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

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 (Ca2+) 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 imported, in an unfolded state, into the organelle through the translocons of the outer and inner membrane complexes, respectively (Maì et al., 2017). Given the crucial role of mitochondria in regulating several cellular processes, the efficient function is fundamental also in the nervous systems. Hence, it is not surprising that the accumulation of mitochondrial dysfunctions 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 (UPRmt): a mitochondria-nucleus transcriptional program, triggered by proteotoxic stress, which promotes mitochondrial protein biogenesis, metabolic adaptations, and ROS detoxification to lead survival and mitochondrial network recovery. (4) Mito-inflammation: the mitochondria-mediated inflammatory response, 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, when exaggerated or abnormal activation may exacerbate the mitochondrial stress leading to deleterious consequences (the evil represented by Mr. Hyde).

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

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Table 1

| Condition | Description |
|-----------|-------------|
| Alzheimer’s disease | Pathological hallmark of cognitive decline and memory loss |
| Mitochondrial dysregulation | Imperfections in the normal function of mitochondria |
| Apoptosis | Programmed cell death |
| Mitophagy | Selective autophagy of mitochondrial debris |
| Mito-inflammation | Mitochondria-induced inflammatory response |

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...
Mitochondrial fusion and fission are regulated by a plethora of proteins, the majority belonging to the family of dynamin-related GTPases (Zhang et al., 2021). The main protein involved in the mtDNA-mitochondrial network 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, pre-translational modifications occur to DRP-1 for its mitochondrial recruitment, where it induces scissors upon GTP hydrolysis by constriction of OMM (Korlait et al., 2013).

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Mitochondria dynamics

Mitochondria are the primary energy source of the cell and are involved in numerous cellular processes, including the synthesis of ATP, the production of reactive oxygen species (ROS), and the regulation of calcium (Ca) levels. The balance between mitochondrial fusion and fission is crucial for maintaining the integrity and function of mitochondria. Mitochondrial fusion involves the coalescence of two mitochondrial membranes, whereas mitochondrial fission involves the division of a single mitochondrial membrane into two daughter membranes.

Mitochondrial fusion is mediated by the mitofusin-2 (MFN2) and the tetraspanin-2 (TSP2) proteins, which interact with the outer mitochondrial membrane (OMM) to facilitate the docking and fusion of the inner mitochondrial membrane (IMM). Mitochondrial fission is mediated by the dynamin-related protein-1 (DRP1), which forms a helical bundle on the IMM, inducing the formation of fission sites and promoting mitochondrial division.

The mitochondrial fusion-fission balance is crucial for the maintenance of mitochondrial morphology and function. Disruption of this balance can lead to mitochondrial dysfunction, which is associated with various diseases, including neurodegenerative disorders.

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 and close OMA1 turnover |
| | GSH | Modifies disulfide bonds of MFNs |
| | PTEN-Parkin | Regulator of mitochondrial morphology |
| | TIM23/TOM complex | Regulates PINK1 translocation in mitochondria |
| | MFN | Mitochondrial target of Parkin |
| | LC3, NDP52, optineurin | Mitophagy receptors |
| | TAX1BP1 and p62 | Mitophagy receptors |
| | OMA1 | Import PINK1 into mitochondria independently from TIM23/TOM |
| | FUNDC1, CL, NLRX1 and NIX/BP3L | Regulate the PINK1-Parkin independent process |
| | AMPK | Positive regulator of autophagy and mitochondrial metabolism |
| Mitochondrial unfolded protein response (UPRmt) | Ub1-5, dve-1 and atf-1 | Regulate the UPRmt in C. elegans |
| | ATF5, CHOP and ATF4 | Main regulators of the UPRmt in mammal |
| | eiF2 | Regulatores of the mammalian integrated stress response |
| | CLPP, HSPG, and YME1L | UPRmt in marker genes |
| Mitofusin-2-associates with the recruitment of the fission factor, and mitochondrial fission 1 that mediate the binding (Loson et al., 2013). Upon cellular stimulation, pre-translational modifications occur to DRP-1 for its mitochondrial recruitment, where it induces scissors upon GTP hydrolysis by constriction of OMM (Korlait et al., 2013).

Fusion of mitochondria consists of two steps, where firstly OMM and after (MID49 and MID51) that mediate the binding (Loson et al., 2013). Upon cellular stimulation, pre-translational modifications occur to DRP-1 for its mitochondrial recruitment, where it induces scissors upon GTP hydrolysis by constriction of OMM (Korlait et al., 2013).

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L-OPA1 is currently considered a critical component of the whole protein expression pattern in neurodegeneration as it ensures, through different molecular pathways, cysteine morphology, ATP production, and a correct function of electron transport chain during neuronal stress (Quintana-Cabrera et al., 2016). To its unexpected, the primary prohibitin (PHB), which acts as a scaffold at the IMM (Kasashima et al., 2008), and a balanced function of the peptideptides metalloendopeptidase (OMA1) and ATP-dependent zinc metalloendopeptidase (ZMP), which process OMA1, 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 rate of processing of the IMM, promotes oxidative stress from neuroinflammation and apoptosis (Korwitz et al., 2016). Interestingly, this OPA1 processing mediated by PHB and OMA1 in neurons can also be modulated by the mitochondrial phospholipid cardiolipin (CL). Indeed, it has been demonstrated that the presence of a mitochondrial Complex 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). Syndrome 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 neuronal protective network. Experiments showed that an OPA1 mutation carrying the recurrent OPA1 mutation (present in approximately 30% of all dominant optic atrophy patients) confirmed this possibility. OPA1 mutation leads to progressive visual failure and loss of locomotor behavior, indicating a role of mitochondrial dysfunction in the disease. As with OPA1 mutation, the OPA1 mutation-dependent mitochondrial dysfunction was accompanied by an increase in autophagy, mitophagy, and mitochondrial proliferation (Sarri et al., 2012). This excessive mitochondrial turnover may alter the ultrastructure of mitochondria and provoke myoneuronal weakness. Preserving an optimal mitochondrial network is also fundamental for cellular metabolism. Profound metabolic signatures have been unveiled in mice with OPA1 mutation since they display alterations in the content of mitochondria phospholipids, amino acids, and nucleotides (Chao de la Barca et al., 2017). In line with this, OPA1 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 (Vantini et al., 2021), confirming the relevant role of the mitochondrial network for the brain. The neural stem cells activated SIMH to completely suppress the exposure to nicotine, which in turn induced mitochondrial 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 and the development of a cellular aging (Zhang et al., 2019). The SIMH pathway may 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) knockout mice (Wang et al., 2021). Mitophagy is a cell-protective process that eliminates affected or non-functional proteins and controls cell fate. Autophagy exists in diverse forms that are specialized to clear organelles and specific protein aggregates or complexes. One of the main targets of this process is to rid the cell of misfolded or aggregation-prone proteins. NF-kB is a transcription factor that regulates the cell fate, controlling cellular metabolism and influencing the inflammatory response in several pathological conditions (Patergnani et al., 2021c). Although NF-kB is continuously kept at low expression levels, thanks to a high-regulated stability controlled by IkBα and NF-kB; and by the transforming growth factor-β-activated kinase 1, that phosphorylates the NF-κB inhibitor, alpha (IκBα), 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 there are three essential components in the induction of the increased 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 issue, 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., 2016). 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 genotoxic insults), and limits disease progression. Autophagy controls cell fate. Autophagy exists in diverse forms that are specialized to sequester and degrade specific intracellular material. Proteinophagy identifies the involvement of autophagy in the degradation of altered proteins; lipophagy points to the degradation and removal of lipids and organelles; mitophagy is a result of bacteria or virus infection, xenophagy is activated. In addition to these specialized forms of autophagy, selective forms of autophagy targeting parts of the organelle, 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 mitochondria, ensuring the homeostasis of the cell (Giacca 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 stability controlled by IkBα and then degraded or recycled through the lysosomes (Klionsky et al., 2016). 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, promoting ubiquitination of mitochondrial 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 (NPC2), 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 Pallikaras, 2020). Undoubtedly, PD is widely characterized by mutations in the mitophagy regulators Parkin and PINK1 (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 described, and the loss of functionality 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; Vowels et al., 2000; Riederer 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., 2010; Geisler et al., 2011). However, it has been suggested that recruitment of Parkin on the mitochondrial surface may occur even in presence of PINK1 mutations. Indeed, suppression of the protease OMA1 (that can import PARK1 into mitochonndria for its degradation) or deficiency frictions of TIM23/TOM activity and state of mitochondria) restores the mitochondrial accumulation of parkin even in presence of PD-Related PINK1 mutations (Sekeine et al., 2019). It also exists mitophagy molecular mechanisms that are PINK1 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 its phosphorylation of the autophagy-related gene 4 (ATG4) and 16, can mediate important functions regulating mitophagy. Moreover, the expression of FUNDC1 increases with age in Caenorhabditis elegans (Ye et al., 2015). This determines the accumulation of damaged mitochondria, increased ROS production and activated ATG production and it can react as 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, locomotor deficiencies, and to die early in neurodegeneration (Leuck et al., 2017). Surprisingly, mice with PINK1 and Parkin deletion did not have evident PD-phenotypes. Indeed, Parkin-deficient mice did not exhibit profound deficiencies in neurological function, learning, memory and the substantia nigra pars compacta dopaminergic neurons (Hastings and Bredt, 2005). However, an 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 mild loss of locomotor activity and impaired memory, after increasing activity following exhaustive exercise, which severely stressed mitochondria (Kelm-Nelson et al., 2018; Sliter et al., 2018). Despite this, the levels of pro-inflammatory cytokines and serum level of the DNA damage biomarker, in resting and exercised mice 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 mitophagy 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 PINK1 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 (a-syn), and tau, which form aggregates of filamentous tubular filaments and of APOE and hypoxia-hypometabolic, responsible for intracellular and extracellular neurofibrillary tangles, respectively. In recent years, several reports suggest that mitophagy regulates the turnover of 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).

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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 autopsy and mitophagy markers in the same treatment settings 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 this regard, further research is needed to investigate critical points in 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 blood 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 and/or fusion of mitophagy) permitted the recovery of motor function. Finally, we uncovered that apart from mitophagy, also the selective ferritin-autophagy, mediated by the nuclear receptor coactivator 4, was responsible to clear the damaged mitochondrias reported in the model 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 hippocampus and sensory lobe cortices of refired 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., 2019). It has been proved that one of the main actors of this process is the UPR

Oxidative and proteostatic stresses play a key role in the activation of UPR

Differently from other mitochondrial stress responses, the role of UPR

The emerging role of UPR

Protective or detrimental? The role of mitophagy in neuronal disease is controversial; its cytoprotective effect is questioned by the persistence of UPR

The Role of Mitochondrial Unfolded Protein Response (UPR

UPR

UPR

The mechanisms and functions of UPR

AB deposits in the brain are also present in mitochondria of AD mice and patients (Koistinaho et al., 2017; Ochs et al., 2012). A previous study has shown that UPR

Nuclear factor erythroid 2-related factor 1 (Nrf2) and its downstream effector proteins, such as Hsp27 and Hsp60, are considered protective against oxidative stress, promoting mitochondrial biogenesis and enhancing antioxidant defenses, in order to reduce oxidative stress (Feng et al., 2018). Nrf2-dependent mitochondrial biogenesis and the Nrf2-heme oxygenase 1 (HO-1) pathway play a protective role against cerebral ischemia-reperfusion injury (Qing et al., 2019). However, the precise role of UPR

To date, independent and parallel pathways are linked to UPR

To sum up, mitophagy is not only a secondary mechanism that exacerbates the progression of pathology, becoming a novel potential therapeutic target against MS, but also a key stress response that regulates the fate of damaged mitochondria in multiple neurological diseases.
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 a complex mitochondrial damage-associated condition 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 NLRP3 inflammasome (Rimessi et al., 2015; Zhong et al., 2018). Mitochondrial damage (Orr et al., 2008; Yano et al., 2014). AFFS accumulation has occurred 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 immune cells, although with a variable anti- or pro-inflammatory, depending on the context (Todkar et al., 2021). Encapsulated mitochondria-derived constituents released from microglia, in the end, may contribute to disease progression 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 (Torrabia et al., 2018).

In the post-mortem brain of PD patients, the deficit of complex I observed in platelets and fibroblasts represents the principal cause of mitochondrial ROS production, responsible for oxidative damages, even at the mtDNA level (Kohino et al., 1992; Haas et al., 1995; Keeney 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 (Walke et al., 2014). The level of circulating mtDNA is thus a potential biomarker for early-stage of PD and ALS (Torralba et al., 2018). These observations strongly support the hypothesis that mtDNA modifications are 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 phosphatidylserine and 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 Am 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 Ca2+ or oxidative phosphorylation impairment, activate the NF–κB pathways, first signal (priming) of inflammasome activation. This results in the transcriptional upregulation of inflammasome molecules and cytokines, such as NLR family pyrin domain containing 3 (NLPR3) and interleukin 1β (IL-1β) (Figure 2). NLRP3 inflammasome (Rimessi et al., 2015; Zhong et al., 2018). Perturbations in mitochondrial Ca2+ signaling contribute to boosting the production of mitochondrial ROS with important repercussions on the inflammatory status (Rimessi et al., 2015). This may happen directly, by activating mitochondrial enzymes, such as NADH dehydrogenase subunit 1 and glycerol 3-phosphate dehydrogenase (Murphy, 2009; Gorlach et al., 2015), or indirectly, mediating the Ca2+-dependent activation of nitric oxide synthase, which blocks the mitochondrial complex IV via nitric oxide and through the Ca2+-dependent mitochondrial membrane depolarization via reverse electron transport (Biasut et al., 2016).

The mitochondrial ROS is also involved in NLPR3 inflammasome activation in SOD1mutant mice-derived microglia, where the protein aggregates have an essential role to induce mitochondrial dysfunction in ALS (Deora et al., 2020). NLPR3 is an emerging pattern recognition receptor, a key player in neuroinflammation, activated by mitochondrial ROS, mtDNA, cardiolipin, and Ca2+ in a two-step process (Figure 2). It accumulates to mitochondria where oligomerizes with apoptosis-associated speck-like protein containing a CARD (ASC) 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 required for NLRP3 inflammasome activation (Figure 2). Interestingly, inflammasome activation and mitochondrial damage were abolished when the mitochondrial compartment was stabilized with the inhibition of mitochondrial membrane permeability transition, thereby suggesting a close relationship between inflammasome recruitment and mitochondria activities. This was confirmed since the authors not only demonstrated that NLPR3 can bind CL, but they also provided evidence that an inhibitor required for NLPR3 activation and its pro-inflammatory content (Neuspiel 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 progression of PD and motor impairment (Herrmann et al., 2018; Fan et al., 2020). The recruitment of inflammasomes 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 activate the NLRP3 inflammasome in human monocytes and stimulate microglial cells. While the functional activation of NLRP3 inflammasomes in microglial cells remains controversial (Gusti 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 (MPTP), which via mitochondrial impairment 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 pregnant mice. Here, it was demonstrated that the neurotoxic prion peptide PyP105-126 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 adapter-inducing interferon-β fails to activate autophagy (Lai et al., 2015). In line with this finding, the expression 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 (Mouitch-Lignon et al., 2015). The administration of the PD-induced NLRP3 activator, the CAS-1 inhibitor, Ac-YVAD-CMK, or the Cyclosporine A derivate, NIM811, improved the number of dopaminergic neurons reducing the activation of NLRP3 inflammasomes (Mao et al., 2017; Zhang et al., 2020a).

The deposition of misfolded αS is the pivotal cause of NLRP3 inflammasome activation in microglia in AD pathology. αS may bind Aβ deposits facilitating inflammasome activation. NLRP3 inflammasome activation has been observed in Parkinson and PINK1 KO mice and patients (Saresella et al., 2016). Besides microglia also peripheral blood mononuclear cells isolated from AD patients can detect higher expression levels of NLRP3 inflammasome members, such as NLRP3, ASC, CAS-1, and the NLR subfamily member, NLRX1. The expression of the peripheral NLRP3 inflammasome 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 activation in MS (Smard et al., 2006). Besides microglia also peripheral blood mononuclear cells isolated from AD patients can detect higher expression levels of NLRP3 inflammasome members, such as NLRP3, ASC, CAS-1, and the NLR subfamily member, NLRX1. The expression of the peripheral NLRP3 inflammasome is increased in AD (Saresella et al., 2016).

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 organ homeostasis. Historically, and accordingly, to the macroscopic morphological alterations in programmed cell death, this process was classified into cell death types: 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 discuss its involvement in NDs.

A brief overview of the apoptotic process

Mitochondrion have a recognized role in regulating cell apoptosis being the final effectors of the death of cells. The mitochondrial death signal is mediated by the mitofusins, complex I, II, and III, and the pro-apoptotic members of the Bcl-2 family (Paterniani 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 (Bax). Among them, the BAX has been shown to be crucial for the initiation of apoptosis in PD-induced rat models of MPTP (Keane et al., 2018; Voet et al., 2018). However, the cognitive impairments observed in PD mice models were not reversed upon deletion of BAX has been shown to exert a pivotal role in neurodegeneration. In line with this, the administration of the BAX deficiency provokes excessive neurogenesis and consequent formation of enlarged brains (Cecconi et al., 1998). Downregulation of the ant apoptotic gene BCL-XL results to be lethal during gestation (Los et al., 2002).

Mitochondria, that are the powerhouse of the cell, contain high concentrations of Ca^2+. Changes in the intracellular Ca^2+ concentrations of Ca^2+ stores, including ER, present high concentrations of Ca^2+. It has been demonstrated that following ER stress, oxidative stress, and chemotherapy, the mitochondrial permeability transition pore can open in response to the ER into the cytoplasm that is sufficient to activate a class of cysteine proteases (calpain), which can trigger the caspase activation. In addition, the close juxtaposition between ER and mitochondria potentiates the Ca^2+ transition from the mitochondrial to the ER, thus facilitating the mitochondrial permeability transition, mitochondrial swelling, thereby activating the apoptotic cascade (Giorgi 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 organ homeostasis. Historically, and accordingly, to the macroscopic morphological alterations in programmed cell death, this process was classified into cell death types: 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 discuss its involvement in NDs.
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 BAX/BAX and mitochondrial permeability transition pore (mPTP). These events promote the release of Cytochrome c and the formation of apoptosis-inducing factor (AIF) 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 tangles, 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 BID-t. t-BID represents the point of connection between extrinsic and intrinsic pathways promoting BAX/BAX pore formation and ultimately Caspase-3 activation. In epilepsy, the apoptotic pathway is induced by the excessive stimulation of glutamatergic 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; BAX: B-cell lymphoma 2 (BCL2)-like protein 4; BAX: B-cell lymphoma 2 (BCL2) associated 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; TM: translocans of the outer membrane; α-syn: alpha-synuclein. Created with BioRender.com

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

In addition, 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, as both are strictly connected to the mitochondrial calcium homeostasis (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, which facilitates the formation of the punctate Fas receptor with consequent FasL-receptor binding, FasL-receptor binding 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 neurofilaments (NFs) in AD. Particularly, both 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 (Globe, 2001; Gamblin et al., 2003). The cognitive decline has also been 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 Aβ cleavage is caspase-dependent (Henderson et al., 2020). Loss of myelinated axons, 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., 2013). Besides, the role of energy contraceptors controlling the mitochondrial homeostasis is pivotal for AD, as mitochondria are important players in intracellular Ca\(^{2+}\) homeostasis (Marchi et al., 2018). Excessive Ca\(^{2+}\)-uptake into mitochondria leads to the opening of mitochondrial permeability transition pores and the induction of mitochondrial DNA damage (Marchi 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 addition, the intracellular mitochondrial Ca\(^{2+}\) levels were increased in this protein induced with plaque deposition and neuronal death in a transgenic mouse model of cerebral amyloidosis. Consistently, Ru360, a selective blocker of mitochondrial Ca\(^{2+}\) uniporter, reduced the neuronal Aβ-accumulation and decreased the 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. Particular, tau inhibits mitochondrial Ca\(^{2+}\)-uniporter blocking the activity of the mitochondrial Na\(^{+}\)/Ca\(^{2+}\) exchanger in primary cultures of neurons and astrocytes. This provokes depolarization of mitochondria and makes neurons vulnerable to Ca\(^{2+}\)-overload-induced apoptosis and neuronal death (Britti et al., 2020). Interestingly, similar levels are 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 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 and demyelination, which is sufficient to activate MAPK family members, in particular p38 kinase. Indeed, p38 kinase induces BAX phosphorylation and its translocation to mitochondria where promotes the apoptotic process (Henderson et al., 2017). Thus, targeting the apoptotic pathway might serve as a therapeutic strategy for improving MS therapy.

Epilepsy is another neurological disorder, which stands out for apoptosis-inducing properties. The main feature of the disease 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 4-Hydroxyalk-2-enals are substrates for glutathione transferase. FEMS Lett 179:267-270.

References

Abrams AJ, Hufnagel RB, Rebelo A, Zanna C, Patel N, Gonzales MA, Campeanu IJ, Griffin LB, Abrams AJ, Hufnagel RB, Rebelo A, Zanna C, Patel N, Gonzales MA, Campeanu IJ, Griffin LB, Open peer reviewer: identical terms.

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Garcia-Lopez R., Benito-Escudero M., Fernandez-Martinez R., Cid-Fernandez A., Capilla-Diez J., de la Torre-Aragones J., Guzman-Marin F., et al. (2019) Mitochondrial dynamics and neuronal injury: role of the mammalian target of rapamycin. Neuron 102:1071-1087.

Garcia-Lopez R., Benito-Escudero M., Fernandez-Martinez R., Cid-Fernandez A., Capilla-Diez J., de la Torre-Aragones J., Guzman-Marin F., et al. (2019) Mitochondrial dynamics and neuronal injury: role of the mammalian target of rapamycin. Neuron 102:1071-1087.

Garcia-Lopez R., Benito-Escudero M., Fernandez-Martinez R., Cid-Fernandez A., Capilla-Diez J., de la Torre-Aragones J., Guzman-Marin F., et al. (2019) Mitochondrial dynamics and neuronal injury: role of the mammalian target of rapamycin. Neuron 102:1071-1087.
Deregulation of phosphorylation-mRNA expression in T cells of multiple sclerosis patients. J Neuroimmunol 319:100-105.

Papa L, Germain D (2011) Estrogen receptor mediates a distinct mitochondrial unfolded protein response in T cells of multiple sclerosis patients. J Neuroimmunol 319:100-105.

Rainbolt TK, Lebeau J, Puchades C, Wiseman RL (2016) Reciprocal degradation of YME1L and OMA1 adapts mitochondrial proteolytic activity during stress. Cell Rep 14:2041-2049.

Quintana-Cabrera R, Manjarres-Raza I, Vicente-Gutierrez C, Corrado M, Bolanos JP, Scorrano L (2020) Vitamin D protects against hippocampal apoptosis related with seizures induced by kainic acid and pentylenetetrazol in rats. Epilepsy Res 149:107-116.

Sahin S, Gurgen SG, Yazar U, Inci K, Karacabeyli S, Akgun D, Jin H, Anantharam V, Kanthasamy A, Kanthasamy AG (2017) Mitochondrial impairment in animal models of Parkinson's disease. NPJ Parkinsons Dis 3:30.

Qi X, Lewin AS, Sun L, Hauswirth WW, Guy J (2006) Mitochondrial protein nitration primes the blebbistatin-resistant mitochondrial ATP synthase for the physiological function of HtrA2 in the mitochondria. J Biol Chem 281:34277-34287.

Parker C, Naughton P, Tomlinson M, Frey T, Beyer C, Gupta S, Slowik A (2021) Aggregated mitochondrial peptidase PITRM1 induces proteotoxic stress and Alzheimer's disease-like changes in Bcl-2. Hum Mol Genet 19:2974-2986.

Parente G, Pinto M (2009) How mitochondria produce reactive oxygen species. Biochem. J. 417:1-13.

Nargund AM, Pellegrini MW, Fiorese CJ, Baker BM, Haynes CM (2012) Mitochondrial import efficiency of ATFS-1 regulates mitochondrial UPR activation. Science 337:587-590.

Rasola A, Bernardi P (2011) Mitochondrial permeability transition in Ca(2+)-dependent apoptosis and necrosis. Cell Calcium 50:222-235.

Rice J, Chen Z, Zhang W, Mancuso R, Clerici M (2016) The NLRP3 and NLRP1 inflammasomes are activated in systemic neurodegeneration in mouse. Brain 139:163-172.

Rimessi A, Messi M, Pinton P (2016) Mitochondrial reactive oxygen species and inflammation: Molecular mechanisms, diseases and promising therapies. Int J Dev Neurosci 31:281-293.

Rimessi A, Bezerini V, Parnisgeri S, Marchi S, Cabrini G, Pinton P (2015) Mitochondrial Ca(2+) dependent NLRP3 inflammasome activation excites the Pseudomonas aeruginosa-driven inflammatory response in cystic fibrosis. Nat Biotechnol. 33(11):1185-1191.

Roland SG, Sreedharan N, Alenius H, Bhattacharya J, Zhu H, Khurana N, Lehner B, Ichimura Y, Verma D, Chen H, Yu GM, Vats EK, Tong J, Zhao G, Mancuso R, Cleland J, Wadman WJ, Lee MA, McBride HM (2008) Cargo-selected transport from the mitochondria to peroxisomes is required for the physiological function of HtrA2 in the mitochondria. Nature 452:45-51.

Romano-Castoro C, Ogunfowora TO, Wang WJ, Zhou J, Nishimura Y, Pourfar M, Seldin MF, Nishimura R, Lewis RA, Pollen AA, Blau HM, Melillo BM (2019) Cell-intrinsic mitochondrial proteostasis is required for astrocyte migration and glioma invasion. Cell 177:136-149.e30.

Rubinstein RL, Beglov S, Wang C, Marsden PL, Lin Y, Wang X, Zhang L, Hui K (2019) Tricirin protects against 6-OHDA-induced neurotoxicity in Parkinson’s disease model by activating Nrf2/HO-1 signaling pathway and preventing mitochondrial-dependent apoptosis pathway. Toxicol Appl Pharmacol 378:114-147.

Ruffo MA, Zamboni N, DAmico D, Williams R, Fink D, Gyep S, Auwerx J (2015) Multi-omics analysis identifies ATF4 as a key regulator of the mitochondrial stress response in mammals. J Cell Biol 206:217-2025.

Rahdan S (2015) Pathophysiology of mitochondrial dysfunction causing epilepsy and status epilepticus. EpilepsyBehav 49:71-79.

Rainbolt TK, Lebeau J, Puchades C, Wiseman RL (2016) Reciprocal degradation of YME1L and OMA1 adapts mitochondrial proteolytic activity during stress. Cell Rep 14:2041-2049.

Rice J, Chen Z, Zhang W, Mancuso R, Clerici M (2016) The NLRP3 and NLRP1 inflammasomes are activated in systemic neurodegeneration in mouse. Brain 139:163-172.

Rimessi A, Messi M, Pinton P (2016) Mitochondrial reactive oxygen species and inflammation: Molecular mechanisms, diseases and promising therapies. Int J Dev Neurosci 31:281-293.

Rimessi A, Bezerini V, Parnisgeri S, Marchi S, Cabrini G, Pinton P (2015) Mitochondrial Ca(2+) dependent NLRP3 inflammasome activation excites the Pseudomonas aeruginosa-driven inflammatory response in cystic fibrosis. Nat Biotechnol. 33(11):1185-1191.

Roland SG, Sreedharan N, Alenius H, Bhattacharya J, Zhu H, Khurana N, Lehner B, Ichimura Y, Verma D, Chen H, Yu GM, Vats EK, Tong J, Zhao G, Mancuso R, Cleland J, Wadman WJ, Lee MA, McBride HM (2008) Cargo-selected transport from the mitochondria to peroxisomes is required for the physiological function of HtrA2 in the mitochondria. Nature 452:45-51.

Romano-Castoro C, Ogunfowora TO, Wang WJ, Zhou J, Nishimura Y, Pourfar M, Seldin MF, Nishimura R, Lewis RA, Pollen AA, Blau HM, Melillo BM (2019) Cell-intrinsic mitochondrial proteostasis is required for astrocyte migration and glioma invasion. Cell 177:136-149.e30.

Rubinstein RL, Beglov S, Wang C, Marsden PL, Lin Y, Wang X, Zhang L, Hui K (2019) Tricirin protects against 6-OHDA-induced neurotoxicity in Parkinson’s disease model by activating Nrf2/HO-1 signaling pathway and preventing mitochondrial-dependent apoptosis pathway. Toxicol Appl Pharmacol 378:114-147.

Ruffo MA, Zamboni N, DAmico D, Williams R, Fink D, Gyep S, Auwerx J (2015) Multi-omics analysis identifies ATF4 as a key regulator of the mitochondrial stress response in mammals. J Cell Biol 206:217-2025.

Rahdan S (2015) Pathophysiology of mitochondrial dysfunction causing epilepsy and status epilepticus. Epilepsy Behav 49:71-79.

Rainbolt TK, Lebeau J, Puchades C, Wiseman RL (2016) Reciprocal degradation of YME1L and OMA1 adapts mitochondrial proteolytic activity during stress. Cell Rep 14:2041-2049.

Rice J, Chen Z, Zhang W, Mancuso R, Clerici M (2016) The NLRP3 and NLRP1 inflammasomes are activated in Alzheimer’s disease. Mol Neurodegener 11:23.

Rauhala K, Gantel A, Gourley DL, Ojcius DM, Martin W, Pfeiffer H, Wollheim CB, Nussbaum R (2014) Exploration of glycogen synthesis as a novel therapy for preventing brain swelling. Neurocare 21:43-51.
Shpilka T, Du Y, Qiang Y, Meiber A, Uma Naren S, Lavelle J, Kim S, Li P, Westberg H, Li R, Yu J, Zhu H, Liu J, Strittmatter L, Haynes CM (2021) UPR(ert) scales mitochondrial network expansion with protein synthesis through mitochondrial import in Caenorhabditis elegans. Nat Comm 24:2479.

Shutt T, Geoffrion M, Milne R, McBride HM (2017) The intracellular redox state is a core determinant of mitochondrial function. EMBO Rep 13:909-915.

Simard L, Pirola JU, Rivest R (2016) Bone marrow-derived microglia play a critical role in restricting senile plaque formation in Alzheimer’s disease. Neurogn 498:502-512.

Slater DA, Martirte J, Hoi S, Chen X, Sun N, Fischer TD, Burman JL, Li Y, Zhang Z, Narendra MR, Hicks MC, Kelleher R, Youle RJ (2018) PARKN and PINK1 mitigate STING-induced inflammation. Nature 561:258-262.

Soares JL, Olmi Olivetti, Ponti A (2019) Variants in NLRP3 and NLR4 inflammasome associate with susceptibility and severity of multiple sclerosis. Mult Scler Relat Disord 29:26-34.

Song W, Chen J, Petiti A, Loti G, Xiang M, Zou P, Qiu J, Taudj J, Mori M, Hao YA, Shortt T, Geoffrion M, Milne R, McBride HM (2012) Bone marrow-derived microglia plays by inhibiting their apoptosis and enhancing mitochondrial autophagy. Brain Res Bull 153:30-38.

Villace P, Mella RM, Kortazar D (2017) Mitochondria in the context of Parkinson’s disease. EMBO Rep 18:1109-1114.

Valente EM, Salvi S, Ialongo T, Marongiu R, Elia AE, Caputo V, Romito L, Albanese A, Dallapiccola B, Torralba D, Baixauli F, Villarroya-Beltri C, Fernandez-Delgado I, Latorre-Pellicer A, Acin-Perez R, Tatton NA (2000) Increased caspase 3 and Bax immunoreactivity accompany nuclear GAPDH accumulation in neuronal cells in Alzheimer’s disease. Faseb J 14:2721-2727.

von Herrmann KM, Salas LA, Martinez EM, Young AL, Howard JM, Feldman MS, Christensen BC, Wilkins OM, Lee SL, Hickey WF, Havrdc MA (2018) NLRP3 expression in mesencephalic neurons and characterization of a rare NLRP3 polymorphism associated with decreased risk of Parkinson’s disease. NPJ Parkinsons Dis 4:4-24.

Wallot TD, 3rd, Bola RA, Hong JD, Au J, Bell MJ, Koehane PM, Clark RS, Aneja RK (2014) Cerebrospinal fluid mitochondrial DNA: a novel DAMP in traumatic brain injury. Brain 137:1766-1779.

Wallisch JS, Simon DW, Bavy H, Bell MJ, Koehane PM, Clark RS (2017) Cerebrospinal fluid NLRP3 is increased after severe traumatic brain injury in infants and children. Neurosurgery 80:990-993.

Wang JS, Murie DA, Power C (2014) Inflammasomes in the CNS. Nat Rev Neurosci 15:58-97.

Wang DD, Jin MF, Zhao Di, Ni H (2019a) Reduction of mitophagy-related oxidative stress and mitochondrial damage using melanin-congugated Curcumin as an in vitro and iiih227287:36-46.

Yano H, Baranov SV, Baranova OV, Kim J, Pan Y, Babbage S, Ferrante RJ, Kim AH, Keating SE, Wellstone L, Jia W, Chang F, Wang R (2011) NLRK negatively regulates TRIF-induced NF-kappaB signaling by targeting TRAF6 and IKB. Immunity 34:843-853.

Yong Q, Wang X, Mei W, Wang A, Dang Y, Cao H (2020) MicroRNA-216a inhibits neuronal apoptosis in a cortical Parkinson’s disease model by targeting Bax. Metab Brain Dis 35:627-635.

Zhang Y, Shi Q, Sun J, Li Y, Ma Y, Chen C, Xiao K, Wu Z, Dong XP (2019) Altered aberrations of mitochondrial factors Drp1 and Opal in the brains of scrapie resistant rodents. J Mol Neurosci 61:586-378.

Zhang Y, Xu H, Yang Q, Melber A, Uma Naresh N, Lavelle J, Kim S, Liu P, Weidberg H, Li R, Yu J, Scopa G, Yi J, Jia W, Chang F, Wang R (2011) NLRK negatively regulates TRIF-induced NF-kappaB signaling by targeting TRAF6 and IKB. Immunity 34:843-853.

Zuo K, Wang X, Mei W, Mei A, Dang Y, Cao H (2020) MicroRNA-216a inhibits neuronal apoptosis in a cortical Parkinson’s disease model by targeting Bax. Metab Brain Dis 35:627-635.

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Eura 2019-007947.

Xiang T, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X (2009) Impaired balance of mitochondrial and mitophagy defects in Alzheimer’s disease models and human brains. Acta Neuropathol 121:141-165.

Yamaguchi H, Baranov SV, Baranova OV, Kim J, Pan Y, Babbage S, Ferrante RJ, Kim AH, Keating SE, Wellstone L, Jia W, Chang F, Wang R (2011) NLRK negatively regulates TRIF-induced NF-kappaB signaling by targeting TRAF6 and IKB. Immunity 34:843-853.

Yong Q, Wang X, Mei W, Wang A, Dang Y, Cao H (2020) MicroRNA-216a inhibits neuronal apoptosis in a cortical Parkinson’s disease model by targeting Bax. Metab Brain Dis 35:627-635.

Zhang Y, Shi Q, Sun J, Li Y, Ma Y, Chen C, Xiao K, Wu Z, Dong XP (2019) Altered aberrations of mitochondrial factors Drp1 and Opal in the brains of scrapie resistant rodents. J Mol Neurosci 61:586-378.

Zhang Y, Xu H, Yang Q, Melber A, Uma Naresh N, Lavelle J, Kim S, Liu P, Weidberg H, Li R, Yu J, Scopa G, Yi J, Jia W, Chang F, Wang R (2011) NLRK negatively regulates TRIF-induced NF-kappaB signaling by targeting TRAF6 and IKB. Immunity 34:843-853.

Zuo K, Wang X, Mei W, Mei A, Dang Y, Cao H (2020) MicroRNA-216a inhibits neuronal apoptosis in a cortical Parkinson’s disease model by targeting Bax. Metab Brain Dis 35:627-635.

Xiang T, Su B, Lee HG, Li X, Perry G, Smith MA, Zhu X (2009) Impaired balance of mitochondrial and mitophagy defects in Alzheimer’s disease models and human brains. Acta Neuropathol 121:141-165.

Yamaguchi H, Baranov SV, Baranova OV, Kim J, Pan Y, Babbage S, Ferrante RJ, Kim AH, Keating SE, Wellstone L, Jia W, Chang F, Wang R (2011) NLRK negatively regulates TRIF-induced NF-kappaB signaling by targeting TRAF6 and IKB. Immunity 34:843-853.

Yong Q, Wang X, Mei W, Wang A, Dang Y, Cao H (2020) MicroRNA-216a inhibits neuronal apoptosis in a cortical Parkinson’s disease model by targeting Bax. Metab Brain Dis 35:627-635.