathogenesis of neurodegenerative disorders. This review explores advancements in mitochondrial biology studies that highlight the pivotal connection between mitochondrial dysfunctions and neurological conditions such as Alzheimer's, Parkinson's, Huntington's, ischemic stroke, and vascular dementia. Mitochondrial DNA mutations, impaired dynamics, and disruptions in the ETC contribute to compromised energy production and heightened oxidative stress. These factors, in turn, lead to neuronal damage and cell death. Recent research has unveiled potential therapeutic strategies targeting mitochondrial dysfunction, including mitochondria targeted therapies and antioxidants. Furthermore, the identification of reliable biomarkers for assessing mitochondrial dysfunction opens new avenues for early diagnosis and monitoring of disease progression. By delving into these advancements, this review underscores the significance of understanding mitochondrial biology in unraveling the mechanisms underlying neurodegenerative disorders. It lays the groundwork for developing targeted treatments to combat these devastating neurological conditions.

Keywords Mitochondria · Neurodegeneration · Oxidative stress · MtDNA dynamics · Biogenesis · Therapeutics

Introduction

Over 1.5 billion years ago, mitochondria (Mt) came into existence through the process of endosymbiosis, a process in which a eukaryotic ancestor cell incorporated a prokaryote resembling contemporary α-proteobacteria progenitors [1–3] that are derived from ocean dwelling clade [4]. Mt are the double membrane bound cell organelle that produce chemical energy as adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS) and empower the cell to carry on its functions and reactions [5–7]. Mt contain their own circular DNA or genomes of maternal origin [8], provided majority of mitochondrial proteins are powered by nuclear genome which are synthesized by cytosolic ribosomes and transferred to outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM), intermembrane space (IMS), and matrix [9]. The mutation in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA) disrupts its functions and causes disorders such as cancer [10, 11], neurodegenerative diseases [12, 13], ageing [14, 15], and cardiovascular diseases [16]. Numerous mitochondrial and nuclear genes play specific roles in maintaining mitochondrial integrity and behavior, as detailed in Table 1. Understanding these roles is crucial for devising effective strategies in mitochondrial research for health and disease, extending beyond neurological disorders.

Structure and Function of Mitochondria (Mt)

When utilizing electron microscopy, the Mt exhibit a distinctive double-membrane structure comprised of essential phospholipids. These lipids play a critical role in various processes, including the regulation of membrane curvature,

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Table 1 List of genes, its chromosomal location, proteins, size, and their biological functions

Gene	Chromosomal location	Protein	Size	Biological function	References
OPA1	3q29	Optic Atrophy 1 (OPA 1)	120 kDa	Mitochondrial fusion at inner membrane	[17]
OMA 1	1p32.2–p32.1	OMA 1	60.1 kDa	Drive mitochondrial outer membrane	[18]
BAK	6p21.3	Bak	23.4 kDa	Apoptosis	[19–21]
BAX	19q13.3–q13.4	Bax	21 kDa	Apoptosis	[19–21]
BCL- 2	18q21.33	Bcl–2	26.2 kDa	Anti-apoptosis	[19–21]
BCL—XL	20q11.21	Bcl–XL	83.55 kDa	Anti-apoptosis	[19–21]
LL-37	3q21	LL-37	~4.5 kDa	Anti-microbial peptide	[22]
VDAC 1	5q31	VDAC 1	32 kDa	Gatekeeper for entry and exit of mitochondrial metabolite	[23–25]
VDAC 2	10q22.2	VDAC 2	~30 kDa	Anti-apoptosis	[26]
FIS 1	7q22.1	Fis 1	16 kDa	Mitochondrial fission protein	[27, 28]
DRP 1	12p11.21	DRP 1	~80 kDa	Mitochondrial fission protein	[27, 28]
MFN 1	3q26.33	Mitofusin 1	~84.1 kDa	Mitochondrial fusion protein	[27, 28]
MFN 2	1q36.2	Mitofusin 2	~86.4 kDa	Mitochondrial fusion protein	[27, 28]
MFF	2q36.3	mitochondrial fission factor Protein	~38.4 kDa	Mitochondrial division control	[29]
MIEF2	17p11.2	MiD49	~49 kDa	Assist mitochondrial binary fission	[29]
MIEF1	22q13.1	MiD51	~51 kDa	Negative regulator of mitochondrial fission	[29]
PINK—1	1p36.12	PTEN-induced kinase 1 (PINK 1)	63 kDa	Protection from stress	[30]
BNIP3	10q26.3	Bcl-2/adenovirus E1B protein interacting with protein 3 (BNIP3)	24–35 kDa	Apoptosis	[31]
NIX	8q21	Nip3-like protein X (Nix)	~19 kDa	Anti-apoptosis	[31]
FUNDC1	Xp11.3	FUN14 domain-containing protein 1 (FUNDC1)	17 kDa	Mitochondrial quality control	[31]
PPARGC1A	4p15.3	Proliferator-activated receptor γ coactivator-1 α (PGC-1α)	~91 kDa	Regulation of mitochondrial biogenesis and metabolism	[32, 33]
NRF 1	17q21.3	Nuclear respiratory factors 1	67 kDa	Activation of mitochondrial transcription factor A (Tfam)	[32, 33]
NRF 2	2q31.2	Nuclear respiratory factors 2	45 kDa	Activation of mitochondrial transcription factor A (Tfam)	[32, 33]
IMMT	2p11.2	Mic 60/mitofilin	90 kDa	Mitochondrial structural stability	[34, 35]
CHCHD3	7q33	Mic 19/chchd3	26.1 kDa	Mitochondrial structural stability	[34, 35]
SAM 50	22q13.31	Sam 50	~51.9 kDa	Mitochondrial structural stability	[34, 35]
TOMM6	6p21.1	Tom6	8 kDa	Outer membrane complex subunit	[36]
TOMM5	9p13.2	Tom5	~6 kDa	Outer membrane complex subunit	[36]
TOMM7	7p15	Tom7	~6.2 kDa	Outer membrane complex subunit	[36]
TOMM22	22q12–q13	Tom22	~15.5 kDa	Outer membrane complex subunit	[36]
TOMM20	1q42.3	Tom20	~16.2 kDa	Outer membrane complex subunit	[36]
TOMM40	19q13.32	Tom40	~37.8 kDa	Outer membrane complex subunit	[36]
TOMM70	13q12.2	Tom70	~67.4 kDa	Outer membrane complex subunit	[36]
NGB	14q24.3	Neuroglobin	~16.9 kDa	Regulation of endogenous protective mechanisms	[37]
INF2	14q32.33	Inverted formin 2	~135.6 kDa	Involvement in mitochondrial fission mediated by Drp 1	[38]
AKAP1	17q22	A kinase anchor protein 1	~9.7 kDa	Protects neurons from I/R injury	[39–41]
PRKAA1	5p13.1	AMP (activated protein kinase)	~62.3 kDa	Regulation of cellular metabolism	[42]
GBA1	1q22	LLRK 2	286 kDa	Regulation of mitochondrial dynamics	[43]
PARK7	1p36.23	Protein deglycase (DJ-1)	~20 kDa	Regulation of mitochondrial dynamics	[43]

Table 1 (continued)

Gene	Chromosomal location	Protein	Size	Biological function	References
SNCA	4q22.1	α-Synuclein	~15 kDa	Mitochondrial membrane permeabilization	[44]
PARP1	1q42.12	Parp 1	116 kDa	DNA repair enzyme	[45, 46]
TARDBP	1p36.22	TDP–43	43 kDa	Disruption of mitochondrial complex 1 activity	[47–49]
STING 1	5q31.2	Stimulator of interferon genes	~42.1 kDa	Activates other signaling pathways like NF–kB, IFN 1	[50]
GSK3B	3q13.33	Glycogen synthase kinase 3□	~46.7 kDa	Apoptosis	[51]
MAP3K5	6q22.33	Apoptosis signal-regulating kinase 1	~154.5 kDa	Apoptosis	[52]
BBC3	19q13.32	Apoptotic p53/Bcl-2-binding component 3 (BBC3)	~26.4 kDa	Apoptosis	[52]
JUN	1p32.1	c-Jun NH2-terminal kinase	~35.6 kDa	Apoptosis	[52]
DIABLO	12q24.31	Direct IAP-binding protein with low PI (DIABLO)	~27.1 kDa	Apoptosis	[53]
HTRA2	2p13.1	High-temperature requirement protein A2 (HTRA2)	49 kDa	Apoptosis regulator	[53]
XIAP	Xq25	X-linked inhibitor of apoptosis (XIP1)	~9 kDa	Apoptosis inhibition	[54]
APAF1	12q23.1	Apoptotic protease activating factor 1 (APAF1)	~141.8 kDa	Apoptosis	[55]
MTOR	1p36.22	Mammalian target of rapamycin (mTOR)	~250 kDa	Cell growth regulator	[56]
NLRP3	1q44	NLR family pyrin domain containing 3 (NLRP3	118 kDa	Membrane pore opening	[57]
ATF1	12q13.12	Activating transcription factor associated with stress 1 (ATFS-1)	~29.2 kDa	Trigger mitochondrial turn over	[58]
VAPB	20q13.32	Vesicle-associated membrane protein-associated protein-B (VAPB)	~27.2 kDa	Regulate the ER-mitochondria associations and calcium homeostasis in neurons	[59, 60]
RMDN3	15q15.1	Protein tyrosine phosphatase-interacting protein-51 (PTPIP51)	~52.1 kDa	Regulate the ER-mitochondria associations and calcium homeostasis in neurons	[59, 60]
RHOT1	17q11.2	Miro 1	~70.7 kDa	Adaptor protein	[61]
ULK1	12q24.33	Unc-51 like autophagy activating kinase 1 (ULK1)	~112 kDa	initiator of autophagy/mitophagy	[62]
CALCOCO2	17q21.32	Nuclear dot protein 52 kDa (NDP52)	~52 kDa	Cargo adaptors	[63, 64]
TBK1	12q14.2	Tank-binding kinase 1 (TBK1)	~89.6 kDa	Mitophagy enhancer	[65]
AMBRA1	11p11.2	Activating molecule in BECN1-regulated autophagy protein 1 (AMBRA1)	~142.5 kDa	Induce mitophagy	[66]
PHB2	12p13.31	Prohibitin 2 (PHB2)	34 kDa	Mitophagy	[67]
PHB1	17q21.33	Prohibitin 1 (PHB1)	32 kDa	Mitophagy	[68, 69]

remodeling, and mitochondrial dynamics. Mt is integral to a multitude of cellular functions, such as phospholipid synthesis, hemoglobin biosynthesis, lipid synthesis, stem cell reprogramming, cell cycle progression, cellular proliferation, cell differentiation, ATP production, the citric acid cycle, fatty acid oxidation, innate immunity, iron-sulfur (Fe-S) cluster production, generation and maintenance of reactive oxygen species (ROS), redox signaling, calcium homeostasis, apoptosis, and autophagy [50, 70–77]. These vital cellular processes involve proteins distributed across four distinct mitochondrial compartments: the matrix, IMS, OMM, and IMM [78]. The OMM connects to the cytosol, while the IMM extends into the mitochondrial matrix, housing mtDNA [79]. MtDNA, consisting of approximately 1000–10,000 copies per cell, includes transfer RNAs (tRNAs) [74], two ribosomal RNAs (rRNAs) [13], and complex protein subunits (C1, C2, C3, C4, and C5) [80–82]. Over 1500 different proteins [83, 84], including 13 transported from the matrix to the oxidase assembly translocase (TOM complex), contribute to these processes.

The mitochondrial matrix hosts the tricarboxylic acid (TCA) cycle, housing essential enzymes, NADH, and

FADH, utilized by the electron transport chain (ETC) to generate a mitochondrial membrane potential (Mtmp) crucial for OXPHOS [85]. OXPHOS facilitates significant ATP production in Mt. Mitochondrial NAD^+ ($MtNAD^+$), regulated by enzymes like nicotinamide phosphoribosyltransferase (NAMPT) and mitochondrial nicotinamide mononucleotide adenylyltransferase (NMNAT3), contributes to the intracellular NAD^+ pool [86]. Mt NAD^+ transporters, SLC25A51 and SLC25A52, aid in maintaining normal NAD^+ levels in humans [87]. Disruption of NAMPT, for instance, can interfere with mitochondrial respiration in mammals[88, 89]. The IMM comprises the inner boundary membrane (located near the OMM) and the cristae membrane (found in the innermost regions of the IMM) [90]. The cristae membrane houses pro- and anti-apoptotic proteins, as well as regulators of mitochondrial fusion and fission.

Outer Membrane and Inner Membrane

Major phospholipids in the mitochondrial membrane include phosphatidylcholine, phosphoethanolamine, cardiolipin (CL), and phosphatidic acid (PA). PA, a saturated lipid, aids in the remodeling of the Mt membrane[91]. The OMM proteome comprises integral proteins grouped based on their structure, such as α-helical transmembrane segments and β-barrel proteins with multiple β-strands [92]. These proteins act as a physical barrier, restricting large molecule diffusion into the organelle while allowing the passage of small molecules through different import mechanisms. Outer membrane proteins are initially synthesized as precursors by cytosolic ribosomes, assisted by molecular chaperones in transit through the hydrophobic cytosol. Dedicated protein translocases facilitate their insertion into the Mt surface[9, 93–95]. The TOM complex and related membrane proteins mediate interactions between Mt and other cellular organelles, such as the endoplasmic reticulum (ER). These interactions facilitate the exchange of lipids and calcium ions, regulating Mt biogenesis and dynamics [96, 97]. The OMM appears adapted for storing charge with multi-spanning proteins like Ugo1, Mcp3, Ubx2, Om14, Scm4, mammalian PBR, and mammalian MITOL [98–103]. The 33-kDa protein Ayr1 functions as an ion channel in the OMM, also found in the ER. With around 200 proteins, the OMM acts as a specialized transport system with channel-like functions[104, 105]. Anion channels (ACs) on the OMM, classified as outer membrane AC (OMAC) and inner membrane AC (IMAC), can be anion selective (ASAC), cation selective (CSAC), or non-selective (NSAC).

Voltage-dependent anion channel (VDAC), porins on the OMM, controls metabolic communication between Mt and the cell[106, 107]. VDAC, comprising three isoforms (VDAC1-3)[23, 32, 108], has a 3D structure with antiparallel β-strands, a β-barrel transmembrane pore, and an N-terminal domain forming an α-helix [109]. VDAC1, positioned between cytosol and Mt, serves as the primary conduit for ions and metabolites, influencing cell bioenergetics and the flow of Krebs cycle intermediates[110–113]. Nine distinct channel-forming proteins transport metabolites, inorganic ions, and proteins across the OMM [114]. VDAC transports calcium to Mt [115]. VDAC1 is crucial for oxygen consumption and the function of ETC enzymes, while VDAC2 regulates cell death and survival through interactions with Bak and Bax [26]. Similarly, VDAC3 provides electrophysiological characteristics and undergoes post-translational modifications[116–118]. Figure 1 illustrates all the inbound and outbound activities of Mt and their association with neurodegenerative diseases.

Cristae

The organization and morphology of the IMM are intricate and can be divided into two compartments. One of these compartments is situated opposite to the OMM, while the other extends to the IMS through tubular projections known as cristae junctions (CJ)[119]. The IMM structure is established through the formation of protein-lipid complexes known as MICOS (Mitochondrial Contact Site and Cristae Organizing System), which have evolved from α-proteobacteria. Cristae, the folds within the IMM, house essential components such as ETC complexes, F_0F_1-ATP synthase, OPA1, and MICOS. Notably, the morphology of cristae undergoes changes during mitochondrial respiration [120, 121]. In the context of ferroptotic cells, modifications occur in the structure of cristae, marked by an increase in mitochondrial membrane content and a reduction in cristae structures [122]. OPA1, identified as a dynamin-related GTPase, plays a crucial role in maintaining cristae structure. It exists in two forms, i.e., L-OPA1 (long) and S-OPA1 (short), both of which act as anchors at CJ, preventing the release of cytochrome C (Cyt C) from the intercristae space. This information highlights the complexity of the IMM and cristae structure, underscoring the role of MICOS and OPA1 in maintaining mitochondrial integrity and function. The morphological changes observed in cristae during mitochondrial respiration and in ferroptotic cells further emphasize the dynamic nature of these structures.

Mt in Cellular Energetics

In the IMM, complex I serves as the exclusive electron acceptor from NADH, receiving electrons from the mitochondrial matrix. NADH and FADH2, generated in the TCA cycle, transport electrons across the IMM to the ETC, establishing a high positive potential in the mitochondrial matrix (mtmp). The ETC comprises five complexes, i.e.,

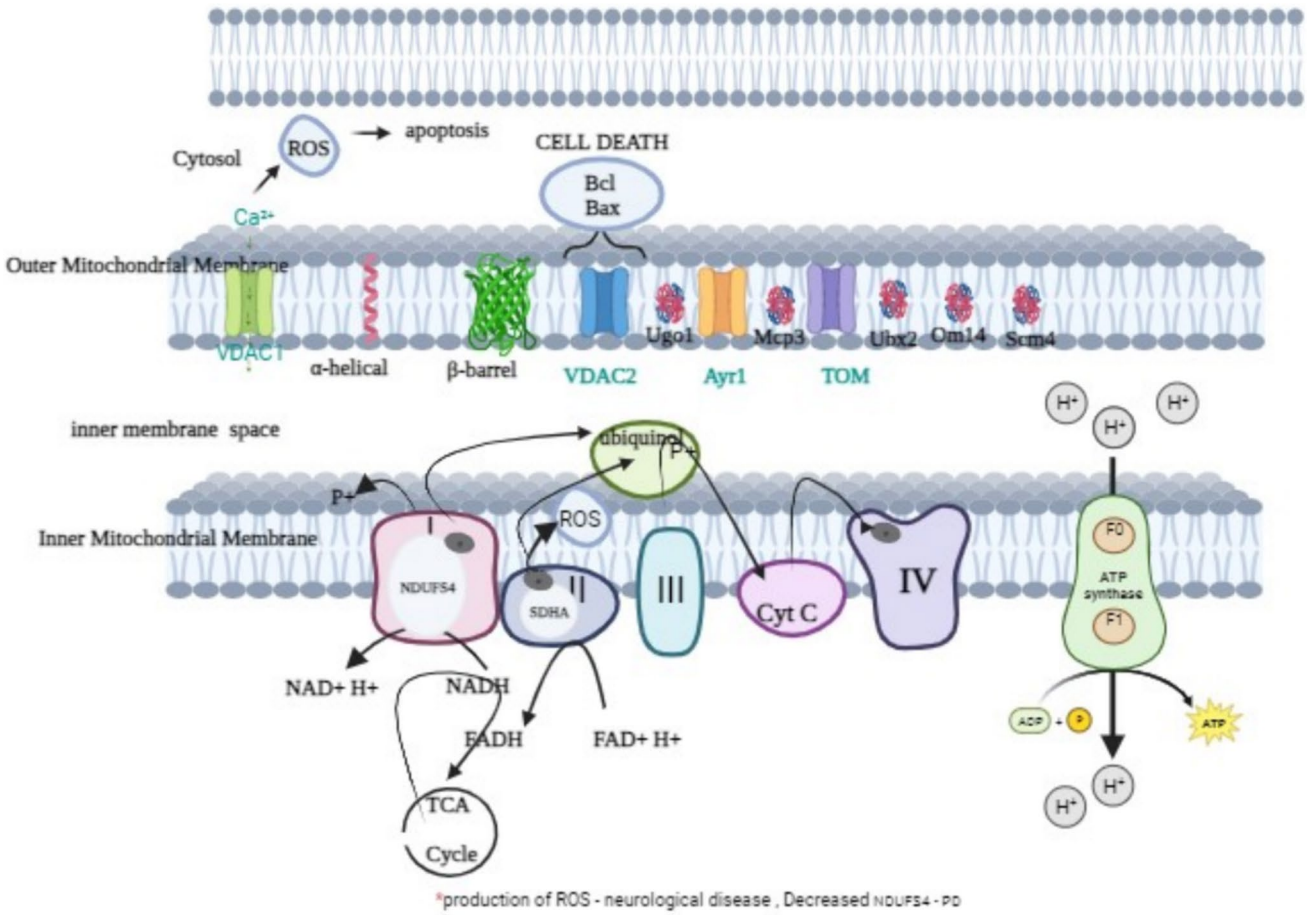

Fig. 1 Mitochondrial dynamics: Ugo1, Mcp3, and Ubx2 are the outer mitochondrial membrane (OMM) multi-spanning proteins for storing charge and 33-kDa protein Ayr1 act as ion channel. VDAC on OMM as a β-barrel transmembrane pore and an N terminal domain forming α-helix. In IMM, complex I accept electron from NADH and transferred to NADH and $FADH_2$ and at the mt matrix, NADH and $FADH_2$ carry electrons from TCA cycle to the ETC across the IMM. NADH: ubiquinone oxidoreductase subunit S4 (NDUFS4) is a subunit of C1 that releases four protons to IMS during NADH oxidation after transmitting two electrons to IMM to ubiquinone (UbQ) through flavin extending to centers of iron and sulfur (Fe–S). In C2, FAD and succinate undergo redox with SDHA (succinate dehydrogenase complex flavoprotein subunit A) and the electron transfer to UbQ is achieved by SDHB (succinate dehydrogenase complex flavoprotein subunit B). C2 modulates ROS along with C1 and C3, and loss in C2 function leads to severe ROS accumulation that is a basis of neurodegenerative disorders. C3 releases four protons to IMS catalyses ubiquinol (CoQH2) to Cyt C. C4 catalyzes electron transfer from Cyt C to molecular oxygen; the F_1F_0 (ATP synthase) produces ATP from ADP

complex I (C1), complex II (C2), complex III (C3), complex IV (C4), and complex V (C5), encoded by both mitochondrial and nuclear genomes [123]. A vital subunit of C1, known as NADH—ubiquinone oxidoreductase subunit S4 (NDUFS4)—ensures the stability of C1 [124, 125]. During NADH oxidation, C1 releases four protons into the IMS while transferring electrons to ubiquinone (UbQ) through flavin, extending to Fe–S centers [124–131].

In C2, redox reactions occur with FAD and succinate catalyzed by SDHA, and the subsequent electron transfer to UbQ is facilitated by SDHB [132, 133]. C2, along with C1 and 3, plays a role in modulating ROS. Dysfunction in C2 can result in severe ROS accumulation, a contributing factor to neurodegenerative disorders [134–137]. Complex III releases four protons to the IMS and catalyzes the transfer of electrons from ubiquinol (CoQH2) to Cyt C [138, 139]. Complex IV facilitates electron transfer from Cyt C to molecular oxygen. The F_1F_0-ATP synthase, also known as ATP synthase, resides in the IMM. It consists of two domains: the hydrophobic F_0 domain responsible for proton translocation and the hydrophilic F_1 domain present in the matrix. This complex produces ATP from ADP and phosphate using the proton gradient[140–142]. Mutations in mitochondrial components can reduce the activity of F_1F_0-ATP synthase, resulting in diminished energy production[143–146].

Overview of Mitochondrial Dynamics and Biogenesis

Mt exhibit diverse shapes, ranging from tiny round structures to shorter lengths and larger tubular forms. The interplay between these morphologies involves the binding and rupturing of both the OMM and IMM, a phenomenon known as "Mt dynamics" that regulates the Mt network [147]. The dynamic nature of Mt enables them to adapt their shapes according to specific cellular functions. For instance, during the energy-intensive DNA replication phase (S phase), Mt can become hyperfused to enhance ATP production [148]. Proteins located on the OMM, including fission 1 (FIS1) and mitochondrial fission factor (MFF), assemble at specific locations. CL and PA, constituting 2% and 5% of total lipids in mammalian cells, respectively, play a role in this process. Although these lipids are enriched in Mt, the assembly of Dnm2, a GTPase involved in mt fission, occurs at membrane constrictions, resulting in individual Mt formation [149, 150].

The precise control of mt morphology is crucial for mitochondrial function and homeostasis (Fig. 2). Overexpression of Bif-1b/c enhances neuronal survival by promoting mt elongation, maintaining membrane potential, and reducing apoptosis [151]. The fusion of Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2) in the OMM forms oligomers that expand the mitochondrial surface both within individual Mt and between nearby Mt [152]. Dynamins involved in division are thought to oligomerize in a GTP-dependent manner, forming helices that wrap around Mt [153]. Additionally, proteins like MFF, uniquely found in humans on the OMM, are essential for mt division [154]. These physical contacts persist under dynamic conditions, emphasizing the significance of the ER-Mitochondrial (ER-Mt) interface for proper functioning [155].

Dynamics

Mitochondrial fusion is a process where two Mt merge to create healthier organelles, while mitochondrial fission involves the division of a single mitochondrion into several daughter organelles, facilitating the removal of damaged and fragmented Mt [156–158]. The term "mitochondrial dynamics" encompasses the interplay of mitochondrial translocation, fusion, and fission. This intricate process is regulated by nuclear-encoded enzymes, primarily big GTPases, as well as mitochondrial lipids, including CL and PA [50, 159]. Throughout the various cellular life processes, mitochondrial fusion and fission can occur rapidly, especially in response to external stress, leading to transient partial fusion events [150, 160].

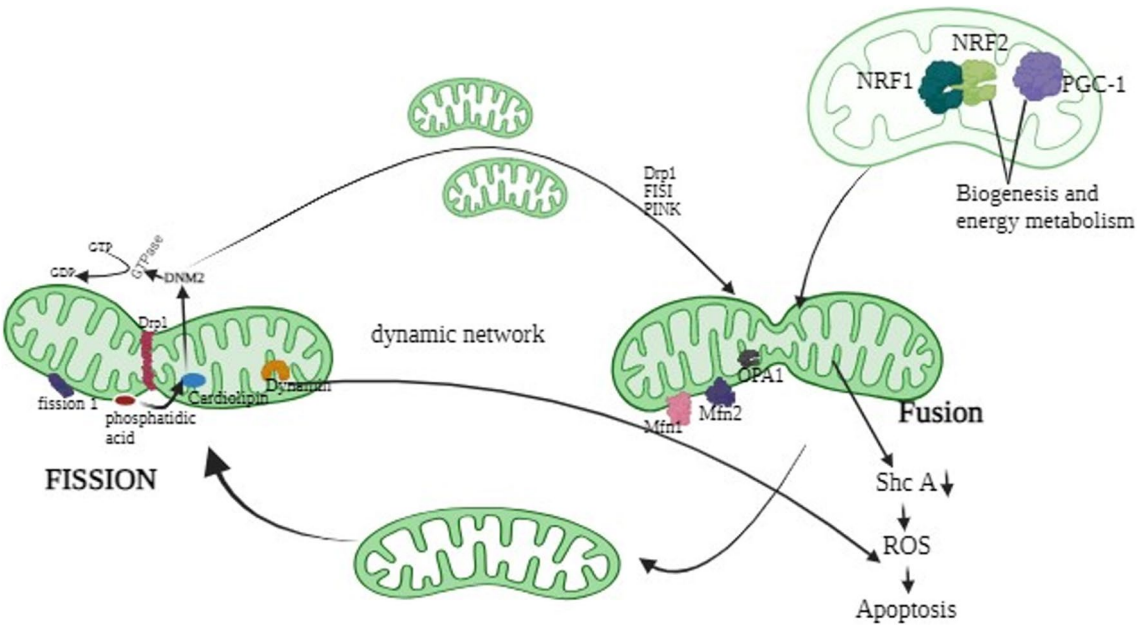

Fig. 2 Mitochondrial fission and fusion: The intricate processes of mitochondrial dynamics, encompassing both fission and fusion events. Mitochondrial fission: The division of a mitochondrion into two separate entities, facilitated by the recruitment of dynamin-related protein (Drp1) to the outer mitochondrial membrane (OMM). This process ensures the maintenance of mitochondrial quality control and distribution. Mitochondrial fusion: The merging of two individual Mt, orchestrated by mitofusins (Mfn1 and Mfn2) on the OMM and optic atrophy 1 (OPA1) on the inner mitochondrial membrane (IMM). Fusion is crucial for the exchange of contents, complementation of damaged Mt, and the preservation of mitochondrial function. These dynamic processes collectively contribute to the regulation of mitochondrial morphology and function within the cell

At least five proteins play essential roles in regulating and maintaining mitochondrial structural dynamics. These include optic atrophy 1 (OPA1), Mfn1, and Mfn2, which facilitate mitochondrial fusion, FIS1, and dynamin-related protein 1 (DRP1), crucial for mitochondrial fission [161–164]. Mitochondrial dynamics are critical for the regulation of cell death [165]. The mitochondrion, as a dynamic network, plays a pivotal role in the cell by generating ROS, supplying energy, and controlling programmed cell death [166]. Elevated levels of Drp1, Fis1/Mfn1, and PINK1 suggest a shift in mitochondrial dynamics from fission to fusion, despite a reduction in ShcA, a protein regulating ROS [167]. Depletion of any fission-related proteins alters mitochondrial dynamics, leading to elongated mitochondrial morphology [149, 168].

To maintain a healthy mitochondrial network, Mt must achieve a stable state with balanced communication between fission and fusion events. Concurrent fusion and fission processes, controlled by proteins like Drp1, regulate the overall shape, size, and population of Mt [169]. This coordinated control of mitochondrial dynamics, synchronized with the cell cycle, ensures equal distribution of Mt to daughter cells. Drp1, in particular, plays a primary role in coordinating mitochondrial dynamics with mitosis [170]. Therefore, intricate and well-balanced regulatory mechanisms linking mitochondrial dynamics and mitochondrial quality control (mtQC) mechanisms are essential for maintaining the fitness of mitochondrial pools and networks in biological systems.

In the absence of Drp1, Fis1 can collaborate with Mfn2 and OPA1 to facilitate mitochondrial fission by reducing GTPase activity, thereby safeguarding against fusion-induced mitochondrial fragmentation [171]. The depletion of MFF results in a substantial decrease in mitochondrial fission in HeLa cells or MEFs, preventing the recruitment of Drp1 to the OMM. Conversely, an overexpression of MFF leads to the recruitment of Drp1 to the Mt, inducing hyperfission in these cells [172]. Within mammals, the paralogs MiD51 and MiD49 serve as mitochondrial receptors, facilitating the cytosolic translocation of Drp1 to Mt [173, 174].

A proposed mechanism for the rapid exchange of metabolites, mtDNA, and membrane components is referred to as mitochondrial fusion [175–181]. Conversely, mitochondrial fission is believed to facilitate the separation of mtDNA and individual Mt from the network, allowing for their subsequent degradation [182–186]. These processes, mt fission and fusion, play a pivotal role in influencing various aspects of mitochondrial function, including respiration, calcium buffering, and apoptosis [28, 187–190].

The dynamics of mitochondrial fusion and fission are further regulated by specific phosphilipid, PA and CL that are promoting fusion and fission respectively [191]. The Miro-Milton complex, subject to calcium-dependent regulation, links Mt with kinesin motors, thereby controlling mitochondrial motility and the delicate balance between fission and fusion [192]. In the context of cellular transport, small, spherical Mt resulting from mitochondrial fission are crucial for axonal cell transport, whereas mitochondrial fusion provides protection against external stimuli [193].

Disruptions in the equilibrium between mitochondrial fission and fusion can have far-reaching consequences, impacting mitochondrial function and contributing to various diseases [194]. Enhanced expression of mitochondrial fission promotes fragmentation of the mitochondrial network, leads to the release of Cyt C from Mt, and increases apoptosis [27, 28]. Additionally, upon fracturing the mitochondrial network, FIS1 has been observed to reduce the abundance and survival of mitochondrial fusion proteins, including Mfn1, Mfn2, and OPA1 [171, 195].

Biogenesis

The process of mitochondrial biogenesis encompasses several vital steps, including the replication of mtDNA, synthesis of both IMM and OMM, production of proteins encoded by the Mt, and import as well as synthesis of nuclear-encoded mitochondrial proteins. Regulatory proteins nuclear respiratory factors 1 and 2 (NRF1 and NRF2) engage with the transcriptional coactivator peroxisome proliferator-activated receptor coactivator-1 (PGC-1), forming a crucial network that oversees mitochondrial biogenesis and energy metabolism [32, 196].

An essential player in this regulatory network is the mitochondrial transcription factor A (Tfam), which plays a pivotal role in mtDNA transcription and replication. Activation of Tfam is orchestrated by the concerted action of NRF1 and NRF2. These transcription factors not only govern the mtDNA processes but also regulate the import of nuclear-encoded mitochondrial proteins. Furthermore, they exert control over the five complexes constituting the mitochondrial ETC [33, 197]. In summary, the collaborative action of NRF1, NRF2, and PGC-1 orchestrates various aspects of mitochondrial biogenesis and function, influencing both mtDNA processes and the composition of the mitochondrial ETC.

Significance of Mt Dysfunction and mtDNA Alterations in Neurological Conditions

Mitochondrial dysfunction stands as a critical factor influencing both health and disease across a spectrum of physiological and pathological conditions [198] (Fig. 3). The mitochondrion, often referred to as the powerhouse of the cell, plays a pivotal role in energy production and serves as a hub for various cellular processes. In a state of optimal function, Mt orchestrate essential mechanisms such

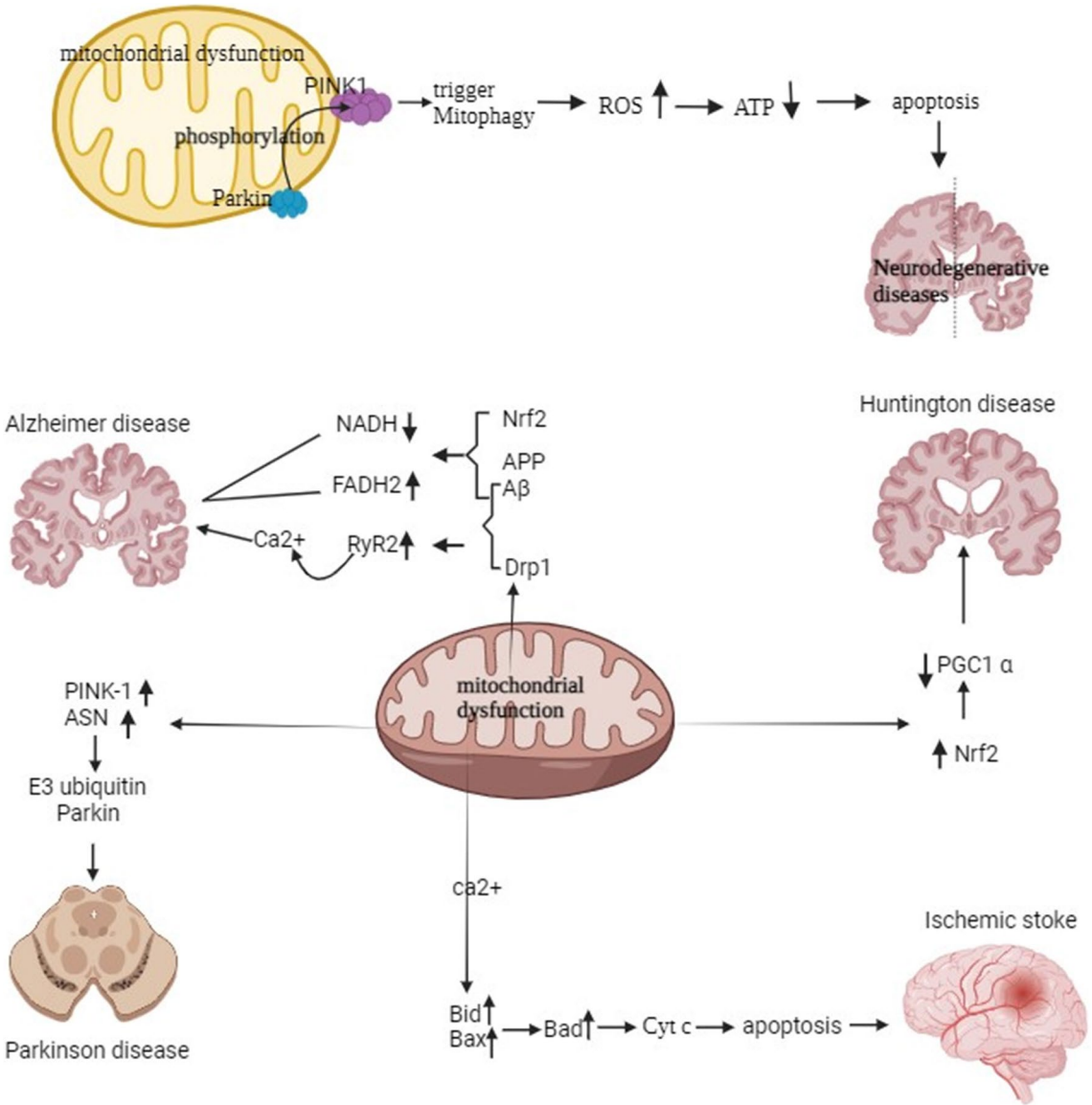

Fig. 3 Mitochondrial dysfunction leading to different neurological disorders: The significance of Mt dysfunction and mtDNA modifications in various neurological disorders, emphasizing their crucial contribution to disease pathogenesis. The comprehensive overview underscores the unique insights into the molecular mechanisms underlying these conditions, highlighting the imperative need for targeted therapeutic interventions

as OXPHOS, contributing to ATP production-the primary energy currency of the cell. Mt are also integral to metabolic pathways, including the citric acid cycle and fatty acid oxidation, crucial for maintaining cellular homeostasis [199]. However, when mitochondrial function falters, it becomes a contributing factor to the onset and progression of various diseases. Neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis, are strongly linked to mitochondrial dysfunction. The repercussions extend beyond the nervous system, encompassing conditions like cardiovascular diseases, diabetes, and age-related degenerative disorders.

Several key aspects contribute to mitochondrial dysfunction and subsequent health issues. Genetic mutations in mitochondrial and nDNA can compromise the integrity of proteins involved in mitochondrial function, leading to aberrant processes such as impaired OXPHOS and disrupted energy production. Environmental factors, including exposure to toxins and oxidative stress, further exacerbate mitochondrial damage. Mitochondrial dysfunction also plays a role in the aging process [107]. As cells age, mitochondria accumulate damage, leading to a decline in their function. This aging-associated mitochondrial dysfunction is implicated in a range of age-related diseases. Understanding and

addressing mitochondrial dysfunction have become focal points in contemporary medical research. Therapeutic avenues include gene therapies targeting mtDNA, small molecules that enhance mitochondrial function, and strategies to promote mitochondrial biogenesis. Additionally, emerging technologies like mitochondrial transplantation hold promise for mitigating the effects of dysfunctional Mt. In the pursuit of overall health and the prevention of diseases linked to mitochondrial dysfunction, ongoing research aims to unravel the intricate molecular mechanisms governing mitochondrial function. As scientists delve deeper into these complexities, new diagnostic and therapeutic strategies will likely emerge, offering hope for improved treatments and preventive measures against diseases rooted in mitochondrial dysfunction.

The onset of neurodegeneration is prompted by the accumulation of diverse stressors, coupled with the simultaneous disruption of multiple cell-protective systems [47]. In neurodegenerative disorders, a shift in mitochondrial activity significantly contributes to the transition from a normal physiological state to a degenerative one. Pathological protein aggregation, reduced ATP synthesis, and the formation of plaques associated with dopaminergic neuronal death result from the adverse effects of several genetic abnormalities working in concert[200]. Mutations in Parkin and PINK1 exert their influence on Mt monitoring and cell biology[200]. PINK1 is initially translated into the outer OMM and subsequently translocated into Mt for proteolytic degradation in healthy Mt. This underscores the fact that PINK1 levels are typically low in normal mitochondrial conditions. However, when mitochondrial dysfunction occurs, such as membrane depolarization, PINK1 persists as a membrane-anchored component in the OMM. Parkin is activated in its new location through PINK1-mediated phosphorylation. Upon activation, Parkin-mediated ubiquitination signals trigger mitophagy, which is the selective elimination of Mt via the autophagosome [201]. This process leads to functional and anatomical transformations in Mt, impacting various cellular processes. These include excessive ROS generation, a decline in brain energy due to reduced ATP levels, alterations in calcium homeostasis, and the initiation of apoptosis[202, 203].

The circular mtDNA exhibits a mutation rate 10–17 times higher than that of nDNA, playing a crucial role in maintaining mitochondrial integrity[204–206]. Circulating mtDNA has been identified in human blood and serves as a potential biomarker for mitochondrial dysfunctions. Mutations in mtDNA, coupled with synaptic damage, result in the inhibition of transcription replication[207], increasing the likelihood of AD by 63% [136]. The impairment of synapses and mitochondrial dysfunction are key contributors to the development of AD[208]. Deletions and point mutations in mtDNA lead to compromised mitochondrial respiration [209–214]. LonPeptidase 1 (LONP1) is integral in orchestrating OXPHOS, mtDNA maintenance, and the expression of mitochondrial genes, forming a homo-hexameric complex in the mitochondrial matrix [215–217]. Mutations in LONP1 contribute to OXPHOS deficiencies [218], indirectly linking to pathophysiological disorders such as CODAS syndrome and Perrault syndrome. These disorders are associated with disruptions in CLPXP or ERAL1, sometimes manifesting as progressive cerebellar ataxia and intellectual deficit [219, 220].

Mutations in the YME1L gene lead to optic atrophy, developmental delay, and hearing loss, while DRP1 mutations can result in abnormal brain development, microcephaly, and optic atrophy. GDAP1 is implicated in Charcot Marie Tooth disease (CMT). Furthermore, mitochondrial proteins, including ATP5A, NDUFS3, SDHB, and other members such as tetraspanins CD9 and CD63, are found in decreased concentrations in small vesicles of PD patients. In summary, the heightened mutation rate of circular mtDNA, coupled with its interplay with nDNA, underscores its significance in mitochondrial integrity. Dysregulation of these processes contributes to various disorders, emphasizing the intricate connections within the mitochondrial network and their implications for neurodegenerative diseases.

Alzheimer's Disease

The root cause of AD pathology is attributed to Mt cascade dysfunction [221, 222]. Two critical components in the course of AD are tangles and plaques [223, 224]. This involves the accumulation of β-amyloid in brain vessels [225, 226] and intracellular neurofibrillary tangles resulting from tau protein aggregation [198, 233]. The interaction between amyloid precursor protein (APP) and Aβ with Mt proteins leads to processes responsible for neurodegeneration [227, 228], induced by enhanced mitophagy and Mt defects. In AD patients, a reduction in the activity of Mt C4 has been observed in the hippocampus and platelets [229]. Suppression of communication between Aβ and Aβ-binding alcohol dehydrogenase (ABAD) has been shown to reduce Aβ-induced neuronal death and free radical production. Aβ inhibits two crucial Mt enzymes, α-ketoglutarate dehydrogenase and cytochrome oxidase, both found at low levels in the brains of AD patients. Aβ attaches to the Mt matrix protein, ABAD, following overwhelming complex IV and α-ketoglutarate dehydrogenase [230].

Overexpression of APP, including Nrf2, downregulates Mt fusion, biogenesis, and mitophagy [231]. Inactivated Nrf2 reduces ETC complexes' activity and lowers NADH and FADH2 expression [232], contributing to the advancement of tau and amyloid in AD patients [233]. The tau protein, losing its physiological activities as AD progresses, reaches the dendrite soma, interacting with β-oligomers and enhancing excitotoxicity, forming neurofibrillary tangles

[199, 234]. Aβ plaques, precipitated with high iron amounts, contribute to the development of hazardous Aβ oligomers and ROS, causing Mt malfunction and cell death [235–237]. Aberrant metal ion distribution or metabolism leads to synaptic dysfunction directly tied to Mt in the synapses [238]. Excess zinc, generated by increased metalloprotein release, stimulates Aβ synthesis and deposition, initiating a cascade reaction. Inhibition of protein phosphatase and tau hyperphosphorylation, linked with toxicity related to N-methyl-D-aspartate channel activation and Aβ, is due to increased ROS production from soluble oligomers in the brain and cerebrospinal fluid of AD patients [226, 237, 239].

Chronic hypoxia reduces α-secretase expression, increasing Aβ formation and stimulating mt ROS development [240]. AD brains exhibit decreased fusion protein expression but increased fission protein expression or activity [241]. The increase in S-nitrosylation of dynamin-related protein 1 (Drp1) mediates Mt fission, contributing to AD pathogenesis [242, 243]. In AD brains, ryanodine receptor 2 (RyR2) expression levels are elevated [244], leading to excessive $Ca2^{+}$ release affecting synaptic plasticity [243, 245, 246]. This induces iron-induced mt fission and stimulates mt $Ca2^{+}$ uptake, indicating RyR malfunction and neurodegeneration [17, 247, 248].

Parkinson's Disease

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in the substantia nigra and the accumulation of α-synuclein (ASN) oligomers [223, 249], often referred to as Lewy bodies, making it the second most prevalent neurodegenerative condition after AD. The aggregation of ASN oligomers, coupled with disruptions in Ca^{2+} homeostasis, leads to Mt membrane permeabilization and the opening of the mitochondrial permeability transition pore (MPTP). This cascade results in the generation of ROS [250], release of Cyt C, and induction of apoptosis.

The manifestation of PD includes progressive muscle rigidity and tremors, attributed to a diminished dopaminergic modulation of striatal neurons, thereby modifying motor systems [251–253]. Several genetic mutations, including Parkin, PINK-1, LRRK2, DJ-1, and ASN, have been associated with familial PD. These gene products not only participate in mitophagy but also influence ER-Mt connections and signaling in PD [44, 254–256]. ASN and the PRKN gene, coding for the E3 ubiquitin-protein ligase parkin, are known to be mutated in early-onset PD, affecting around 10% of patients [257–259]. Autosomal recessive PD is linked to mutations in PINK1 and Parkin, resulting in striatal mitochondrial respiration deficiency, neuronal vulnerability, oxidative stress, and impaired mitophagy activation [221, 260–265].

Autosomal recessive PD is associated with mutations in PINK1 and Parkin, disrupting the degradation of damaged Mt through the activation of mitophagy [221, 263–265]. Both PINK1 and Parkin contribute to the degradation of the mitochondrial fusion proteins Mfn1/2 and induce fission by enhancing fission protein activity while reducing the trafficking proteins Miro 1/2. However, the inactivation of the PINK1-Parkin pathway halts the removal of damaged Mt, leading to a slowdown in mitochondrial protein turnover [266]. Genetic degradation of PINK1 results in deficiencies in striatal mitochondrial respiration and increased vulnerability of neuronal cells, ultimately causing oxidative stress [260–262]. The reduction in Mtmp leads to the accumulation of PINK1 at the OMM, where Parkin subsequently removes damaged Mt [186, 254]. Similarly, the absence of Parkin disrupts synaptic plasticity and causes dysfunction in striatal Mt [265].

Parkin ablation induces synaptic plasticity and striatal mitochondrial dysfunction [265]. Mutations in Parkin cause defective mitochondrial morphology in iPSC-derived neurons of PARK2 patients. A prevalent DNA lesion associated with oxidative stress is 8-hydroxy-deoxyguanine (8-oxo-dG), an oxidized form of guanine frequently observed in neurological illnesses like AD and PD [267]. PD patients exhibit elevated levels of oxidized CoQ-10 and 8-hydroxy-2-deoxyguanosine in their cerebrospinal fluid (CSF), implicating mitochondrial oxidative stress and DNA damage in PD pathogenesis [268]. A53T transgenic mice and the brains of PD patients also show mitochondrial degeneration with DNA damage [269]. The GBA gene, encoding the enzyme glucocerebrosidase (GCase) involved in lysosomal hydrolysis, plays a crucial role. GBA mutations cause mitochondrial defects and are associated with Gaucher disease (GD) and PD [270–272]. Approximately 5–15% of PD patients have mutations in the GBA gene, making it the most significant genetic risk factor for PD [273].

Huntington's Disease (HD)

Huntington's disease (HD) is an autosomal dominant neurological disorder characterized by an accumulation of trinucleotide CAG repeats within the huntingtin (HTT) gene, leading to polyglutamine repeats in the huntingtin protein (mtHtt) [274, 275]. This mutation affects ion channels, induces oxidative and metabolic stress, and results in Mt malfunction. Mutant HTT inactivates GAPDH, impairing Mt protein transport, causing mtDNA degradation, and contributing to deletions in HD brains [276]. Neurodegeneration occurs through mutant HTT aggregates, disrupting Mt trafficking and altering neuronal movement [277]. Additionally, there is a reduction in mitophagosomes via mitophagy receptors, hindering mt clearance and leading to a buildup of damaged Mt [278].

MtQC dysfunction is evident in HD, with upregulated fusion proteins and downregulated fission protein expressions causing excessive mt fission [279]. HD pathophysiology includes mt dysfunction, impaired cellular antioxidants, and symptoms affecting motor coordination, cognition, and mental health [280, 281]. Stress induction in lymphoblast cell lines from HD patients reveals increased apoptotic cell death mediated by caspase-3, caspase-8, and caspase-9 activation [282–284]. Notably, exposure to stress induces apparent Mt differences and increased apoptosis in lymphoblasts from HD patients [204].

Mt failure is a pivotal factor in HD progression, with anomalies such as mtDNA errors, oxidative stress, calcium imbalance, and increased lipid peroxidation observed in HD mouse models [285–288] and human brains [281, 289]. These abnormalities are linked to disease progression [286, 288] and severity [281]. The antioxidant system's inefficiency may result from the mtHtt protein, which reduces acetylase activity through CBP/p300 dimer interaction [290, 291] and affects Nrf2 stability and cellular localization [292]. The decrease in PGC1α, among other dysregulated proteins, contributes to HD pathogenesis by linking with transcriptional dysregulation and mt damage processes [293, 294].

Ischemic Stroke

During ischemia, intramitochondrial calcium levels increase, triggering the activation of mitochondrial phosphatases and subsequent dephosphorylation of the OXPHOS complexes, particularly Cyt c and Cyt c oxidase [295–298]. This leads to the loss of allosteric regulation by ATP. In the absence of oxygen as the final electron acceptor, OXPHOS is highly stimulated in a feed-forward manner [297, 299]. Simultaneously, due to the lack of cellular energy, the Na^+/K^+ ATPase pump fails, resulting in neuronal membrane depolarization and the release of excess excitatory neurotransmitters, particularly glutamate [300].

CL, a dimeric phospholipid in the IMM, interacts with various OXPHOS complexes and Cyt C, making it susceptible to oxidative damage [298, 301]. Its peroxidation results in the redistribution to the OMM, causing a 50% decrease in Cyt C oxidase activity. This leads to the release of mitochondrial apoptotic proteins, including Cyt C, apoptosis-inducing factor (AIF), Smac/DIABLO, and HtrA2/OMI, into the cytosol [53, 302–304]. These proteins contribute to cell death in the ischemia penumbra through various mechanisms.

During reperfusion, pro-apoptotic proteins from the Bcl-2 family, such as Bid and Bax, increase, with Bid being cleaved into truncated tBid by elevated mitochondrial calcium. tBid interacts with other pro-apoptotic proteins in the mitochondrial membrane. Activated Bad translocates to the OMM, suppressing antiapoptotic proteins [305, 306]. Upon opening of the mitochondrial permeability transition pore (MPTP), Cyt C is released into the cytosol, forming the apoptosome with APAF1 and procaspase-9, initiating apoptosis. SMAC/DIABLO and Omi/HtrA2, released from the mitochondrial IMS, enhance caspase-independent apoptosis by inhibiting inhibitor-of-apoptosis protein (IAP) family members, such as XIAP [55, 307].

Activation of autophagy has a protective effect in the early stages of ischemia by preventing defective Mt from producing harmful chemicals [308–310]. Mt normally undergo cellular recycling through autophagy, involving signaling pathways like beclin-1/class III PI3K, AMPK/mTOR, and PI3K/Akt/mTOR [56]. However, prolonged autophagy upregulation can lead to increased cell death.

Implications for Neurological Disorders and Potential Therapeutic Targets

The advancements in understanding mitochondrial function and its intricate involvement in neurological disorders have significant implications for the development of therapeutic interventions. The multifaceted nature of these disorders, ranging from PD and AD to traumatic brain injuries, necessitates a diverse and targeted approach to mitigate their impact on neuronal health. The identification of compounds, such as Szeto-Schiller peptides, Mt-penetrating peptides, and MitoQ, designed to enhance mitochondrial activity, opens up new avenues for therapeutic exploration. These compounds specifically target mitochondrial membranes, addressing the core issues of mitochondrial dysfunction observed in various neurological disorders.

Investigations on the present therapeutic approaches for AD show that among 30 agents at clinical trials, only one (caprylic triglyceride) focuses on their metabolism and its bioenergetics [311]. Similarly, in the case of PD, among 74 and 22 phase 2 and phase 1 clinical trials respectively, only 2 agents (nicotinamide riboside and terazosin) focus on Mt and the energy metabolisms [312]. There lies an inevitable need for mitochondrial therapies, and also the exploration of molecular targets needs to be expanded through research advancement [312].

Among the developing therapeutic approaches for the treatment of mitochondrial disorders, optogenetics marks its position. This technique is achieved by the ion channels/electron pumps/enzymes or transcription factors that are light-sensitive, allowing precise control of the biochemical signaling pathways. It is employed in a more advanced way, such that optogenetics controls mitochondrial fission through light-induced MLCs in many cell types, including HeLa cells, PC12, and $SLC25A46^{-/-}$ HDFn, where $SLC25A46^{-/-}$ HDFn affords to treat mitochondrial disorders [313].

Deep brain stimulation (DBS) is another technique used in the treatment of PD, targeting the subthalamic nucleus

for symptomatic PD treatment. The hyperactivity in PD rodents was examined in the M1 pyramidal cells through DBS, where the study also sheds light on in vivo recording of intracellular and juxtacellular network recruiting the GABAergic networks. The activation of cortical SST interneurons by optogenetics mitigates the major symptoms of PD in mice [314]. Though it has promising research findings, DBS is still in the initial stages of medical application [315].

CRISPR-Cas9 is an intricate process to carry out mitochondrial gene editing as there is no guide to deliver the RNA and Cas9 enzyme complexes into the Mt. A recent study by Hussain et al. made a concept proof that the stem loop element sgRNA can be added [316], which will in turn help in precise travel to Mt and also interact functionally with Cas9, which mediates sequence-specific mtDNA cleavage, thus making a great system for targeted mitochondrial genome editing.

Another promising study revealed the set of genes impacting the mTORC1 pathway, which identifies mitochondrial dysfunction [317]. It targets the known leading genes at TORC1 pathway MIOS, RPTOR, WDR24, SEH1L, LAMTOR2/4, RHEB, RRAGA, and MTOR, where the ATF4 KO cells treated with oligomycin showed the induction of Sestrin2 and Redd1is essential to inhibit mTORC1 signaling [318].

Szeto-Schiller (SS) peptides

The Szeto-Schiller (SS) peptides, Mt-penetrating peptides, and MitoQ (ubiquinone covalently linked to lipophilic cation triphenylphosphonium) represent novel compounds designed to target Mt membranes and enhance mitochondrial activity, as reported by Jin et al. [319]. The respiratory chain's complex II reduces MitoQ to active ubiquinol antioxidant, restoring its efficiency against lipid peroxidation in isolated Mt [320]. CERE120, a riluzole-containing drug with an adeno-associated virus, non-steroidal anti-inflammatory drugs, and caffeine A2A receptor antagonists, has shown promise in reducing the risk of neurodegenerative complications [321].

TIGAR

TIGAR, interacting with various signaling proteins and exhibiting significant mitochondrial functions and cell survival properties, emerges as a potential therapeutic target for conditions like cancer, cardiovascular, and neurological disorders. Despite incomplete understanding of its controls, the localization of TIGAR in subcellular organelles other than Mt, such as the ER and nucleus, warrants further investigation into the mechanisms governing its migration in response to stress [322].

Ursodeoxycholic Acid

Ursodeoxycholic acid (UDCA), an FDA-approved medication for biliary cirrhosis, has demonstrated neuroprotective effects in preclinical studies on PD models by preventing mitochondrial dysfunction [323, 324]. Managing glutathione levels with mitochondrial diseases and using mycophenolate mofetil (MMF) to activate Nrf2 represent promising therapeutic approaches in PD, with limited side effects [325]. Tecfidera, an oral formulation of dimethyl fumarate for multiple sclerosis, activates Nrf2, stimulating genes that promote anti-inflammatory, antioxidant, and mitochondrial biogenetic processes, protecting against MPTP-induced brain toxicity [326].

Niclosamide

Niclosamide's ability to activate PINK1 and its regulatory enzyme suggests its potential as a treatment for PD [327]. Photobiomodulation, a low-level laser therapy, has been used to induce vascularization in injured muscle tissue with minimal side effects [328]. Treating AD with photobiomodulation aims to directly impact Mt by providing photons to Complex IV, reducing ROS generation from damaged Mt [328]. DNA methylation and transcription changes are explored as tools for reprogramming or differentiating induced pluripotent stem cells to treat neurodegenerative diseases [74, 329].

Edaravone

Edaravone, a drug scavenging free radicals, is approved for post-ischemic stroke and amyotrophic lateral sclerosis, but its effectiveness and safety in traumatic brain injury patients are still under investigation [330]. Apocynin, a NOX inhibitor, and TBHQ, an NRF2 activator, administered together show promising effects in rescuing white and gray matter in traumatic brain injury [331]. Mitoquinone (MitoQ), an antioxidant, leads to downstream effects, increasing NRF2 release and antioxidant enzyme gene expression, and uncouples mitochondrial respiration and phosphorylation to reduce ROS generation and prevent oxidative damage [330, 332, 333].

Mdivi (Mitochondrial Division Inhibitor-1)

Mdivi-1 is an inhibition molecule that suppresses the mitochondrial division by specifically targeting dynamins. The Mdivi-1 not only blocks the Cyt C [334] but also act on Drp1 in neurodegenerative diseases helps reducing the disease specific phenotypic appearance [182, 335]. The Mdivi prevents the Drp1 and GTPasey assembly by binding onto the GTPase and thus suppresses the GTPase activity

[334]. In seizures, the death of hippocampal neuron was greatly saved by Mdivi-1 by preventing the Cyt C release and caspase 3 which are already activated [336]. Besides that, the enhanced mitochondrial fission and oxidative also got reduced drastically by Mdivi-1 in epileptic rat [337]. A condition of ischemia/reperfusion, i.e., cerebral damage, was sharply decreased by the Mdivi-1, and downregulated Drp1 and Cyt C was prevailed in ischemia/reperfusion mice [338]. In addition to the Cyt C blocking, Mdivi-1 significantly prevented the Bax from entering into the Mt in Rhabdomyolysis-induced rat [339]. In ischemic cases, Mdivi-1 increased the life of retinal ganglion cells [340].

Luteolin-Flavonoid

Luteolin enforces the mitochondrial respiration amd ATP production provided it depends on ER Ca^{2+} release channels. It has the hydrogen peroxide inducing property, and mitochondrial respiration increasing ability [341, 342]. It establishes the availability of nicotinamide adenine nucleotide (NADH) and electron carrier by activating the pyruvate dehydrogenase [343]. In mouse synaptosomes, enhanced ATP production was rendered by luteolin [344]. Luteolin facilitated the Nrf2 activation by translocating it to nucleus and thereby upregulated the heme oxygenase1 and NQO1 [345].

Others

Various flavonoids, such as 7,8-dihydroxyflavone, cudraflavone B, liquiritigenin, morachalcones, EGCG, procyanidins, huperzine A, geissoschizine methyl ether, sanguinarine, and fangchinoline, prevent mitochondrial oxidative injury and nerve cell death in HT22 cells induced by glutamate/erastin. Puerarin, derived from *Pueraria lobata*, exhibits protective effects against glutamate-induced toxicity in SH-SY5Y cells [346–356]. Coenzyme Q10 supplementation, involved in ATP formation, improves mitochondrial function, slowing motor deficits, atrophy, and improving survival in R6/2 mice [357–359]. Research on PMX500FI, a synthetic L-carnitine-conjugated alpha-lipoic acid (ALA) derivative, suggests its effective traversal of both the blood–brain and blood-retinal barriers. Additionally, it inhibits histone deacetylase activity, enhances mitochondrial function, and exhibits superior in vivo pharmacokinetics compared to traditional ALA [360–364].

The diverse array of compounds and strategies discussed here highlights the evolving landscape of potential therapeutic targets for neurological disorders. Further research and clinical trials are essential to validate these findings and translate them into effective treatments, offering hope for individuals affected by these challenging conditions.

Biomarkers of Mitochondrial Dysfunction in Neurological Conditions

Some of the present mitochondrial disease detection by laboratory tests are through lactate profiling, amino acid, and organic acid profiling and testing for species of acylcarnitine in mitochondrial diseased patients; and samples like blood, urine and CSF are the established means of detection. Many of the mitochondrial diseases still lie under the rare genetic disorders with approx. more than 350 gene mutations, yet do not contain the sensitive testing methods for the same [365]. The testing of serum creatine kinase levels, which is a muscular isoform, will be normal or only slightly higher in patients with mitochondrial disorders [366]. The identification of the peripheral vascular function in the mitochondrial diseased patients with a confirmed m.3243A > G mutation, which acts as a biomarker of mitochondrial function examined through flow mediated skin fluorescence testing [367]. The technique of near infrared spectroscopy (NMR) was employed in the examination of oxygenated and deoxygenated hemoglobin in skin and muscles at mitochondrial diseased patients, and it did not show significant changes with respect to oxygen consumption and blood flow in muscles [367]. The field of nuclear medicine also supports the diagnosis of some cases of mitochondrial diseases like PD with its single photon emission tomography study, expressing the mtDNA deletions at patients with tremor signs [368].

Focusing on the physical features, short stature is a well-established feature of mitochondrial diseases that are caused by both mtDNA and nDNA [369]. The mitochondrial disorders are the disorders that have a multivariant differential system diseases containing unique phenotypes which occur from changes in genetic makeup of Mt [370]. The most precise and direct way of approaching the mitochondrial identification is through the gene mutation and deletions identification that comprises of *MT-TL1*, *MT-TK*, *LARS2*, *MTFMT*, *C12orf65*, *NDUFA4*, *SURF1*, *COX10*, *LRPPRC*, *OPA1*, *POLG*, *RRM2B*, *TWINK*, and *ESCH1*gene mutations and mtDNA deletions [369].

The primary lowering of mitochondrial beta oxidation and 12–14 long-chain acylcarnitines (LCACs) serves as biomarker for PD. Among many diagnostic biomarkers for PD, LCACs serve to be the best tool for diagnosing PD with its high specificity for PD at early stage [371]. Mostly the neurodegenerative disorders are approached with nutrient supplements for treatment which comprises of CoQ10, Selenium, NADH/NAD/nicotinamide, vitamins B and D3, and alpha-lipoic acid [372]. CoQ10 is said to have significant effect on CSF biomarkers for treating AD [373]; selenium partially reversed the damaged dopaminergic neurotransmission in MPTP induced PD mice [374] and high-dose selenate showed improvement in mini mental state score

in AD patients [375]; NADH/NAD administration for AD patients did not show any progressive cognitive impairment and also showed increased MDRS (Mattis Dementia Rating Scale) scores [375]; vitamin B supplementation showed increased cognitive function at AD patients [376]; vitamin D3 supplementation found to decrease the osteopenia risk in PD subjects [377] and alpha lipoic acid supplementation had good effects on developing cognitive function in AD patients [378].

Nanotechnology and its implications at therapeutic field makes the promising attempt to make a revolution at targeted drug delivery. This makes the way for delivering the CoQ10 by encapsulating inside nanocapsules and targeting the brain Mt which helps in oxidative stress reduction and enhancing the function of Mt [379]. Another application in nanomaterial delivery for treating dysfunction of AD is by conjugated liposomes which functions in aiming ligands such as transferrin or apolipoprotein E, and a Mt-derived cyclosporin A enhances the mitochondrial functioning and decreases cell death [380]. With many mitochondrial regulators at research, the direct inducers of mitophagy could be the key for its related pathways like PINK1/Parkin pathway in AD, which thus help improve the survival and functional property of glutamine and cholinergic neurons, amyloid beta, and tau pathologies [381].

In a recent study, the sFGF21 and sGDF15, the serum fibroblast growth factor 21 and serum growth differentiation factor 15, respectively, are employed in detection of mitochondrial disorders [382]. In AD, the ratio of L:P and hyperlactacidemia is used in the investigation of role of mitochondrial dysfunction [383]. In the study on hepatocerebral phenotype children, they were found to have complex 1 deficiency, depletion of mtDNA, and also POLG1 mutation [384]. The indicator of neuronal loss or dysfunction of neurons in mitochondrial encephalopathy is by the observation of N-acetylaspartate and choline, which tends to be the specific metabolic profile specific to mitochondrial dysfunction [385]. The lactic acid is neurotoxic, where the reduction of their levels is important but the research on the agents acting on lactic acidosis gave disappointing results [386, 387].

Mitochondrial Biology in Precision Medicine for Neurological Disorders

Mitochondrial mutations always occur in a heteroplasmy state which explains a cell with mitochondrial de novo mutation would also have a normal mtDNA in it [388]. They can be either inherited along generations or they can also be acquired through modifications by environmental changes as well as epigenetic factors, where distinguishing them into primary and secondary mitochondrial dysfunction and treating them accordingly is inevitable [389]. The need for personalized medicine is unavoidable as each mitochondrial dysfunction follows a distinct path of pathophysiology. Their specialized personalized therapies include the therapeutic approach by nucleotide supplementation, replacing the oocyte's defective mtDNA and exogenous mitochondrial supplementing [390]. Mt being complex needing the demand of precision medicinal approach also shows that their unique dynamics allows them to be engineered for next generation of targeted therapy development [391].

Mitochondrial gene editing is the novel way of treating mitochondrial dysfunctions. Zinc finger deaminases have the potential ability of intrinsic cell penetration, which makes it suitable for gene editing both in nuclear mtDNA and cellular mtDNA paving the way for altering mtDNA mutations that are pathogenic [392]. There is a need for more precise mitochondrial gene editing and it can be achieved by the bacterial toxin DddA derived cytosine base editors (DdCBEs) made of cytosine deaminase, specific to dsDNA. The transcription activator which is similar to effector that is custom made with DNA binding proteins and inhibitor of uracil glycosylase enables the therapeutic modification of mt DNA possible in patients [393]. Achieving such a precise gene editing is further developed by adding the zinc finger base editors (ZnF-DdCBEs) to enhance the precision technology architecture as it contains N or C terminals that enable additional target options [394]. The screening of ZnF-DdCBEs are easy and they are cost effective, adding to the point ZnF are abundant endogeneous proteins of human cells which is much less receptive to factors that translate on reduced immunogenecity, making it more compatable [394]. This needs more cutting research to en-groove its potentiality, to improve methods for counter action for DddAtox deaminase enzyme that spontaneously splits during interactions of independent DNA binding [393]. Many optimized ZnF-DdCBEs have been employed in mtDNA and nDNA mutation specific diseases. Even this is aimed to efficiently discrtuct the mutational diseases at Mt by implication on post antal mice study by delivering a AAV9 to its heart, liver, and skeletal muscles [394].

Artificial Intelligence in Neurodegenerative Disorders

In the developing world, each and every field is empowered using artificial intelligence (AI) in different forms, which is even employed at the medical field. The computer systems using the interdisciplinary science, AI is applied to bring out automation at interfaces in recognition of visual, speech, decision-making, and also translating languages [395] which is applied to health care sector to provide patients, physicians, and lab technicians with time-efficient appointment books, and drug availability detailing, suggesting

cost-effective alternative drugs and treatments. The three broad classifications of AI systems in the healthcare are majorly into patient oriented (AiCure), clinician oriented (Aidence, Bot MD), and administrative and operational oriented (Aiva Health, Babylon Health) [396] with the combinations of machine learning (ML) and deep learning (DL) algorithms [397]. The imaging techniques often support the neurodegenerative disorders for detecting the brain pathologies, with PET, SPECT, fMRI for the molecular imaging, fMRI and PET for functional imaging, and CT and MRI for structural imaging that are also employed with AI for accessing their different clinical data sources [398]. The neurodegenerative disease like AD has speech and language skills to be considered the most valuable clinical data as they will be reduced in the course of progression of the disease; thus, their collection in sources like voice data and implementing more of AI powered computational speech processing has been the new tool at processing of AD diagnosis and prediction of their disease progression [399]. The neurological disease diagnosis is achieved by AI mostly using either the ML or DL algorithms and by the elimination of interference factors of the data like unnecessary noises, redundancy factors, and variations which make it more accurate in measuring and analyzing the molecular gene analysis data like the major SNP reports obtained from patients and healthy controls. There are many ML studies carried out on PD, which compared the different biological pathways based on the different features of gene expression in PD diagnostic models with an accuracy rate of 93.8% [400]. There are also similar ML studies in AD with an accuracy of 97.8% which had ML employed to analyze the biomarkers at AD diagnosis which includes the clinical imaging, responsible genes, proteins, and the data of the cognitive tests [401] the ML algorithms also apply at the analysis of various gene-related variations that are found in many mitochondria-related genes [402]. Many generalized studies on neurodegenerative disorders involving ML and DL algorithms find its role in the comparing of the patient data from the control data using the deep analysis of multiple genes involving genes of neuron functioning, cell cycle, and immune responses with an accuracy of 95.2%[403] and the distinguishing of 68 different disease severity in neurological disorders with an accuracy of 88.6%[404]. There are many ways to research on the cognitive monitoring of the neurological disorders, in which AI is found to have the best base with the datasets developed by Gosh et al.[405] which had over 6400 MRI images where each were segregated into different stages (moderate dementia, non-dementia, very mild dementia, and mild dementia) of complexity in progression of the AD using the convolutional neural network technique using image data. Though there are many advances in the diagnosis techniques of ND using AI, as each has its own limitations, AI also has its own way of limitations. The limitations include the availability of data set which may have discrepancies in versions of the data taken, the training data set which has the chances to be small and fragmented, the biased model making which arises when the research set is focused on a single aspect of data, and processing the large datasets may lead to loss in accuracy, but can be eventually achieved when the training data set achieves the best in data volume. With the development of research in neurodegenerative disorders, each aspect of the research development needs its role in development of the diagnosis, where AI would definitely give its hands for future diagnosis of ND with nearing perfect accuracy.

Conclusion

Mt dysfunction is a significant contributor to the pathogenesis of many neurological diseases like AD, PD, HD, ischemic stroke, sepsis, POAG, ALS, multiple sclerosis, LGS, and prion disease. Mt is the essential organelle for neuronal function and survival, containing about 1500 proteins of which mutations in them lead to malfunctioning of the Mt. They perform a broad spectrum of functions comprising of fusion, fission, mitophagy, biogenesis, maintenance of homeostasis, regulation of apoptosis, cell cycle progression, cellular proliferation, and cell differentiation; also comprising of physiological functions like innate immunity, autophagy, redox signalling, calcium homeostasis, and stem cell reprogramming; and other crucial cellular process like production of ATP through OXPHOS, citric acid cycle, fatty acid oxidation, phospholipid synthesis, hemoglobin biosynthesis, generation, and maintenance of ROS. The five complexes of ETC are encoded by the mt and nuclear genomes, where mutation or chemical inhibition in them causes Mt-related diseases and also results in low energy production. The defects in proteins of mtDNA maintenance or repair machinery leads to secondary multiple deletions, duplications or depletion of mtDNA which leads to poor mt respiration, and dysfunction linking to broad spectrum of mt and age-related diseases. There are various mitochondrial and nuclear genes that have its specific role in the maintenance of Mt and its behavior that is discussed (Table 1) which will be the best approaching strategy for mitochondrial research for health and disease, and not only for neurological disorders.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Consent to Participate Not applicable.

Consent to Publication All authors agreed to publish the contents.

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