The "mitochondrial stress responses": the "Dr. Jekyll and Mr. Hyde" of neuronal disorders

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From the Contents

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Abstract

Neuronal disorders are associated with a profound loss of mitochondrial functions caused by various stress conditions, such as oxidative and metabolic stress, protein folding or import defects, and mitochondrial DNA alteration. Cells engage in different coordinated responses to safeguard mitochondrial homeostasis. In this review, we will explore the contribution of mitochondrial stress responses that are activated by the organelle to perceive these dangerous conditions, keep them under control and rescue the physiological condition of nervous cells. In the sections to come, particular attention will be dedicated to analyzing how compensatory mitochondrial hyperfusion, mitophagy, mitochondrial unfolding protein response, and apoptosis impact human neuronal diseases. Finally, we will discuss the relevance of the new concept: the "mito-inflammation", a mitochondria-mediated inflammatory response that is recently found to cover a relevant role in the pathogenesis of diverse inflammatory-related diseases, including neuronal disorders.

Key Words: Alzheimer's disease; apoptosis; mitochondrial dynamics; mito-inflammation; mitophagy; multiple sclerosis; neurodegeneration; Parkinson's disease; UPR^{mt}

Introduction

Mitochondria are ubiquitous organelles in eukaryotic cells that play a key role in many different cellular processes that span from adenosine 5′-triphosphate (ATP) synthesis, production of reactive oxygen species (ROS), metabolism of amino acids, regulation of cell death and calcium (Ca^{2+}) homeostasis (Suomalainen and Battersby, 2018; Danese et al., 2021; Patergnani et al., 2021a). They consist of an outer mitochondrial membrane (OMM) and an inner mitochondrial membrane (IMM) that define an intermembrane space and an internal matrix, where the mitochondrial DNA (mtDNA) is located. On the IMM are accommodated the proteins involved in the electron transport chain and ATP production (Pfanner et al., 2019). Among all mitochondrial proteins, 13 of the proteins involved in the oxidative phosphorylation are encoded by mtDNA and the remaining ~1200 by the nuclear genome and imported, in an unfolded state, into the organelle through the translocons of the outer and inner membrane complexes, respectively (Mai et al., 2017). Given the crucial role of mitochondria in regulating several cellular processes, their efficient function is fundamental also in the nervous systems. Hence, it is not surprising that the accumulation of mitochondrial dysfunctionalities plays a key role in the pathogenesis of different diseases, including neuronal disorders (ND) (Han and Xu, 2021). The mitochondrial quality control is operated through the coordination of diverse mitochondrial stress responses, mechanisms that intervene to ensure cell and mitochondrial homeostasis (Patergnani et al., 2020a). In addition, many findings assign to mitochondria an alternative role in triggering and sustaining the cellular inflammatory response to different stimuli, introducing a new concept: the "mito-inflammation". Despite distinct clinical and pathological hallmarks, the mitochondrial stress responses significantly impact the pathogenesis of ND, resulting in the "Dr. Jekyll and Mr. Hyde" for these diseases: (1) Compensatory mitochondrial hyperfusion: an alteration in mitochondrial dynamics which favors the fusion of mitochondria to perform the functional complementation. (2) Mitophagy: a selective autophagic response that segregates and eliminates dysfunctional mitochondria. (3) Mitochondrial unfolded stress response (UPR^{mt}): a mitochondria-nucleus transcriptional program, triggered by proteotoxic stress, which promotes mitochondrial proteostasis, mitochondrial biogenesis, metabolic adaptations, and ROS detoxification to lead survival and mitochondrial network recovery. (4) Mito-inflammation: the mitochondria-mediated inflammation, that occurs to preserve cell integrity, but when exacerbated, it promotes detrimental effects becoming a cause of pathogenesis of several inflammatory-related diseases. (5) Apoptosis: an irreversibly cellular response activated by drastic and prolonged stress.

Their activation contributes to limiting the expansion of mitochondrial stress providing a protection role (the good represented by Dr. Jekyll); however, dysregulation or abnormal activation may exacerbate the mitochondrial stress leading to deleterious consequences (the evil represented by Mr. Hyde).

In this review, we describe the diverse mechanisms activated by mitochondrial stress and how they are implicated in the development and progression of the most common ND, including Parkinson's disease (PD) and Alzheimer's disease (AD).

Search Strategy and Selection Criteria

All years were chosen in the search. These searches were performed between June and December 2021 by using PubMed database.

Mitochondrial Stress Responses in Neuronal Disorders

The molecular and signaling mechanisms by which mitochondria respond to a stress signal begin with basic defense mechanisms (such as the simple antioxidant response resulting from excessive ROS production) and end with highly connected and tuned processes, which permit to maintain the correct functioning of the mitochondrial network and the cell (**Table 1**). These protective mitochondrial responses often hide a dark side; they may turn into deleterious responses if their activation is abnormal and persists over time. The next sections aim to explore these specialized mechanisms and link their contribution to the pathogenesis of different ND.

The Role of Compensatory Mitochondrial Dynamic in Neuronal Disorders

Mitochondria are dynamic interconnected organelles, which constantly undergo cycles of fusion and fission that, together with de novo biogenesis

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Table 1 | **Summary of key components of the pathway regulating the mitochondrial stress responses**

Pathway	Name	Function
Mitochondrial dynamics	DRP1	Fission
	MID49 and MID51	Adaptors of DRP1
	MFNs	Fusion
	OPA1	Fusion
	SLC25	Fusion
	BAX	Mediates the DRP1-mediated fission and inhibit the MFN2-mediated fusion
	PHB	Stabilizes L-OPA1 isoform
	OMA1 and YME1L	Process the cleavage of OPA1
	CL	Processes the cleavage of OPA1 and regulate OMA1 turnover
	GSH	Modifies disulphide bonds of MFNs
Mitophagy	PTEN-Parkin	Positive regulators of mitophagy
	TIM23/TOM complex	Regulate PINK1 translocation in mitochondria
	MFN	Mitochondrial target of Parkin
	LC3, NDP52, optineurin TAX1BP1 and p62	Mitophagy receptors
	OMA1	Import PINK1 into mitochondria independently from TIM23/TOM
	FUNDC1, CL, NLRX1 and NIX/BNIP3L	Regulate the PINK1-Parkin independent mitophagy
	AMPK	Positive regulator of autophagy and mitophagy
Mitochondrial unfolded protein response (UPRmt)	Ubl-5, dve-1 and atfs-1	Regulate the UPRmt in *C. elegans*
	ATF5, CHOP and ATF4	Main regulators the UPRmt in mammals
	eIF2	Regulates the mammalian integrated stress response
	CLPP, HSP60, and YME1L	UPRmt in marker genes
	Erα, HTRA2, SIRT3, and FOXO	Regulators of CHOP-ATF5 independent UPRmt
Mito-inflammation	mtDNA, ROS, Ca^{2+} and CL	DAMP released from mitochondria during inflammatory conditions that are harmful to mitochondria
	PRRs	Receptors expressed on microglia, astrocytes, and macrophages that recognize mitochondrial DAMP
	MDV	Vesicular system for the release of mitochondrial DAMP
	NLRP3 inflammasome	Activated by mitochondrial DAMP
	CL	Required for NLRP3 docking on mitochondria
Apoptosis	Cyt-c and Smac/DIABLO	IMS-resident pro-apoptotic factors released into the cytosol following apoptotic stimuli
	CAS-9 and APAF	Cytosolic interactors of Cyt-c
	Ca^{2+}	Positive modulators of apoptosis
	MPT	Alteration in the permeability of the IMS
	BCL2 and BCL-XL	Anti-apoptotic factor
	BAX	Pro-apoptotic factor
	CAS-3	Executioner caspase
	P38K and tBID	BAX activator
	CAS-8	Mediates the cleavage of BID in tBID
	FAS/FASL	Activates CAS-8

AMPK: 5-Adenosine monophosphate-activated protein kinase; APAF: apoptosis protease-activating factor; atfs-1/ATF: activated transcription factor; BAX: B-cell lymphoma 2 (BCL2) associated X, apoptosis regulator; BCL2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; Ca^{2+}: calcium; CAS: caspase; CHOP: C/EBP homologous protein; CL: cardiolipin; CLPP: caseinolytic mitochondrial matrix peptidase proteolytic subunit; DAMPs: damage-associated molecular patterns; DRP-1: dynamin-related protein-1; eIF2: eukaryotic translation initiation factor 2; FOXO: forkhead box O; FUNDC1: FUN14 domain-containing protein 1; GSH: glutathione; HSP60: heat shock protein 60; HTRA2: htrA serine peptidase 2; IMS: mitochondrial intermembrane space; LC3: microtubule-associated proteins 1A/1B light chain 3; MDV: mitochondrial-derived vesicles; MFN: mitofusin; MID49 and MID51: mitochondrial dynamics proteins of 49 and 51 kDa; MPT: mitochondrial permeability transition; NDP52: calcium binding and coiled-coil domain 2; NIX/BNIP3L: NIP3-like protein X; NLRP: nod-like receptor protein; NLRX1: nod-like receptor family member X1; OMA1: metalloendopeptidase; OPA1: optic atrophy 1; p38K: p38 kinase; PHB: prohibitins; PRRs: pattern recognition receptors; SIRT3: sirtuins; SLC25: members of the mitochondrial carrier family; TAX1BP1: tax1-binding protein 1; tBID: truncated BH3-interacting domain death agonist; TIM: translocons of the inner membrane; TOM: translocons of the outer membrane; YME1L: ATP-dependent zinc metalloprotease.

and mitophagy, maintain their physiological integrity and control inter-organellar connections to participate in fundamental cellular processes (Marchi et al., 2014). In general, fission is responsible to generate smaller mitochondria, ensuring an efficient organization and movement within the cell, and permitting to the mitochondrial population to be inherited. Mitochondrial fusion consents to the sharing of material between mitochondria to guarantee a balanced mitochondrial network at both functional and structural levels. Alterations in the mitochondrial re-organization are increasingly associated with the development and progression of ND. This section aims to describe the machinery involved in mitochondrial dynamics and clarify their contribution to ND.

Mitochondrial dynamics

Mitochondria fission and fusion are regulated by a plethora of proteins, the majority belonging to the family of dynamin-related GTPases (Zhang et al., 2019a). The main protein involved in the mitochondrial fission process is the cytosolic GTPase dynamin-related protein-1 (DRP-1). DRP-1 is reversibly associated with OMM after its recruitment by many adaptors [mitochondrial dynamics proteins of 49 and 51 kDa, (MID49 and MID51), mitochondrial fission factor, and mitochondrial fission 1] that mediate the binding (Loson et al., 2013). Upon cellular stimulation, post-translational modifications occur to DRP-1 for its mitochondria recruitment, where it induces scission upon GTP hydrolysis by constriction of OMM (Koirala et al., 2013).

Fusion of mitochondria consists of two steps, where firstly OMM and after IMM of two mitochondria that both express mitofusin (MFN) are fused (Guillery et al., 2008). The activity and amount of MFN are modulated by different post-translational mechanisms, such as de-ubiquitination that stabilizes and activates MFN, or phosphorylation events, which trigger MFN inhibition and degradation (Chen and Dorn, 2013; Yue et al., 2014; Pyakurel et al., 2015). The fusion is also mediated by the 120KDa dynamin-like GTPase protein optic atrophy 1 (OPA1) and it is coordinated by the member of the mitochondrial solute carrier family SLC25 named SLC25A46 (Cipolat et al., 2004; Abrams et al., 2015; Li et al., 2017). In the cells, there are two isoforms of OPA1, depending on its alternative splicing and proteolytic cleavage occurring in mitochondria: long-OPA1 (L-OPA1) and short-OPA1. The balance between them guarantees the physiological mitochondrial morphology. Upon apoptotic stimuli, L-OPA1 is converted to the shortest one to inhibit mitochondrial fusion (Ishihara et al., 2006). The balancing between mitochondrial fusion and fission is fundamental to preserve the overall shape of mitochondria. If it lacks, fragmentation of the mitochondrial network may occur, thereby facilitating the segregation of dysfunctional mitochondria and their consequent elimination by mitophagy or, under abnormal stress conditions, it is responsible for cytochrome c (cyt-c) release and apoptosis (Oettinghaus et al., 2016). During the apoptotic event, the B-cell lymphoma 2 (BCL2) Associated X (BAX) and DRP1 translocate to mitochondria where cooperate to promote the DRP1-mediated fission and inhibit the MFN2-mediated fusion, causing mitochondrial fragmentation. Furthermore, BAX forms channels on the OMM, favoring mitochondrial permeabilization and release of cyt-c. Coincident with BAX activation during apoptosis, the BAX/BAK-triggering DRP1-sumoylation favors the mitochondrial fragmentation stabilizing the association of the fission protein to the mitochondrial membrane (Wasiak et al., 2007). In line with this, the expression of a DRP1 mutant inhibits apoptosis preventing mitochondrial fragmentation (Frank et al., 2001). Simultaneously, modest levels of mitochondrial and endoplasmic reticulum (ER) stress induce an increase in the fusion process, which promotes the formation of long filamentous mitochondria to recover partial functional reductions and thus protect the mitochondria from potential damages. However, whether the stress persists, this compensatory phenotype is lost (Lebeau et al., 2018).

Currently, the phenomenon of compensatory mitochondrial hyperfusion is not totally understood as much evidence matched it either to pathological states (Ueda and Ishihara, 2018; Longo et al., 2020) or with protective transient mechanisms against aging and neurodegeneration (Mitra et al., 2009; Tondera et al., 2009; Lebeau et al., 2018).

Implications of mitochondrial dynamics in neurodegeneration

Overall, mitochondrial fusion is a protective event in neurons, as it allows the exchange of a plethora of factors (mtDNA, lipids, proteins, equal distribution of metabolites), which would mitigate any damage to the mitochondria, maximizing their oxidative capacity and reducing heteroplasmy (Chen et al., 2007). The physiological balance existing between fusion and fission is deeply impaired in ND in favor of a burst of mitochondrial fragmentation, such as in PD (Santos et al., 2015), AD (Wang et al., 2009), Huntington (Song et al., 2011) and Prion disease (Yang et al., 2017). In agreement, the majority of mitochondrial fusion proteins are downregulated (Flippo and Strack, 2017). However, a transitory mitochondrial response aimed to counteract certain types of pathological stressful conditions through the hyperfusion of the mitochondrial network exists. Events in which a compensatory hyperfused state of the mitochondrial network provides pro-survival effects are firstly described in 2009 in cells stressed by a small number (to date) of stressors, including ultraviolet light, serum deprivation, and chronic inhibition of protein synthesis (Tondera et al., 2009). The form of stress-induced compensatory mitochondrial hyperfusion (SIMH) is a transitory state induced by modest levels of damage. A mechanism independent from MFN2, which requires the expression of L-OPA1 and MFN1, is sustained by the IMM stomatin-like protein 2 (Tondera et al., 2009). This allows maintaining an adequate ATP production and gain of function in cell resistance to modest stress.

L-OPA1 is currently considered a critical component of the whole protein expression pattern in neurodegeneration as it ensures, through different molecular pathways, cristae morphology, ATP production, and a correct function of electron transport chain during neuronal stress (Quintana-Cabrera et al., 2021). To ensure L-OPA1 stability is necessary prohibitin (PHB), which acts as a scaffold at the IMM (Kasashima et al., 2008), and a balanced function of the peptidases metalloendopeptidase (OMA1) and ATP-dependent zinc metalloprotease (YME1L), which process the cleavage of OPA1. Consistent with this, following a toxic insult that promotes mitochondrial dysfunction and energy depletion, OMA1 and YME1L result degraded, and their proteolytic processing to OPA1 is lost, thereby affecting the recovery of mitochondrial morphology, which occurs following a stress-induced fragmentation (Rainbolt et al., 2016). The absence of PHB at neuronal levels triggers neurodegeneration in mice caused by Tau proteins aggregation (Korwitz et al., 2016). The consequent stabilization of OPA1 by the loss of OMA1, which decreases the adverse processing of the fusion protein, promotes protection from neuroinflammation and apoptosis (Korwitz et al., 2016). Interestingly, this OPA1 processing mediated by PHB and OMA1 in neurons can be also modulated by the mitochondrial phospholipid cardiolipin (CL). Indeed, it has been recently demonstrated that CL exists in a molecular complex composed of PHB and OMA1, which is fundamental for promoting the OMA1 turnover in neurons (Anderson et al., 2020). In confirmation of the critical role of OPA1 in neurodegeneration, it has been demonstrated that mutations in OPA1 are the main cause for dominant optic atrophy, an inherited disease that affects the optic nerve integrity (Delettre et al., 2000). Syndromic patients harboring dominant optic atrophy suffer from a progressive loss of retinal ganglion cells accompanied by other symptoms, such as deafness, ataxia, and myopathy (Baker et al., 2011). Furthermore, the patients also display markers of dysfunctional mitochondria and a compromised mitochondrial network, thereby suggesting the importance of the fusion mechanism in a neurodegenerative status. Experiments conducted in an OPA1 mouse model carrying the recurrent OPA1^{delTTAG} mutation (present in approximately 30% of all dominant optic atrophy patients) confirmed this possibility. OPA1^{delTTAG} mutation leads to progressive visual failure and loss of locomotor behavior, inducing severe mitochondrial dysfunctions (Sarzi et al., 2012). In skeletal muscle, the OPA1^{delTTAG} mutation-dependent mitochondrial dysfunction was accompanied by an increase in autophagy, mitophagy, and mitochondrial proliferation (Sarzi et al., 2012). This excessive mitochondrial turnover may alter the ultrastructure of mitochondria and provoke myopathy and weakness. Preserving an optimal mitochondrial network is also fundamental for cellular metabolism. Profound metabolic signatures have been unveiled in mice with OPA1^{delTTAG} mutation since they display alterations in the concentrations of phospholipids, amino acids, acylcarnitines, and carnosines (Chao de la Barca et al., 2017). In line with this, OPA1^{delTTAG} mutation also affects the size of axonal mitochondria, which reflects in a downregulation of the (re)myelination status in different central nervous system tracts (Ineichen et al., 2021). Interestingly, this effect was also found in mice with MFN2^{R94Q} mutation (Ineichen et al., 2021), confirming the relevant role of the mitochondrial network for the brain. The neural stem cells activated SIMH to counteract the exposure to nicotine, which in turn induced mitochondrial ROS production, mtDNA damage, and excessive mitophagy. This study indicated that a short-term exposure to nicotine is a stressful condition, sufficient to induce mitochondrial dysfunction and alteration in mitochondrial quality control, contributing to cellular aging (Zahedi et al., 2019). The SIMH seems to have beneficial effects only for short-term adaptions. A chronic induction of SIMH led to further stress caused by a static drop of mitochondrial turnover in the absence of fragmentation and mitophagy, as reported in apolipoprotein E (APOE) expressed astrocytes. Indeed, the severe reduction of MFN1 ubiquitination concurs in maladaptive phenotypes in AD, where APOE constitutes a major risk factor (Schmukler et al., 2020).

The antioxidant activity of glutathione (GSH) is also accompanied by compensatory mitochondrial hyperfusion with the concomitant protection of cells from death and excessive mitophagy (Shutt et al., 2012). Many neurodegenerative disorders are characterized by increased oxidative stress which is widely recognized as a key contributor in the progression of the disease, such as in AD and PD (Chen et al., 2012). In these contexts, a tight feedback loop exists, particularly when a proteostatic stress induces ROS production, which in turn exacerbates the proteostatic damage (Angelova and Abramov, 2018; Wang et al., 2021). In response to increased oxidative stress, neuronal cells use GSH to neutralize ROS during stressful conditions, converting its oxidized form glutathione disulfide. The link between glutathione disulfide accumulation and mitochondrial remodeling relies on the ability of the enzyme to modify several disulphide bonds, especially targeting cysteines (Okumura et al., 2011). MFNs reach in these amino acids and are the main protein targets to add new disulphide bonds, stabilizing them and promoting mitochondrial hyperfusion (Shutt et al., 2012). GSH not only protects cells from ROS, but also from other dangerous compounds, like the highly electrophilic aldehyde 4-hydroxy-trans 2-nonenal (4-HNE), an end-product of lipid peroxidation. In this case, the enzyme glutathione S-transferases (GSTs) mediates the conjugation of 4-HNE to GSH as a substrate (Alin et al., 1985). It has been demonstrated that 4-HNE represents a cause of oxidative stress-induced signaling and toxicity for neurons and oligodendrocytes (McCracken et al., 2000). The GST isoform 4α (GSTA4) helps to overcome the 4-HNE-mediated toxicity and improve the myelination process by reducing the intracellular levels of 4-HNE, increasing the mitochondrial functioning *in vitro* and *in vivo* in a demyelination/remyelination model (Carlstrom et al., 2020). The fact that oxidative stress is fundamental in neurological disorders was also confirmed in the experimental autoimmune encephalomyelitis (EAE) mouse model (an autoimmune inflammatory disorder of primary central nervous system demyelination) (Qi et al., 2006). After EAE induction, oxidative damage, impairments in mitochondrial functioning, and compromised mitochondrial network are detected in optic nerves, retinas, brains, and spinal cords (Qi et al., 2006). Consistent with this, mitochondrial dysfunction and increased mitophagy process (which reflect the impairment in the mitochondrial network) have been also unveiled in organotypic brain slice pre-treated with the demyelinating agent, lysolethicin, and in a cuprizone-induced mouse model (often used to investigate the demyelination/remyelination events) (Patergnani et al., 2021c). Although the best-characterized responses induced by SIMH support improved bioenergetics of cells, the importance of this adaptive mechanism also involves the activation of antiapoptotic molecular routes that allow beneficial effects in neuronal survival. One of these is the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. NF-κB is reported to be of primary importance in long-term memory and synaptic changes for brain adaptation to new information. Indeed, as reviewed in (Kaltschmidt and Kaltschmidt, 2015). NF-κB establishes a gene transcription program in favor of neurogenesis, axogenesis, and neuronal transmission in adult brains. Thus, NF-κB results are relevant in AD, where the cognitive ability and memory are lost (Jha et al., 2019), but also in multiple sclerosis (MS) protecting oligodendrocytes against inflammatory insults (Stone et al., 2017). Although not yet proven in models of neurodegeneration, SIMH is reported to be an upstream event in the upregulation of the NF-κB signaling, which triggers the activation of mitochondrial E3 ubiquitin (Ub) protein ligase 1 MUL1, a gene encoding for an E3 Ub transferase located to OMM. The intricate cascade of downstream events would involve the formation of a multiprotein complex composed of: the ubiquitylated form of tumor necrosis factor receptor-associated factor 2, which acts as a bridge between MUL1 and NF-κB; and by the transforming growth factor-β-activated kinase 1, that phosphorylates the NF-κB inhibitors, an inhibitor of nuclear factor kappa B (IKKß) and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα), respectively (Zemirli et al., 2014).

Overall, the protective role of SIMH as compensatory fusion under stressful conditions remains to be fully elucidated. Findings suggest that three are the essential components in the evaluation of this mitochondrial stress response from which may belong to either beneficial or detrimental features: what proteins take part in which molecular pathway, the type of stress, and the time duration. About the first one, it would be useful to investigate post-translational modifications of fusion proteins that would occur under stress, and which are almost unknown. About the other issues, currently, a transient event (more difficult to study) would be compensatory and beneficial; a chronic mitochondrial hyperfusion would be deleterious also due to persistent mitochondrial mislocalization in cells and limited mobility (Girard et al., 2012).

The Role of Mitophagy in Neuronal Disorders

Autophagy is a cellular catabolic mechanism, in which cytosolic elements and damaged organelle are sequestered into vesicles (called autophagosomes) and then degraded or recycled through the lysosomes (Klionsky et al., 2021). Autophagy was discovered during the 1960s (Deter et al., 1967), but it was deeply investigated over the past ten years. To date, autophagy is recognized as a molecular mechanism that contributes to preserving cellular homeostasis, confers resistance to undesirable conditions (such as infection, stress, and inflammation), regulates cellular and tissue development, and controls cell fate. Autophagy exists in diverse forms that are specialized to sequester and degrade specific intracellular material. Proteinphagy identifies the involvement of autophagy in the degradation of altered proteins; lipophagy points to the sequestration and removal of lipid droplets; as a result of bacteria or virus infection, xenophagy is activated. In addition to these specialized forms of autophagy, selective forms of autophagy targeting portions or entire organelles, such as ER, nucleus, and peroxisomes, also exist. Among them, the most studied selective autophagic response is mitophagy, a process by which dysfunctional mitochondria are sequestered to be eliminated.

Mitophagy

Under severe or prolonged stress conditions mitochondria fusion is inhibited and occurring fission, which leads to mitochondrial fragmentation to facilitate mitophagy. Mitophagy is a selective cellular mechanism that removes damaged or dysfunctional mitochondria, ensuring the mitochondria quality control (Tajiri et al., 2016). Firstly observed in reticulocytes, mitophagy regulates the cell fate, controlling cellular metabolism and influencing the inflammatory response in several pathological conditions (Patergnani et al., 2021b). The molecular pathway in mitophagy is composed of the axis of the phosphatase and tensin homolog deleted on chromosome 10 (PTEN)-induced kinase 1 (PINK1) and Parkin (Kitada et al., 1998). Under normal conditions, PINK1 is continuously kept at low expression levels, thanks to a high-regulated mechanism in which PINK1 is imported into the mitochondria to be degraded. In stressed mitochondria, TIM23/TOM complex activity is corrupted and thus PINK1 accumulates on the OMM. Following a series of phosphorylations (S402, S228, and T257), PINK1 induces Parkin into an active phospho-Ub-dependent enzyme, which determines the ubiquitination of several OMM proteins, including MFN, representing the signal for the recruitment of a series of Ub-binding autophagic receptors, such as the autophagic cargo receptor NBR1, microtubule-associated proteins 1A/1B light chain 3 (LC3), calcium-binding and coiled-coil domain 2 (NDP52), optineurin, tax1-binding protein 1, and p62/Sequestome-1 (Geisler et al., 2010; Pickles et al., 2018).

In these years, mitophagy has acquired more and more value among the NDs, with a role characterized by "lights and shadows" (Doxaki and Palikaras, 2020). Undoubtedly, PD is widely characterized by mutations in the mitophagy regulators, Parkin and PINK1 (**Figure 1**) (Shefa et al., 2019). To date, more than a hundred autosomal recessive mutations have been unveiled for the *Parkin* gene, representing the primary cause for the early-onset PD and the common cause of autosomal recessive juvenile parkinsonism. About 130 PINK1 mutations have been characterized and the loss of function mutations represents the second most frequent cause of autosomal recessive PD. Several studies demonstrated that mutated PINK1 and Parkin are responsible to decrease the capacity of the cell to initiate mitophagy (Kitada et al., 1998; Valente et al., 2004a, b; Geisler et al., 2010; Morais et al., 2014; Gautier et al., 2016; Puschmann et al., 2017). Fibroblasts and neurons obtained from patients with PINK1 or Parkin mutations showed impaired recruitment of Parkin on the mitochondrial surface or an altered PINK1 activation (Piccoli et al., 2008; Seibler et al., 2011). However, it has been suggested that the recruitment of Parkin on the mitochondrial surface may occur even in presence of PINK1 mutations. Indeed, suppression of the protease OMA1 (that can import PINK1 into mitochondria for its degradation independently from TIM23/TOM activity and state of mitochondria) restores the mitochondrial accumulation of parkin even in presence of PD-Related PINK1 mutations (Sekine et al., 2019). It also exists mitophagy molecular mechanisms that are PINK1-Parkin independent. Mitophagy may be executed by the OMM protein FUN14 domain-containing protein 1 (FUNDC1). In basal conditions, FUNDC1 is phosphorylated by SRC proto-oncogene, non-receptor tyrosine (SRC) kinase (Liu et al., 2012). Under hypoxia, the dephosphorylated form of FUNDC1, due to SRC inactivation, may associate with LC3 to prompt the incorporation of mitochondria into autophagosomes (Liu et al., 2012). In line with this, NIP3-like protein X (NIX/BNIP3L) is another OMM-resident protein that mediating to specific WXXL-like motif may bind LC3 to sequester mitochondria (Novak et al., 2010; Yuan et al., 2017). Recently, it has been demonstrated that also IMM and matrix resident proteins can modulate mitophagy. Regarding the IMM protein, an example is CL. Upon a mitophagic stimulus, CL moves from the IMM to the OMM where acts as a signal for the identification and removal of damaged mitochondria, since LC3 protein displays CL-binding sites (Chu et al., 2013). Meanwhile, the matrix protein nod-like receptor (NLR) family member NLRX1 has an LC3-interaction region domain that permits the recruitment of LC3 to activate the mitophagy upon infection with the pathogen *Listeria* (Zhang et al., 2019b).

Mitophagy involvement in neurodegeneration

In AD brains, it has been observed that Parkin resulted to be depleted over the disease, causing alteration of the normal mitophagic route (**Figure 1**) (Ye et al., 2015). This determines the accumulation of damaged mitochondria, increased ROS production, reduced ATP production and it may represent a signal for apoptosis and neuronal cell death. The contribution of mitophagy to the PD pathogenesis has been also confirmed in Drosophila, where PINK1-Parkin mutant flies showed mitochondrial alterations, locomotive deficiencies, and defects in neuron development (Julienne et al., 2017). Surprisingly, mice with PINK1 and Parkin deletion did not have evident PD-phenotypes. Indeed, Parkin-deficient mice did not exhibit profound deficits in neurological function, learning, memory and the substantia nigra pars compacta dopamine neurons were unharmed (Perez and Palmiter, 2005). A similar observation was achieved in PINK1 knock-out (KO) mice, where the number and the morphology of dopaminergic neurons in the substantia nigra were comparable with the wild-type mice (Kitada et al., 2007). PINK1 KO mice only exhibited a modest deficit in locomotor activity and increased inflammation following exhaustive exercise, which severely stressed mitochondria (Kelm-Nelson et al., 2018; Sliter et al., 2018). Despite this, the levels of pro-inflammatory cytokines in the serum of PINK1 KO mice, in resting conditions were comparable to those in wild-type mice (Sliter et al., 2018). Overall, these data suggest that compensatory mechanisms are activated to preserve the neuronal homeostasis, and the fact that PINK1 and Parkin did not induce robust PD-phenotype, indicates that PINK1-Parkin mitophagic pathway under physiological circumstances may be dispensable. Opposite, the PINK1-Parkin axis became essential in response to pathological stimuli or stress conditions. In confirmation of this, by crossing Parkin KO mice with a mouse model that accumulates altered mitochondria (Mutator mice), the mitochondrial dysfunctions exacerbated and lead to dopaminergic neuronal cell death, phenotypes not observed in the parental Mutator or Parkin-KO (Pickrell et al., 2015).

In AD, the neuronal loss is due to uncontrolled protein accumulation of amyloid-β (Aβ), alpha-synuclein (α-syn), Ub, and APOE, which form aggregates of extracellular (amyloid) plaques; and of APOE and hyperphosphorylated tau, responsible for intracellular and extracellular neurofibrillary tangles, respectively. In the last years, several reports suggest that mitophagy represents the main process for AD progression. Aβ, amyloid precursor protein, and its processing enzymes were found to provoke alterations in mitochondrial morphology and function, with failing in mitophagy activation. Notably, this effect was unveiled *in vitro* as well as in the AD mouse model and also in the human post-mortem brain, where the accumulation of altered mitochondria was associated with mitophagy failure (Vaillant-Beuchot et al., 2021). Furthermore, in AD brains, it was also observed that Parkin resulted to be depleted over the disease, causing alteration of the normal mitophagic route with consequent loss of mitochondrial functions (Ye et al., 2015). Defects in mitophagic activity were also reported in the recent work of Fang et al. that unveiled evidence of mitophagy impairment in the hippocampus of AD patients, in neurons derived from induced pluripotent stem cells,

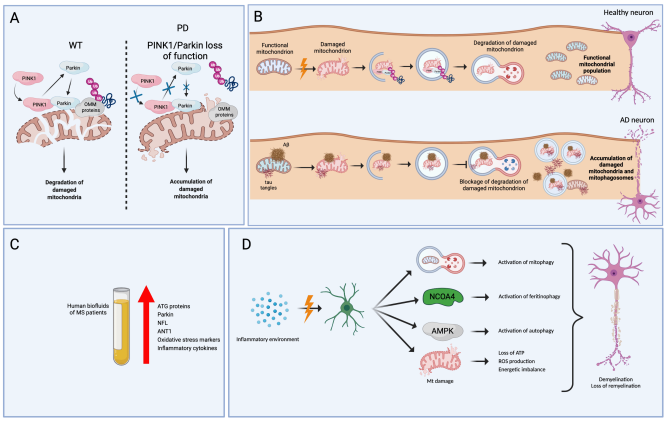

Figure 1 | **Selective mitochondrial autophagic response in neuronal disorders.**
(A) When mitochondria suffer an important damage, PINK1 accumulates to the mitochondria and recruits Parkin to the OMM. Here, Parkin determines the ubiquitination of mitochondrial resident proteins. This represents a signal for the recruitment of a series of ubiquitin-binding autophagic receptors that promote degradation of the non-functional organelle by mitophagy. Among the diverse neurological disorders, PD is characterized by PINK1-Parkin loss and mutations. These conditions alter the normal PINK1 functioning, thus causing failure in Parkin recruitment on the mitochondrial surface. As a result, the mitochondrial autophagy is impaired and results not efficient to remove damaged mitochondria. (B) Mitophagy is also a key process during AD pathogenesis. Indeed, aberrant production and accumulation of Aβ and tau tangles cause loss of mitochondrial functioning and failure of mitophagy execution. When these conditions persist, neuronal cell death is induced. (C, D) Recent works demonstrate that the circulating markers of mitophagy and mitochondrial dysfunctions are highly expressed in circulating body fluid of MS-affected patients. Interestingly, they correlate to an active phase of the disease. Consistently, the sustained inflammatory condition that characterized MS causes oligodendrocyte damage and loss of mitochondrial functioning, and energetic imbalance. Furthermore, this condition activates the AMPK-dependent autophagy and diverse cellular forms of selective autophagy, such as mitochondrial autophagy and nuclear receptor coactivator 4-ferritinophagy. All these conditions are sufficient to provoke demyelination as well as loss of the re-myelination process. AD: Alzheimer's disease; AMPK: 5-adenosine monophosphate-activated protein kinase; ANT: adenine nucleotide translocator; ATG: autophagy gene; Aβ: amyloid-beta; MS: multiple sclerosis; Mt: mitochondria; NCOA4: nuclear receptor coactivator 4; NFL: neurofilament; OMM: outer mitochondrial membrane; PD: Parkinson's disease; PINK1: PTEN-induced kinase 1; WT: wild-type.

in diverse AD animal models, and Aβ *Caenorhabditis elegans* (*C. elegans*) models (Fang et al., 2019). However, using the NAD^+ precursor, nicotinamide mononucleotide, as mitophagic inducer, the cognitive impairments were ameliorated (Fang et al., 2019). Indeed, the overexpression of PINK1 reduced Aβ accumulation and counteracted the cognitive impairments, improving synaptic function and learning memory in AD animal models, through the NDP52- and optineurin-dependent mitophagy (Du et al., 2017). Altered expression of autophagic and mitophagy markers has been observed in biofluids obtained from AD patients, changes that could be used as possible biomarkers for an early detection or monitoring of progression disease (Castellazzi et al., 2019b).

N-terminal truncation of tau protein represents another hallmark of AD and occurs as an early event in the disease (Garcia-Sierra et al., 2008). It has been demonstrated a stable association between an N-terminal fragment of tau with Parkin, correlated to cognitive impairments in AD animal models as well as in the human AD brain (Corsetti et al., 2015). This protein interaction blocked the recruitment of Parkin on the mitochondrial membrane, determining impairments in mitophagy (Cummins et al., 2019).

Disarrangements in mitochondria quality control have been observed also in MS. 5-adenosine monophosphate-activated protein kinase (AMPK) is the primary activator of diverse selective autophagy responses, including mitophagy. It has been demonstrated that MS-like conditions determined myelin loss with a concomitant change in the energetic status of oligodendrocyte and loss of several mitochondrial functions, which provoked ROS production and triggered autophagy by AMPK activation (Bonora et al., 2014b). The fact that a deregulated mitochondrial status is determinant to trigger autophagy in MS was also demonstrated *in vivo* in various MS animal models (Alirezaei et al., 2009; Joubert et al., 2009; Akatsuka et al., 2017; Becher et al., 2018; Paunovic et al., 2018). However, these studies lack to demonstrate that the mitophagy process is directly involved in MS pathogenesis. First evidence was achieved when circulating markers of mitophagy were found in both sera and cerebrospinal fluid (CSF) of MS patients (**Figure 1**) (Patergnani et al., 2018). Interestingly, they correlated with the active phase of the disease and with the release of pro-inflammatory cytokines (Castellazzi et al., 2019a). Other clinical studies confirm this first study, elevated circulating levels of Parkin, ATG5, neurofilament light chain (an adverting biomarker of axonal damage) and reduced levels of mitochondrial adenine nucleotide translocase 1 were detected in biofluids of MS patients (Hassanpour et al., 2020; Joodi Khanghah et al., 2020). All these findings, not only suggest a sustained activation of the mitochondrial quality control

program aimed to remove the altered mitochondria during MS, but also propose circulating mitophagic proteins as potential predictive biomarkers. However, before this, it is necessary to validate these observations in greater patient cohorts and monitor the expression of autophagy and mitophagy markers during the active treatments used against MS. In addition, it is of fundamental importance to understand the origin of these markers and verify whether they may be only the result of cell death events that occur in MS. In these studies, the authors lack to investigate these critical points and translate their findings into other experimental models. A deeper investigation of the role of mitophagy in MS comes from our recent study (Patergnani et al., 2021c). Here, we confirm the excessive presence of mitophagy markers in both CSF and sera of MS patients. Indeed, we demonstrated the direct activation of mitophagic machinery in an *in vivo* demyelinating mouse model. Our results have also translational potential since we show that blocking the abnormal mitophagy with anti-psychotic compounds (identified as potential inhibitors of autophagy) permitted the reactivation of myelination *in vivo*. Finally, we uncovered that apart from mitophagy, also the selective ferritin-autophagy, mediated by the nuclear receptor coactivator 4, was responsible to prompt the inflammatory response in all MS models analyzed (**Figure 1**) (Patergnani et al., 2021c). These findings show that mitophagy acts as a secondary mechanism that exacerbates the progression of pathology, becoming a novel potential therapeutic target against MS.

Similar considerations should be done also for epilepsy, where several studies have demonstrated that impairment in mitochondrial functions is critical for the development and progression of the disease, and these mitochondrial dysfunctions are accompanied by persistent mitophagy (Rahman, 2015). Mediating TEM analysis, it has been observed the accumulation of autophagosomes and damaged mitochondria in tissue samples from hippocampi and temporal lobe cortexes of refractory temporal lobe epilepsy patients (Wu et al., 2018). To date, it has been demonstrated that glutamate-induced excitotoxicity caused neuronal death in epilepsy (Ambrogini et al., 2019), influencing also the mitophagy functioning (Jin et al., 2018; Wang et al., 2019a). It was observed that glutamate-induced excitotoxicity activated mitophagy in mouse hippocampal neurons. The maintenance of an adequate level of mitochondria was performed by administration of melatonin and leptin, which reduced mitophagy and neuronal cell death. Similarly, persistent mitophagy and neuronal degeneration were observed in different status of epileptic rat models (Zhang et al., 2020b).

Protective or detrimental? The role of mitophagy in neuronal disease is controversial; its cytoprotective effect is questioned by the persistence activation of the process that exacerbates its action contributing to neuronal vulnerability.

The Role of Mitochondrial Unfolded Protein Response (UPR^{mt}) in Neuronal Disorders

UPR^{mt} was originally identified in mammals but it is thanks to studies in *C. elegans* that the genes involved in sensing and responding to this mitochondrial stress response have been identified (Martinus et al., 1996). Oxidative phosphorylation dysfunction, proteostatic stress, ATP depletion, dissipation of mitochondrial membrane potential, and pathogen infections play a key role in the UPR^{mt} activation (Yoneda et al., 2004; Haynes and Ron, 2010). Findings permitted to identify in the proteins ubiquitin-like 5, Homobox protein dve-1, and stress-activated transcription factor (ATFS-1) the essential members of UPR^{mt} in *C. elegans*. In mammals is activating transcription factor 5 (ATF5), the homologous to ATFS-1, the principal actor of UPR^{mt}, where its expression is influenced by the transcription factors C/EBP homologous protein (CHOP) and ATF4, respectively (Quiros et al., 2017). Differences among *C. elegans* and mammals are not only restricted to this, indeed in mammals, but UPR^{mt} is also part of a broader stress response program called the integrated stress response. During this adaptive translational program, stress stimuli activate four kinases, which activities converge on phosphorylation of the eukaryotic initiation factor 2. It has been demonstrated that integrated stress response responds to the mitochondrial dysfunction and participates with UPR^{mt} to the recovery of mitochondrial homeostasis (Fessler et al., 2020; Guo et al., 2020). Furthermore, eukaryotic initiation factor 2 phosphorylation increases translation of ATF4 (Guo et al., 2020), indicating integrated stress response as an essential mechanism to sustain the UPR^{mt} activation, mediating ATF5. In the next section, we describe the molecular mechanisms of UPR^{mt} and report how these are involved in NDs.

Mechanisms and function of UPR^{mt}

UPR^{mt} is a protective mitochondrial to the nuclear signal response that involves a set of transcription factors, which up-regulate nuclear gene expression to induce mitochondrial chaperones, proteases, and antioxidant enzymes to reduce the protein-folding burden of the organelle or remove toxic proteins. Array analysis revealed that UPR^{mt} also induces the transcription of mitochondrial fission, metabolic, biogenesis, inflammatory, and mitokine genes (Aldridge et al., 2007; Nargund et al., 2012; Tian et al., 2016; Yi et al., 2018). It is activated in response to alterations of mitochondrial proteostasis, variations of membrane potential caused by various stress conditions, such as oxidative, metabolic stress, protein folding or import defects, and mtDNA alteration (Houtkooper et al., 2013; Moehle et al., 2019).

To date, independent and parallel pathways are linked to UPR^{mt}. The first one involves the transcription factor CHOP, which promotes the transcription of mitochondrial proteases and chaperons, such as ATP-dependent Clp protease proteolytic subunit (CLPP) and the heat shock protein 60 (HSP60), in response to proteotoxic stress through the transcriptional regulator ATF5 (Zhao et al., 2002; Fiorese et al., 2016). ATF5 has a mitochondrial localization and nuclear targeting sequence, which under physiological conditions it is constitutively imported and degraded into mitochondria (Teske et al., 2013; Harbauer et al., 2014; Fiorese et al., 2016). When a mitochondrial stress condition occurs, the mitochondrial translocation of ATF5 is blocked, resulting in its relocalization to the nucleus, where activates the transcription of UPR^{mt} marker genes, like HSP60 and CLPP (Haynes and Ron, 2010; Nargund et al., 2012; Rolland et al., 2019).

The other two UPR^{mt} activating ways are CHOP-ATF5 independent. In the estrogen receptor alpha (ERα) pathway, ROS production induces the AKT phosphorylation and the subsequent ER-α activation with the induction of the intra-mitochondrial-space protease htrA serine peptidase 2, the mitochondrial biogenesis regulator NFR1 and the increase in proteasome activity (Papa and Germain, 2011). In the Sirtuin 3-axis, forkhead box O activation induces the expression of the antioxidant *superoxide dismutase* (SOD)-1, -2, and *catalase* genes as well as mitochondrial biogenesis and mitophagy genes (Papa and Germain, 2014; Kenny and Germain, 2017).

The emerging role of UPR^{mt} in neurodegeneration

Differently from other mitochondrial stress responses, the role of UPR^{mt} in neuronal diseases is emerging, where ATF5 (in mammalian) or ATFS-1 (in *C. elegans*) pathways seem to have significant implications. Regarding PD, analysis of the postmortem brain revealed enhanced levels of UPR^{mt} activation markers, such as HSP60 (Pimenta de Castro et al., 2012). Parkinsonian toxins used in PD models, including inhibitors of mitochondrial complex I and enhancers of ROS production, are considered potent UPR^{mt} inducers (de Castro et al., 2011). Consistent with this, the proteostatic stress induced by the aggregation in the mitochondrial compartment of the highly soluble unfolded protein α-syn, which accumulates in Lewy bodies and Lewy neurites in PD and other synucleinopathies, represents a critical step in the recruitment of UPR^{mt} (Franco-Iborra et al., 2018). Accumulation of α-syn in mitochondria, imported by specific interaction with TOM20, has been reported in substantia nigra pars compacta of PD patients (Devi et al., 2008; Di Maio et al., 2016). It has been demonstrated that the α-syn PD-related variant A53T, accumulating into the mitochondria, inhibits the UPR^{mt} peptidase marker, CLPP, which sustained the UPRmt activation over time with detrimental effects in dopaminergic neurons (Hu et al., 2019). Abnormal UPR^{mt} activation has been also obtained in the *C. elegans* model of PD overexpressing the α-syn PD-related variants, A53T and A30P, conditions in which the beneficial effects of UPR^{mt} are lost when persisting the UPR^{mt}-overactivation inducing neurotoxic consequences (Martinez et al., 2017). The overexpression and overactivation of ATFS-1 potentiate the proteotoxicity of α-syn in dopaminergic neurons, demonstrating that UPR^{mt} overactivation contributes to exacerbating the pathogenesis in PD (Martinez et al., 2017). However, the survival of dopaminergic neurons is initially subjected to ATFS-1 and UPR^{mt} activation, as shown in *C. elegans* mutants for mitochondria-related genes implicated in monogenic PD (Cooper et al., 2017). The accumulation of dysfunctional mitochondria in *pdr-1* and *pink-1* mutants led to the activation of UPR^{mt}. In this case, ATFS-1 was required for the longevity of PD mutants and mitigated the detrimental effects of mutants on the dopamine neurons (Cooper et al., 2017). These two facets of the same pathway suggest that ATFS-1-dependent UPR^{mt} activation is potentially a hermetic process: beneficial during transient activation, but detrimental during chronic activation.

Aβ deposits in the brain are also present in mitochondria of AD mice and patients (Caspersen et al., 2005). Aβ precursor is cleaved by the mitochondrial HtrA2 protease, which controls the Aβ oligomerization delaying its proteotoxic effect (Park et al., 2006; Kooistra et al., 2009). Like in PD, the proteotoxic effect of mitochondrial Aβ activated UPR^{mt} in human cells and mice (Shen et al., 2019). However, the Aβ-induced proteinopathy was exacerbated by pharmacological inhibition of UPR^{mt}, indicating that also in AD the UPR^{mt} has initially a protective role (Perez et al., 2020). Prefrontal cortex derived from AD patients presented high expression levels of UPR^{mt}-induced genes, such as mitochondrial chaperone HSP60 and ATP-dependent zinc metalloprotease YME1L, which correlated with an increase in severity of disease (Beck et al., 2016; Sorrentino et al., 2017).

Oxidative and proteostatic stresses play a key role in the activation of UPR^{mt} also in amyotrophic lateral sclerosis (ALS) and a spectrum of TDP-43-related proteinopathies, such as frontotemporal lobar degeneration (Gomez and Germain, 2019; Wang et al., 2019c). Mutations in mitochondrial SOD1 are one of the principal causes of ALS, where the paralysis due by damages of motor neurons and the spinal cord is a consequence of increased production of ROS (Beckman et al., 2001) and abnormalities in multiple organelles in neurons, including mitochondria (Magrane et al., 2014). In particular, the mutant SOD1^{G93A} accumulates in mitochondria *in vivo*, on the OMM, where interacts with apoptotic-regulating proteins and/or Ca^{2+}-effector proteins, such as B-Cell Lymphoma 2 (BCL2) and voltage-dependent anion-selective channel, respectively (Israelson et al., 2010; Pedrini et al., 2010). Furthermore, SOD1^{G93A} may also accumulate in the IMS, where alter the import and maturation of mitochondrial proteins, thus promoting mitochondrial fragmentation and alterations in mitochondrial dynamics in motor neurons (Kawamata and Manfredi, 2010; Igoudjil et al., 2011). The oxidative and proteostatic stress, activating UPR^{mt} in ALS, is also sustained by mutated TDP-43 and CHCHD10 (coiled-coil-helix-coiled-coil-helix domain containing 10), which accumulate into mitochondria, induce ROS production, mitochondrial dysfunction, and the up-regulation of UPR^{mt}-related transcription factors CHOP and ATF5 *in*

vivo (Anderson et al., 2019; Wang et al., 2019c; Straub et al., 2021). The activation of UPR^{mt} has a protective role in the onset of ALS, but its function may exacerbate the disease progression causing neurodegeneration, as demonstrated by the abnormal accumulation of mitochondrial TDP-43 due to the downregulation of mitochondrial LONP1 protease. In addition, UPR^{mt} activation may be conditioned by sex difference, as emerged in SOD1^{G93A} mutant mice (Riar et al., 2017; Pharaoh et al., 2019; Wang et al., 2019c).

Proteostatic effects have been also associated with mutant huntingtin although to date it is not reported a direct involvement in active UPR^{mt}. Huntingtin impairs the mitochondrial protein import, localizing to mitochondria *in vitro* and *in vivo* in HD models and the caudate nucleus of HD patients (Orr et al., 2008; Yano et al., 2014). ATF5 accumulation has been reported within the characteristic polyglutamine-containing neuronal nuclear inclusions in the brains of HD patients and mice (Hernandez et al., 2017). In the HD model, the overexpression of ATF5 mitigated the neurotoxicity induced by self-aggregating poly-glutamine, suggesting that UPR^{mt} and ATF5 have a protective role in HD. On the contrary, the sequestration of ATF5 into polyglutamine-containing neuronal nuclear inclusions seems to abolish its neuroprotective activity, rendering the neurons more susceptible to mutant huntingtin-triggered death. High levels of ATF5 have been also found in adult neurons of epilepticus mice and were correlated as a pro-survival mechanism (Torres-Peraza et al., 2013).

In these years, the relationship between UPR^{mt} and neuronal diseases is growing, generally considered as beneficial for cellular homeostasis; however, evidence has started to reconsider this mitochondrial response, showing that the abnormal UPR^{mt} activation may be detrimental to the cell under some pathological conditions.

The Role of "Mito-inflammation" in Neuronal Disorders

Relationship between inflammation and mitochondria: the mito-inflammation concept

Chronic neuroinflammation is a common implication of NDs, characterized by microglia and/or astrocytes activation, which provoke an increased release of cytokines or chemokines and in some cases disruption of the blood-brain barrier with infiltration of immune cells. A process may be induced by mitochondrial dysfunction that, in turn, may promote and exacerbate the mitochondrial damage (Lin and Beal, 2006; Bader and Winklhofer, 2020). This vicious cycle leads to the release of mitochondrial damage-associated molecular patterns (mtDAMPs), such as mtDNA, ROS, Ca^{2+}, CL, and other mitochondrial-derived molecules, in part following a vesicle pathway, which activates specific inflammatory cascades. mtDAMPs, in turn, play a key role in several inflammatory-related pathological conditions, including the NDs (Lezi and Swerdlow, 2012; Swerdlow, 2012; Patergnani et al., 2021a) (**Figure 2**).

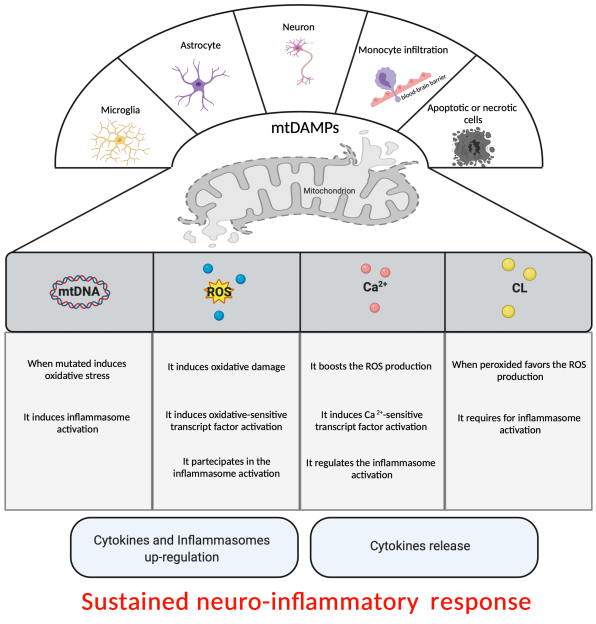

Figure 2 | **Contribution of mito-inflammation in neuronal disorders.**
Dysfunctional mitochondrial in neuronal and in infiltrated cells through the blood-brain barrier release mitochondrial damage-associated molecular patterns (mtDAMPs), such as mitochondrial DNA (mtDNA), mitochondrial reactive oxygen species (ROS), ion calcium (Ca^{2+}), and cardiolipin (CL) to sustain the neuroinflammation in neuronal disorders. The mito-inflammation is the contribution of the organelle to inflammatory response, when mitochondrial constituents and products are released to induce the up-regulation, activation, and release of inflammasomes and pro-inflammatory mediators, respectively. Created with BioRender.com.

Involvement of mito-inflammation in neurodegenerative diseases

The high susceptibility to mitochondrial alterations observed in NDs render the cells of the system nervous more prone to detrimental effects of mito-inflammation. Mito-inflammation is the mitochondrial compartmentalization response of inflammation, mediated by recognition of mtDAMPs from pattern recognition receptors that may be expressed by microglia, astrocytes, and macrophages (Lampron et al., 2013; Walsh et al., 2014; Freeman et al., 2017), but also by oligodendrocytes (McKenzie et al., 2018), neurons (Kaushal et al., 2015) and endothelial cells (Gong et al., 2018). mtDAMPs may be released outside the cell following a specific vesicle pathway, where mitochondrial-derived vesicles are generated through the selective incorporation of protein cargoes, which may include outer, inner membrane, and matrix content (Neuspiel et al., 2008; Soubannier et al., 2012). Findings indicate that mitochondrial-derived vesicles-mediated transfer of mitochondrial content, such as oxidized mtDNA or mitochondrial proteins, influences the inflammatory responses of recipient cells, although the effect can be either anti- or pro-inflammatory, depending on the context (Todkar et al., 2021). Encapsulated mitochondria-derived constituents released from microglia, in the genetic mouse model of ND, contribute to disease propagation by acting as effectors of the innate immune response, targeting adjacent astrocytes and neurons (Joshi et al., 2019). The immune stimulation by mitochondrial-derived vesicles can also occur in absence of inflammation, as in the case of the priming of dendritic cells mediated by antigen-driven activated T lymphocytes through the transferring of mtDNA to induce protection of dendritic cells against pathogen infection (Torralba et al., 2018).

In the post-mortem brain of PD patients, the deficit of complex I observed in platelets and fibroblasts represent the principal cause of mitochondrial ROS production, responsible for oxidative damages, even at the mtDNA level (Yoshino et al., 1992; Haas et al., 1995; Keeney et al., 2006; Villace et al., 2017). Oxidized and degraded mtDNA was found in human CSF plasma and mouse primary astrocytes associated with inflammatory and neurodegeneration states (Mathew et al., 2012). Circulating mtDNA was found increased also in CSF subjects with traumatic brain injury and correlated with unfavorable neurological outcomes (Walko et al., 2014). The level of circulating mtDNA is thus a potential biomarker for early-stage of PD and AD disease (Podlesniy et al., 2013; Pyle et al., 2015). Evidence of oxidative mtDNA modifications is present also in AD patients (Mecocci et al., 1994; Lovell and Markesbery, 2007). Consistent with this, external mtDNA injection into rodent hippocampi induced pro-inflammatory changes, increasing the levels of phosphorylation of pro-inflammatory transcription factors in the cortex (Wilkins et al., 2016). In particular, the authors observed an increased expression of the cell surface colony-stimulating factor 1 receptor, which promoted AKT phosphorylation that, in turn, activated NF-κB signaling (Wilkins et al., 2016). Interestingly, the authors also validated their findings in an AD mouse model, thereby demonstrating how mitochondria and/or mitochondrial fragments may contribute to neuroinflammation.

Mitochondrial-derived ROS, primarily produced from complex I and III due to accumulation of unfolded proteins, excessive Ca^{2+} or oxidative phosphorylation impairment, activate the NF-κB pathways, first signal (priming) of inflammasome activation. This results in the transcriptional upregulation of inflammasome members and cytokines, such as NLR family pyrin domain containing 3 (NLRP3) and interleukin 1β (IL-1β) (**Figure 2**) (Rubartelli, 2014; Chen et al., 2015; Rimessi et al., 2016; Patergnani et al., 2021a). Perturbations in mitochondrial Ca^{2+} signaling contribute to boosting the production of mitochondrial ROS with important repercussions on the inflammatory status (**Figure 2**) (Rimessi et al., 2015). This may happen directly, by stimulating mitochondrial ROS-generating enzymes, such as α-ketoglutarate and glycerol 3-phosphate dehydrogenase (Murphy, 2009; Gorlach et al., 2015), or indirectly, mediating the Ca^{2+}-dependent activation of nitric oxide synthase, which blocks the mitochondrial complex IV via nitric oxide and through the Ca^{2+}-dependent mitochondrial membrane depolarization via reverse electron transport (Biasutto et al., 2016).

The mitochondrial ROS is also involved in NLRP3 inflammasome activation in SOD1^{G93A} mutant mice-derived microglia, where the protein aggregates have an essential role to induce mitochondrial dysfunction in ALS (Deora et al., 2020). NLRP3 is an emerging pattern recognition receptor, a key player in neuroinflammation, activated by mitochondrial ROS, mtDNA, cardiolipin, and Ca^{2+} in a two-step process (**Figure 2**). It accumulates to mitochondria where oligomerizes with apoptosis-associated speck-like protein containing a CARD (ACS) and pro-caspase (CAS)-1 to promote the release of IL-1β and IL-18 (Rimessi et al., 2015; Zhong et al., 2018). Mitochondrial cardiolipin that is regulated by the transcriptional activity of ATFS-1 (Shpilka et al., 2021) is also required for NLRP3 inflammasome activation (**Figure 2**). Indeed, exposure to the antibiotic linezolid provoked mitochondrial dysfunction and activated NLRP3. Interestingly, inflammasome activation and mitochondrial damage were abolished when the mitochondrial compartment was stabilized with the inhibitor of mitochondrial membrane permeability transition cyclosporine-A, thereby suggesting a close relationship between inflammasome recruitment and mitochondria activities. This was confirmed since the authors not only demonstrated that NLRP3 can bind CL, but they also provided evidence that CL is required for NLRP3 activation and its docking to mitochondria (Iyer et al., 2013). CL is downregulated in PD and AD brain, it is frequently found peroxided by the increased oxidative stress that characterizes these pathologies, influencing its regulatory activity on the mitochondrial respiration complex (Ruggiero et al., 1992; Chicco and Sparagna, 2007; Tyurin et al., 2008; Monteiro-Cardoso et al., 2015). In particular in PD pathogenesis, CL interacts with α-syn within the mitochondrial membranes of PD brains,

and this protein interaction interferes with the ability of cardiolipin to regulate the electron transport chain, exacerbating the progression of PD through the production of mitochondrial ROS (Shen et al., 2014; Ghio et al., 2016).

NLRP3 activation has been implicated in the progression of several neuronal disorders. Genetic polymorphisms of NLRP3 and high levels of systemic and localized NLRP3 inflammasome expression, such as in mesencephalic neurons, are associated with the progression of the disease and motor severity (von Herrmann et al., 2018; Fan et al., 2020). The recruitment of inflammasome was also confirmed by high levels of IL-1β and CAS-1 measured in serum and striata of PD patients, respectively (Mogi et al., 1994; Zhou et al., 2016).

α-Syn may active the NLRP3 inflammasome in human monocytes and stabilized microglial cells, while the failure in NLRP3 activation in primary microglial cells remains controversial (Gustin et al., 2015; Gustot et al., 2015; Zhou et al., 2016). The inflammasome activation in primary microglia is instead mediated by mitochondrial dysfunction and by the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, which via mitochondrial ROS led to NLRP3 assembly to induce dopaminergic neurodegeneration (Sarkar et al., 2017; Lee et al., 2019). A contribution to neurodegeneration is also promoted by the negative regulation of autophagy-mediated by NLRP3 inflammasome activation in microglia. Autophagy fails to clear protein aggregates and damaged organelles conditioning the immune responses and neuroinflammation, as reported in prion diseases. Here, it was demonstrated that the neurotoxic prion peptide PrP106-126 activates NLRP3 in a murine microglial cell line, which in turn, promoted CAS-1-induced TIR-domain-containing adapter-inducing interferon-β cleavage. In this state, TIR-domain-containing adaptor-inducing interferon-β fails to activate autophagy (Lai et al., 2018). In line with this finding, the exacerbation of NLRP3 inflammasome activation has been reported in Parkin and PINK1 KO mice- and patients-derived microglia, where the abnormal NLRP3 signaling was also associated with downregulation of the negative regulator of NF-κB, A20 protein (Mouton-Liger et al., 2018). Indeed, the administration in PD-induced rat models of CAS-1 inhibitor, Ac-YVAD-CMK, or the Cyclosporine A derivate, NIM811, improved the number of dopaminergic neurons reducing the activation of NLRP3 inflammasome (Mao et al., 2017; Zhang et al., 2020a).

The deposition of misfolded Aβ is the pivotal cause of NLRP3 inflammasome activation in microglia in AD pathology. Aβ may bind ASC, released from inflammasome activation, exacerbating the formation of Aβ oligomers (Holbrook et al., 2021). Also, tau protein oligomers contribute to NLRP3 inflammasome in human microglial cells (Panda et al., 2021). Microglia with elevated expression of IL-1β have been detected surrounding Aβ plaques in AD patients (Simard et al., 2006). Besides microglia also peripheral blood mononuclear cells isolated from AD patients presented higher expression levels of NLRP3 inflammasome members, such as NLRP3, ASC, CAS-1, and the cytokines IL-1β and IL-18, indicating that also the peripheral NLRP3-signal is increased in AD (Saresella et al., 2016). Similar findings were observed in both peripheral blood mononuclear cells and CSF of MS patients, in which high levels of IL-1β and IL-18 have been reported, indicating a sustained NLRP3-activating signal (Inoue and Shinohara, 2013). The expression of gain-of-function variants of NLRP3 (Q705K) and IL-1β (-511C>T) correlated with severity and progression of MS, indicating that a sustained activation of the inflammasome is associated with a bad prognosis of MS (Soares et al., 2019). Indeed, CAS-1 and ASC have been suggested as biomarkers for MS onset, since elevated expression of CAS-1 has been found at demyelinating lesions levels (Keane et al., 2018; Voet et al., 2018). However, the cognitive impairments and the neuropathology ameliorated when inflammasome was inhibited, as demonstrated by administration of MCC950 or by CAS-1 inhibitor, VX-765, that improved the cognitive function and neuroinflammation in AD mouse models, limiting the deposition of Aβ plaques and favoring their clearance (Dempsey et al., 2017; Flores et al., 2018). The pharmacological inhibition of NLRP3 has shown good results also in EAE and stroke mice models. Indeed, by suppressing the inflammasome activation the severity of the pathologies was attenuated and the clinical outcomes ameliorated (Coll et al., 2015; Ismael et al., 2018). To date, only very few compounds targeting NLRP3 or CAS-1 have entered clinical trials. RP-1127, an NLRP3 inflammasome inhibitor (Lamkanfi et al., 2009) has been tested in a clinical trial for stroke (EudraCT 2017-004854-41) and traumatic brain injury (ClinicalTrials.gov: NCT01454154), after positively evaluated pilot studies (Sheth et al., 2014a, b).

NLRP3 is not the only inflammasome to be associated with mitochondria, continuous findings indicate that NLRC4 (NLR family CARD Domain Containing 4), AIM2 (Interferon-inducible protein AIM2), and NLRP1 (NLR Family Pyrin Domain Containing 1) are also linked to mitochondrial dysfunction and appear to play a key role in neuronal diseases. High expression levels of NLRC4 and AIM2 have been observed in neuronal tissue of sporadic AD patients and mutant SOD1 transgenic animals, respectively (Liu and Chan, 2014; Johann et al., 2015; Gugliandolo et al., 2018). Elevated levels of NLRP1 have been found in traumatic patients with brain injury and in mice with spinal cord injury (de Rivero Vaccari et al., 2008; Adamczak et al., 2012; Wallisch et al., 2017). NLRP1 was significantly increased in the brain of AD patients, its genetic variants are associated with the risk of AD, when genetically modulated in an AD mouse model the cognitive impairments and the neuronal pyroptosis were attenuated (Pontillo et al., 2012; Tan et al., 2014; Kaushal et al., 2015).

In contraposition to inflammasomes, the mitochondria-located innate immune sensor NLRX1 inhibits different pro-inflammatory pathways, such as the NF-κB signaling, to control the microglial activation and the generation of neurotoxic astrocytes, thus preventing the neuroinflammation and the death of neurons and oligodendrocytes (Xia et al., 2011; Imbeault et al., 2014; Killackey et al., 2019). NLRX1 mediated the protection against EAE in a murine model of MS, repressing the inflammation induced by macrophages and microglia (Eitas et al., 2014). The protective role of this NLR receptor in the progression of the disease is supported by the several mutations identified in MS patients, which correlate with an exacerbated clinical outcome (Chen et al., 2021).

The compartmentalization response of neuroinflammation associated with mitochondria is thus mainly correlated to the release of mtDAMPs and by inflammasomes activation in the innate immune brain cells, where the high levels of inflammatory cytokines secreted condition the cell survivor of resident cells (Heneka et al., 2018). The quantity of cytokines released from activated microglia increases about six times more in the AD brain, and a similar secretion has been quantified also in other ND (Griffin et al., 1989; Hunot et al., 1999). However, in brain cells, the expression of receptors for IL-1β and IL-18 is highly related to the cognitive, learning, and memory processes. This suggests that a fine regulation is necessary as the therapeutic target (Tsai, 2017). Treatments with IL-1β neutralizing antibodies or with IL-1 receptor antagonists, such as anakinra, improved the cognitive and motor outcomes in traumatic brain injury and the ALS mouse model (Clausen et al., 2009; Bertani et al., 2017). Surprisingly, anakinra did not show improvements in human ALS patients and the deletion of IL-18 did not protect the AD mice from neuropathy but developed a lethal seizure disorder that was reversed only by anticonvulsants, to confirm the complexity of the physiopathology associated with neuroinflammation (Maier et al., 2015; Tzeng et al., 2018).

The Role of Apoptosis in Neuronal Disorders

Programmed cell death describes a series of different genetically encoded mechanisms that are responsible for the target and destruction of irreversibly damaged cells. These cellular processes are fundamental to human tissue development and are critical for the correct maintenance of organismal homeostasis. Historically, and accordingly, to the macroscopic morphological alterations, programmed cell death was classified into three isoforms: type I cell death or apoptosis, type II cell death or autophagy, and type III cell death or necrosis (Galluzzi et al., 2007). To date, this nomenclature has been extended and there are at least 20 distinct cell death types (Galluzzi et al., 2018). Nevertheless, apoptosis remains the most studied and relevant cell death for both physiological and pathological conditions. In the following sections, we will give a general overview of the apoptotic process and describe its involvement in NDs.

A brief overview of the apoptotic process

Mitochondria have a recognized role in regulating cell apoptosis being the leading actors of the apoptotic intrinsic cascade (Galluzzi et al., 2016; Patergnani et al., 2020b). The loss of membrane integrity induces the release of IMS-resident pro-apoptotic factors into the cytosol, such as the second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low pI (Smac/DIABLO) and cyt-c (Rasola and Bernardi, 2011; Giorgi et al., 2012). Once in the cytosol, cyt-c interacting with CAS-9 and the cofactor apoptosis protease-activating factor (APAF) forms the "apoptosome" that in turn activates the effector caspases, triggering the apoptotic machinery (Bonora et al., 2014a). In this context, Ca^{2+} has a pivotal role. Within the cell, the average Ca^{2+} concentration is very low. However, a series of so-called intracellular Ca^{2+} stores, including ER, present high concentrations of Ca^{2+}. It has been demonstrated that following ER stress, oxidative damage, and/or chemotherapy promote a massive Ca^{2+}-release from the ER into the cytoplasm that is sufficient to activate a class of cysteine proteases (calpains), which can trigger the caspase activation. In addition, the close juxtaposition between ER and mitochondria potentiates the Ca^{2+}-transfer from ER to the mitochondrial matrix to promote mitochondrial permeability transition, mitochondrial swelling, thereby activating the apoptotic cascade (Giorgi et al., 2018).

Apoptosis and neurodegeneration

Apoptosis is a key process for the normal development of the brain and the spinal cord as well as it is crucial for the construction of an efficient neuronal network. The main components of the apoptotic machinery have been found to be crucial for the regulation of neuronal cell death. $APAF1^{-/-}$ mice die before birth, due to impaired apoptosis, as demonstrated by the presence of enlarged brains (Cecconi et al., 1998). Downregulation of the anti-apoptotic gene BCL-XL results to be lethal during gestation (Los et al., 2002). The analysis of embryos revealed excessive apoptotic levels in immature neurons of the spinal cord, brain, and dorsal root ganglia. In line with this, BAX deficiency provokes excessive neurogenesis and consequent formation of medulloblastoma (Garcia et al., 2015). Meanwhile, these findings highlight the importance of apoptosis during neural developments, several other studies demonstrate that excessive apoptosis has the main role in neurodegeneration, due to the massive presence of mitochondrial dysfunction among the cells of the nervous system (**Figure 3**). The characteristics of motor symptoms, occurring in PD, mainly come from dopamine depletion caused by degeneration of the dopaminergic neurons in substantia nigra pars compacta. Apoptosis has been implicated as the predominant mechanism of neuronal death in PD, as indicated by postmortem studies in dopaminergic neurons of PD patients (Hartmann et al., 2000; Mogi et al., 2000; Tatton, 2000). Apoptosome formation occurs in the substantia nigra and locus ceruleus in PD brains (Kawamoto et al., 2014). Among pro-apoptotic proteins involved in PD, in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model, BAX has been shown to exert a pivotal role in substantia

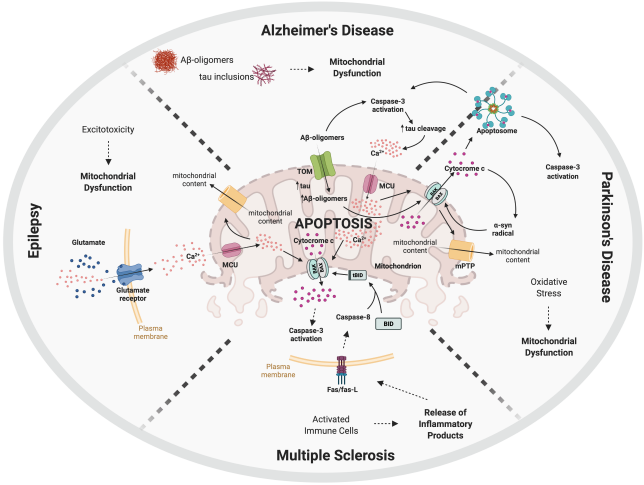

Figure 3 | **Schematic representation of the involvement of apoptosis in neurological disorders.**

Neurological disorders including Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and epilepsy are characterized by a common feature the apoptosis. In all these diseases, intrinsic apoptosis ultimately leads to cell death by the release of mitochondrial content to the cytoplasm involving BAK/BAX and mitochondrial permeability transition pore (mPTP). These events promote the release of Cytochrome c and the formation of apoptosome inducing the activation of cell death effectors like Caspase-3. Events leading to cell death vary among the different pathologies. In AD, the apoptotic pathway is linked to the mitochondrial accumulation of Aβ-oligomers and tau inclusions which leads to mitochondrial dysfunction allowing the activation of the cell death pathway. In PD, the increase of oxidative stress induces the formation of α-synuclein (α-syn) radical promoting the release of cytochrome C and triggering mitochondria-mediated apoptosis. In MS, activated immune cells, through the release of inflammatory products, promote the activation of caspase-8 which in turn promotes the truncation of BID into t-BID. t-BID represents the point of connection between extrinsic and intrinsic pathways promoting BAK/BAX pore formation and ultimately Caspase-3 activation. In epilepsy, the apoptotic pathway is induced by the excessive stimulation of glutamate receptors. This event results in mitochondrial Ca^{2+}-overload and ultimately apoptotic neuronal cell death. The involvement of apoptosis in neurological disorders is widely described in the main text. Aβ: Amyloid-beta; BAK: B-cell lymphoma 2 (BCL2)-like protein 4; BAX: B-cell lymphoma 2 (BCL2) associated X, apoptosis regulator; BCL2: B-cell lymphoma 2; Ca^{2+}: calcium; FAS: fas cell surface death receptor; FAS-L: ligand of fas cell surface death receptor; MCU: mitochondrial Ca^{2+} uniporter; mPTP: mitochondrial permeability transition pore; tBID: truncated BH3-interacting domain death agonist; TOM: translocons of the outer membrane; α-syn: alpha-synuclein. Created with BioRender.com.

nigra pars compacta dopaminergic neuronal death, likely by acting in injured neurons before the onset of irreversible cell death events (Vila et al., 2001). At the demonstration, MPTP injection increases the expression of BAX and decreases the BAX-BCL2 ratio, thereby provoking apoptotic neuronal death. In line with this, BAX-deficient mice are resistant to MPTP-induced neuronal death (Vila et al., 2001). Furthermore, pre-administration of BAX-inhibiting peptides decreased the loss of the nigral dopaminergic neurons in the 6-hydroxydopamine-induced PD rat model and targeting BAX, by the microRNA-216a, inhibited neuronal apoptosis in a cellular PD model (Ma et al., 2016; Yang et al., 2020). Interestingly, the α-syn accumulation and cyt-c could develop a deleterious loop in the surviving dopaminergic neurons. Cyt-c contributed to α-syn radical formation and oligomerization as demonstrated in a pesticide-induced model of PD (Kumar et al., 2016). Indeed, co-exposure to pesticides, such as maneb and paraquat, induced the release of cyt-c into the cytosol. Here, cyt-c co-localizes with α-syn to induce its oligomerization and the protein radical formation in the midbrain of mice treated with maneb and paraquat (Kumar et al., 2016). Furthermore, it has been shown that α-syn localizes on the mitochondrial surface, where induces oxidative stress causing the release of cyt-c triggering mitochondria-mediated apoptosis (**Figure 3**) (Parihar et al., 2008). Therapeutic strategies focused on targeting antioxidant and apoptotic pathways are gaining increasing importance in PD. For example, in the PD model 6-OHDA-induced apoptosis, the addition of the flavone tricetin provided neuroprotection by down-regulating BAX, up-regulating the anti-apoptotic protein BCL2, mitigating mitochondrial membrane potential loss, and protecting cells from mitochondria-dependent apoptotic pathway (Ren et al., 2019). In a PD rat model, administration of glial cell line-derived neurotrophic factor protected against neural apoptosis by inducing AKT and glycogen synthase kinase 3 beta phosphorylation. Consistently, when selective AKT inhibitors (LY294002 and triciribine) were used, the protective effect of glial cell line-derived neurotrophic factor was abolished (Yue et al., 2017). Noteworthy, in rotenone-induced rat models of PD, α-bisabolol, a dietary bioactive phytochemical has been found to attenuate dopaminergic neurodegeneration also by increasing the BAX/BCL2 protein expression levels and reducing the expression of cleaved CAS-3 and -9 in the striatum (Javed et al., 2020). Likewise, piperlongumine, an alkaloid isolated from the long pepper *Piper longum*, exerts an anti-apoptotic role by increasing BCL2 phosphorylation, thus stabilizing the BAX/BCL2 heterodimer and consequently inhibiting apoptosis (Liu et al., 2018). Like in PD, in AD the Aβ oligomers and tau inclusions have been considered to have a pivotal role in the pathogenesis of the disease, leading to neuronal loss, the major cause of neurodegeneration (DeTure and Dickson, 2019). Mitochondrial accumulation of Aβ and tau likely contributes to mitochondrial dysfunction in AD, and it is strictly connected to the mitochondrial apoptosis pathway (**Figure 3**). Indeed, AD patients' brains are characterized by excessive oxidative stress, which is sufficient to activate MAPK family members, in particular p38 kinase. Once activated, p38 kinase induces BAX phosphorylation and its translocation to mitochondria where promotes the apoptotic process (Henderson et al., 2017).

Furthermore, the intrinsic apoptotic pathway activation has been reported to play the main role in Aβ-42-induced apoptosis (Islam et al., 2017). In this case, Aβ-42 enters the cells by forming a channel-like structure on the cell surface. Here, it provokes mitochondrial damage with consequent cyt-c release and activation of the apoptotic process. Interestingly, Aβ-42 was not able to induce apoptotic cells throughout the activation of the death-inducing signaling complex. It is well established that CAS-3 functionally links Aβ deposition and neurofibrillary tangles in AD. Particularly, both the extracellular Aβ deposits and the intracellular Aβ have been reported to activate caspases, and tau protein CAS-3-mediated cleavage has been reported to play an important role in both tau aggregation and disease (Glabe, 2001; Gamblin et al., 2003). The cognitive decline has been also correlated with increased levels of caspase activity and tau truncated by CAS-3 in the forebrain of aged mice. In addition, *in vitro* experiments in human neuroblastoma cells demonstrated that the tau cleavage is dependent on CAS-3 (Means et al., 2016). Coherently, the inhibition of caspases prevented the proteolytic cleavage of tau and the associated formation of neurofibrillary tangles involving the apoptosis pathway in both AD neuronal cell death and cognitive impairment (Means et al., 2016). Besides, the role in bioenergetics control and ROS production, mitochondria are important players in intracellular Ca^{2+} homeostasis (Marchi et al., 2018). Excessive Ca^{2+}-uptake into mitochondria leads to the mitochondrial Ca^{2+}-overload resulting in the opening of mitochondrial permeability transition pore with induction of the apoptosis (Bonora et al., 2017) and neuronal death (Kalani et al., 2018). *In vitro* studies reported that Aβ oligomers induce Ca^{2+} transfer to mitochondria from ER and cytosol (Calvo-Rodriguez et al., 2016). In line with the *in vitro* experiments, it has been reported that increased mitochondrial Ca^{2+} levels were associated with plaque deposition and neuronal death in a transgenic mouse model of cerebral β-amyloidosis. Consistently, Ru360 a selective blocker of mitochondrial Ca^{2+} uniporter reduced the neuronal Aβ-accumulation, indicating that mitochondrial Ca^{2+}uniporter is required for Aβ-driven mitochondrial Ca^{2+}-uptake (Calvo-Rodriguez et al., 2020). Very recently, it has been also reported an important role of both exogenous and endogenous tau in intracellular Ca^{2+} homeostasis. Particularly, tau inhibits mitochondrial Ca^{2+} efflux by blocking the activity of the mitochondrial Na^{+}/Ca^{2+} exchanger in primary cortical co-cultures of neurons and astrocytes. This provokes depolarization of mitochondria and makes neurons vulnerable to Ca^{2+}-overload-induced apoptotic cell death (Britti et al., 2020). Interestingly, similar events were also found in human iPSC-derived neurons bearing a mutation in the gene encoding tau, the microtubule-associated protein tau (Britti et al., 2020). MS is a debilitating disease characterized by inflammation, loss of myelin sheath that causes axonal degeneration, which makes axons vulnerable to a variety of insults and where the oligodendrocytes are the main targets (Lublin et al., 2014; Patergnani et al., 2017) (Ghasemi et al., 2017). The apoptosis of oligodendrocytes has a critical role in the pathogenesis of MS; indeed, caspase-mediated death of oligodendrocytes is crucial for demyelination (Caprariello et al., 2012). One of the principal apoptotic pathways involved in the regulation of immune response is the fas cell surface death receptor (FAS)/FAS ligand system (Volpe et al., 2016). This pathway leads to the activation of CAS-8, which truncates the BH3 (BCL2 homology 3)-only protein BID (BH3-interacting domain death agonist) into truncated (t)BID (**Figure 3**). Following the translocation of tBID to mitochondria, this proapoptotic protein induces oligomerization of BAK, thus promoting cyt-c release and mitochondrial apoptotic pathway (Korsmeyer et al., 2000). Recently, it has been found that GSTA4 restricts apoptosis of oligodendrocytes via modulation of the mitochondria-associated FAS-CAS-8-BID-axis. Importantly, it has been reported that GSTA4 can promote remyelination and improve clinical symptoms of MS-like disease in rodents, opening a new perspective for future reparative MS therapies (Carlstrom et al., 2020). Further, it has been demonstrated that another way to control brain apoptosis is through metformin administration. Indeed, metformin reduces the motor impairment in the CPZ-demyelinating mouse model, improves the amounts of myelinating oligodendrocyte and the ADP/ATP ratio, by regulating the AMPK/MTOR pathway. Furthermore, metformin reduces oxidative stress and improves antioxidant defense. This results in a downregulation of the mitochondrial cascade of apoptosis, as demonstrated by a decreased BAX/BCL2 ratio and CAS-3 activation (Sanadgol et al., 2020). Again, matrine, a tetracyclic quinolizine alkaloid derived from the herb radix sophorae flavescentis, has been shown to ameliorate clinical signs in the MS animal models reducing the expression of CAS-3 and cyt-c (Wang et al., 2019b). Thus, targeting the apoptotic process might serve as a therapeutic strategy for improving MS therapy.

Epilepsy is another neurological disorder, which stands out for apoptosis-induced cell death. Seizure episodes are the main features of this neurological disorder characterized by transient and recurrent symptoms due to abnormal and simultaneous neuronal activity of a neuronal cell population in the brain (Brodie et al., 2018). The excessive stimulation of glutamate receptors results in neurotoxicity, leading to mitochondrial Ca^{2+}-overload, in a process denominated excitotoxicity, which leads ultimately to apoptotic neuronal

cell death (**Figure 3**) (Henshall, 2007). Several studies emphasize the role of apoptosis in seizures-induced cell death increased levels of apoptotic markers were observed in epileptic patients. In this group, it was observed augmented levels of CAS-3 and a direct correlation with pro-inflammatory elements, such as IL-1β, IL-6, and CAS-1 (Kegler et al., 2020). In a rat model of kainic acid (KA) induced-epilepsy, after 48 hours of epileptic seizure onset, the number of apoptotic cells in the neocortex increased (Li et al., 2018a). It has been demonstrated that KA-induced epilepsy determines the release of APAF1 into the cytosol to activate the apoptotic cascade via CAS-9 (Henshall, 2007). Furthermore, in the same model, an important role was also accounted for BAD and BAX. Following seizure-induced brain injury, BAD displaces the existing interaction between the anti-apoptotic protein BCL-XL and the pro-apoptotic BAX, which the last one translocates to the mitochondria to promote cyt-c release and activation of the apoptotic cascade (Henshall et al., 2001, 2002). In line with this, sodium valproate treatment significantly reduced neuronal apoptosis, in a KA-induced rat model, by reducing CAS-3 activity and BAX expression and increasing BCL2 levels (Li et al., 2018b). Valepotriate, isolated from *Valeriana jatamansi*, revealed anti-epileptic effects, in addition to increasing the expression of GABAA, allowing to increased BCL2 and reduced CAS-3 expression levels (Wu et al., 2017). Similarly, vitamin D exhibited neuroprotective effects in hippocampal neurons by reducing BAX and CAS-3 levels in KA- and pentylenetetrazol-induced seizures in rats (Sahin et al., 2019).

Conclusions

Disruption of mitochondrial homeostasis and subsequent mitochondrial dysfunction plays a key role in the pathophysiology of ND. Numerous quality control mechanisms coexist within mitochondria of neural cells to detect and repair defects affecting mitochondrial status and functioning before the point of inescapable cell death is reached. Despite distinct clinical and pathological features, all ND are characterized by alterations of most of these lines of defense and present common harmful cellular events, in particular (i) presence of misfolded and/or aggregated proteins; (ii) anomalies in mitochondrial dynamics; (iii) impairment of autophagy; (iv) mitochondria-driven neuroinflammation; and (v) aberrant apoptosis. Targeting these mitochondria-related processes remains in part complicated, they could be used as a therapeutic target but more needs to be done. To date, we still do not completely understand the exact contribution of the mitochondrial compartment during the forming of misfolded protein aggregates: do they represent the cause or the consequence of these uncontrolled accumulations? Similarly, mitochondrial abnormalities are widely described in the brains of ND-affected persons. However, it is difficult to obtain live monitoring of the mitochondrial dynamics during the progression of the disease.

Several compounds have been described to improve or reduce their activity, but they possess a wide spectrum of side effects. Finally, UPR^{mt} and mito-inflammation represent a relative "young-discovered" mechanism that must be explored in all its facets in the ND context. Further elucidations of ND molecular mechanism, advances in technologies for rapid and constant monitoring of the mitochondrial impairment, major progresses in translating findings from cellular and animal models to humans, and development of specific compounds able to deactivate the mitochondrial imbalances will be a fundamental support to improve the quality of life of people affected by ND.

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