Chapter 6

Mitochondria at the Base of Neuronal Innate Immunity in Alzheimer's and Parkinson's Diseases

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Abstract

Mitochondria are exceptionally primed to play a key role in neuronal cell survival since they are involved in energy production and function as the metabolic center of cells. Several findings provide evidence for the role of mitochondria in neurodegeneration associated with Alzheimer's and Parkinson's diseases (AD and PD). Recent data highlight the role of mitochondrial proteins and mitochondrial reactive oxygen species in the intracellular signaling that regulates innate immunity and inflammation. In this chapter, we will discuss the relevance of the interplay between mitochondria and innate immunity, focusing on mitochondrial damage-associated molecular patterns (DAMPs) and how they can activate innate immunity and elicit AD and PD neurodegenerative process.

Keywords: mitochondria, neuronal innate immunity, Alzheimer's disease, Parkinson's disease, damage-associated molecular patterns

1. Introductory remarks

Mitochondria, derived from an ancestral bacterial endosymbiosis, are important cellular organelles in all cell types, but particularly important in the nervous system, since they are the major source of energy for the brain. Mitochondria are essential for neuronal function and neuronal processes, such as calcium (Ca^{2+}) homeostasis, maintenance of plasma membrane potential, apoptosis, axonal and dendritic transport, release and re-uptake of neurotransmitters at synapses, among others [1, 2]. The brain is particularly vulnerable to oxidative stress due to its high lipid content, its high oxygen demand and its low levels of antioxidant defenses. Therefore, any abnormalities in mitochondria function may impact the aging process and also potentiate the onset of age-dependent neurodegenerative disorders [3, 4].

In Alzheimer's disease (AD) and Parkinson's disease (PD), it has been described that mitochondrial metabolism and dynamics are affected not only in susceptible brain areas but also in peripheral cell models, namely platelets, fibroblasts and lymphocytes. Additionally, it was shown in AD and PD cellular and animal models that mitochondrial network is highly fragmented. Mitochondrial fission is required to selectively target dysfunctional mitochondria for degradation by the lysosome in a process called mitophagy [5, 6]. Nevertheless, it was recently proven that mitochondrial fission leads to the exposure of the inner membrane phospholipid, cardiolipin, which serves an important defensive function for the elimination of damaged mitochondria [7]. Since cardiolipin is found only in mitochondrial and bacterial membranes, it is considered a mitochondrial-derived damage-associated molecular pattern (DAMP) that is detected by a Nod-like receptor (NLR), the nucleotide-binding domain and leucine-rich repeat pyrin domain containing 3 (NLRP3) inflammasome Nlrp3 [8]. NLR and toll-like receptors (TLR) are pattern-recognition receptors that recognize pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide and short-chain fatty acids, and DAMPs that are responsible for the initiation of innate immune responses. NLR and TLR activation trigger the production of proinflammatory cytokines and antimicrobial peptides (AMPs) [9]. So, it is perceived that also neuronal cells are able to mount an innate immune response. Neurons express critical Toll/interleukin-1 receptor (TIR) domain-containing adaptors that transduce signals of TLR, regulating the expression of various cytokines. Indeed, TLR 3 and 7, localized in the neuronal endosomal compartment, play a role in neurite outgrowth. It is assumed that the cytokines produced by neurons may be just enough to recruit and activate local microglia and may not cause global brain inflammation [10].

Overall, mitochondria play a central role in metabolism, thus allowing the maintenance of cellular homeostasis. In this chapter, we will discuss how mitochondria can regulate neuronal innate immunity and how this impact age-related neurodegenerative disorders, such as AD and PD.

2. Alzheimer's disease hallmarks

AD is one of the most frequent age-related neurodegenerative disorder, characterized by neuronal loss and gradual cognitive demise. It is the major cause of dementia in the elderly [11], predominantly affects more women than men [12], and is expected that the number of people with AD will triple by the year 2050 [13]. Patients with AD show an impaired ability to perform everyday tasks and often experience psychiatric, emotional and personality disturbances [14]. Two well-known abnormal protein aggregates in the brain of the patients, cerebral cortex and hippocampus, characterize AD pathologically: the neuritic plaques that are extracellular and composed of insoluble amyloid β peptides (Aβ) and neurofibrillary tangles that are intracellular aggregates, mostly consisted of phosphorylated tau, a microtubule-associated protein [15]. It is assumed that oligomers can induce toxicity for neurons causing synaptic dysfunction, neuroinflammation and oxidative stress [16, 17].

Several authors have mentioned that mitochondrial dysfunction and oxidative damage occur in the AD brain before the onset of Aβ pathology. Mitochondrial dysfunction was reported in brain neurons, platelets and fibroblasts from AD patients and in transgenic AD mice models. These mitochondrial abnormalities have been reported in neurons and astrocytes, suggesting that both types of cell might be affected in brains of AD patients [18]. For example, it has been

described in post-mortem AD brains, a deficit of cytochrome c oxidase (COX) in hippocampus, frontal, temporal, occipital and parietal lobes [3]. Additionally, it is recognized that mitochondrial DNA (mtDNA) is also involved in the mitochondrial dysfunction having a determinant role in AD pathogenesis. When patient's mtDNA is transferred into mtDNA-deficient cell lines, the originated 'cybrids' reproduce the respiratory enzyme deficiency that occurs in the brain and other tissues in AD, suggesting this defect is carried in part by mtDNA abnormalities [19].

Neuroinflammation has been implicated in AD etiology, but its contribution to disease progression is still not yet understood [20]. Astrocytes and microglial cells are the main type of cells involved in inflammatory responses in the central nervous system (CNS) after infection or injury occurs. Indeed, in this process, cellular and molecular immune components, such as cytokines, are important players, which may lead to the activation of glial cells (microglia and astrocytes) [21]. Several studies have described that Aβ, pathogenic infection or cellular debris triggers an initial inflammatory stimulus, which activates the microglia, allowing the maintenance of neuronal plasticity and synaptic connectivity [22]. Data suggest that microglia internalize and degrade Aβ deposits, helping its clearance from the brain. However, during disease process, microglia acquire a 'toxic' phenotype due to chronic activation and continue the production of proinflammatory mediators [23]. In animal models and human brain tissue, both neuritic plaques and neurofibrillary tangles colocalize with activated glial cells. Different studies have reported pathological astrogliosis, in both AD patients and transgenic animal models brains, characterized by an increased glial fibrillary acidic protein (GFAP) and distinct cellular hypertrophy, which is correlated somehow with the severity of cognitive impairment in AD patients [24].

2.1. The role of mitochondrial dysfunction in Alzheimer's disease etiology

Despite its elusive origin, mitochondrial dysfunction is long recognized as a striking feature of sporadic AD, mediating cell pathways that sustain the disorder progression. Brain bioenergetic function is compromised in AD. Images from fluorodeoxyglucose positron emission tomography (FDG-PET) scan show that glucose utilization is significantly lower in AD subjects as compared to age-matched controls in the cortex and the posterior cingulate brain regions [25]. This bioenergetic compromise correlates with decreased COX activities measured in post-mortem brain tissue from AD patients [26]. Mitochondrial deficits in AD have been described not only in the brain but also in peripheral tissues. COX activity was found decreased in platelets and lymphocytes from AD subjects [27–30]. This COX deficiency correlates with decreased oxygen consumption first described in AD subject's brain, where PET scans showed decreased cerebral metabolic rate of oxygen (CMRO2) [31]. Mitochondrial respiration is also compromised in peripheral blood mononuclear cells [32], and in cytoplasmic hybrid (cybrid) cell lines [33], generated by the fusion of mitochondrial DNA (mtDNA) depleted cells with platelets from AD subjects [34]. These cell lines elucidated on the relevance of mtDNA in AD pathology, since the main features of the disease are recapitulated [33, 35, 36]. The same observation was made in a number of transgenic mice models that carry mutations linked to AD familial forms [37–39].

Along with impaired mitochondrial function, it has been widely demonstrated that mitochondria from AD tissues and models have decreased mitochondrial membrane potential (ΔΨmit) [40]. Cumulative evidence consistently showed a positive correlation between ΔΨmit and reactive oxygen species (ROS) production [41]. In the case of neurodegenerative disorders, such as AD, associated with dysfunctions of the respiratory chain components, lower ΔΨmit and

decreased activity of the respiratory chain are observed with a simultaneous increase in ROS production [42]. The primary ROS in mitochondria is the superoxide radical anion $O_2^{\cdot-}$, mainly produced at complexes I and III [43], which is rapidly converted to H_2O_2 by mitochondrial dismutases, superoxide dismutase (SOD). Regardless the contradictory data on the contribution of COX deficiency to ROS production [44, 45], oxidative damage is an utterly feature of AD, from human samples to cellular and animal models [36, 46–48]. Evidence show that mitochondrial dysfunction and ROS production are accentuated by Aβ, a 4 kDa protein, derived from a larger protein, amyloid β-protein precursor (βAPP), that is overproduced during AD progression. Aβ interacts with mitochondrial proteins, namely ABAD, causing increased ROS production, mitochondrial dysfunction and neuronal death [49, 50]. These changes in mitochondrial metabolism seem to be related with morphological alteration of mitochondria of AD tissues and models. Electron microscopy images from AD brain tissue show mitochondria with reduced dimensions and disrupted *cristae* [51]. Similarly, mitochondria from AD subjects transferred to mtDNA depleted cell into cybrids at an ultrastructural level are small and have a swollen-like structure [52], with a fragmented mitochondrial network that correlates with increased mitochondrial content of dynamin-related protein 1 (DRP1) [53] a key protein for mitochondrial division [54]. Concerning mitochondrial content/mass in AD neurons, the matter is not as straight forward [55]. Vulnerable neurons have a decrease in functional mitochondria, but mtDNA is increased [51]. In accordance it was observed, in AD cybrids, an increase in mtDNA content [33]. This increment was first explained as a compensatory response to counteract the loss of mtDNA transcription efficiency [51], but data gathered on the subject point to decreased mitochondria degradation through autophagy (mitophagy), with imprisoned mitochondria within autophagic vacuoles that are accessible for mtDNA detection [53]. A number of studies have shown autophagy dysfunction as a driving force of AD progression, with important impact on Aβ deposition and plaque formation [56–60]. In human brain samples, it could be observed a massive accumulation of autophagic vacuoles and lysosome-related vesicles, which led to the conclusion of simultaneous induction and impairment of autophagy [56, 61]. Purified autophagic vesicles contain βAPP and the proteases responsible for its cleavage [56]. Aβ peptides are produced by sequential proteolytic processing of βAPP by β-secretase (BACE) and γ-secretase complex (presenilin and nicastrin) [62, 63]. These accumulated vacuoles cause swellings along dystrophic neurites and potentiate Aβ production and aggregation [64], which gradually form the extracellular amyloid plaques, one of the most prominent brain pathological hallmarks of AD. It is reasonable to argue that stimulating autophagy would clear the cell waste materials. Although some contradictory data were published, in opposition of ameliorating Aβ pathology, stimulating autophagy, either chemically or starvation-induced, fails to degrade accumulating Aβ and worsens cell function in *in vivo* models [65]. The driver of such failure is the microtubule network, along which autophagic vesicles are transported towards lysosomes, for degradation of cell waste. Mitochondrial metabolism failure compromises microtubule proper dynamics. Destabilized microtubule cytoskeleton negatively impacts autophagic vesicles retrograde transport towards lysosomes and promotes microtubule-associated protein Tau to detach and undergo phosphorylation [5]. Tau is the main component of paired helical filaments (PHF) that form neurofibrillary tangles found in AD brains [66] and is a microtubule-associated protein (MAP) that promotes microtubule assembly and stabilization [67–69]. Ultrastructural analysis performed in AD neurons found that the number and total length of microtubules are decreased in AD subjects [70]. In AD cybrids, microtubule network is disrupted with increased free tubulin

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content, and this correlates with increased Tau phosphorylation, comparing with control cybrids [53]. Targeting microtubule stability is able to protect cells from Tau and Aβ-induced toxicity and restores autophagy function in a variety of AD models [71, 72].

2.2. Immune response in Alzheimer's disease

The role of neuroinflammation in AD dates back to 1907, to the original report of Alois Alzheimer, with microglia surrounding Aβ plaques, thus showing a close relation between the pathway and the disease [73]. Twenty-five years after the postulation of Selkoe and Hardy, the amyloid cascade hypothesis is still the main hypothesis for AD pathogenesis. It is a fact that all AD patients undergo progressive Aβ deposition, and moreover, the sequence of major pathogenic events leading to AD proposed by the amyloid cascade hypothesis is perfectly aligned with the dominantly inherited forms of AD. However, different mechanisms have to be considered to explain the development of AD in sporadic cases, which constitute the vast majority of the cases [74]. Even though Aβ peptide and tau protein oligomers are considered the major contributors to disease progression and the deposition of Aβ occurs decades before any other alterations, there are some missing links between the accumulation and oligomerization of Aβ and tau pathology, synaptic dysfunction and cognitive decline [15, 75]. In this follow-up, neuroinflammation is consistently reported to be deregulated in AD and to facilitate disease progression [76, 77]. Indeed, various forms of Aβ oligomers and aggregates are detected by numerous receptors (TLRs), receptor for advanced glycated end-products (RAGE), CD14, CD36, CD47, α6β1 integrin, class A scavenger receptor and NOD-like receptor family pyrin domains (NLRP) that activate innate immunity response (mainly via MAPK/Erk and NF-κB-mediated signaling) [22, 78–80]. In neurodegenerative diseases, such as AD, the inflammatory response starts by innate immune system activating monocytes (in periphery) and microglial cells, astrocytes and perivascular cells (in the CNS) [81].

Microglia, the resident macrophages of the CNS, play an active role surveying the brain for pathogens and maintaining neuronal plasticity and synaptic connectivity [82]. In AD, stimulation of microglia involves the microglial polarization to a M1 phenotype that triggers the production of proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-12 and IL-18) [83, 84] and chemokines (CCL2, CCR3, CCR5) [85, 86] and is accompanied by impaired phagocytic capacity [87]. Interestingly, deregulation of Aβ clearance from the CNS is a key pathogenic mechanism in pathology progression, whereas microglial phagocytosis activation plays a crucial role (in combination with the endolysosomal pathway, being Aβ enzymatically digested by neprilysin, insulin-degrading enzyme and matrix metalloprotease proteases) and is controlled by two microglial cell surface receptors: TREM2 (positive regulator) and CD33 (negative regulator) [88, 89]. Moreover, caspases are known mediators of apoptosis, but they also regulate inflammation. Upon binding of Aβ to NLRP, there is an inflammasome-dependent activation of caspase-1 that mediates the production of mature IL-1β by cleavage of an inactive pro-IL-1β peptide [90, 91]. Therefore, elevated concentrations of active caspase 1 detected in the brains of patients with AD [92] are in accordance with the increased NLRP3 activation observed in monocytes from AD patients [93]. In addition, mitochondrial DAMPs were shown to increase AD-associated biomarkers, such as App mRNA, APP protein and $A\beta_{1-42}$ levels, in SH-SY5Y and mice brains [94, 95]. Together, these studies suggest that mitochondria and mitochondrial DAMPs have the potential to promote inflammation in the brain, with important consequences relevant for neurodegenerative disorders such as AD.

Pathological responses of astrocytes include reactive astrogliosis directed at recovery of injured neural tissue and neuroprotection [96]. In AD, astrocytes, like microglia, are a major source of cytokines (TNF-α and IL-1β are readily released upon astrocytic Aβ detection) [97, 98] and chemokines. Indeed CCL4 has been detected in reactive astrocytes near Aβ plaques [99] and has a high capacity to degrade $A\beta_{1-42}$ in a more efficient way than their microglial counterparts [100]. In addition, post-mortem brains from AD patients are characterized by hypertrophic reactive astrocytes, elevated GFAP and S100B expression surrounding senile plaques [101]. Interestingly, studies have shown that reactive astrogliosis occurs early in the course of pathogenesis and correlates with the severity of cognitive impairment in AD patients [102]. Furthermore, resident microglia and astrocytes in AD have been shown to stimulate inducible nitric oxide synthase (iNOS) and NADPH oxidase [103]. These upregulations lead to the production of high concentrations of ROS (such as nitric oxide, superoxide, hydrogen peroxide, peroxynitrite), which not only further promote microglia activation but also lead to post-translational modifications (nitration, S-nitrosylation, and dityrosine formation), including Aβ nitration leading to a higher propensity to aggregate and seriously suppress hippocampal LTP [103–105]. Likewise, the complement system is another major constituent of the innate immune system that shows enhanced levels in disease settings. In the brain, activated microglia and astrocytes are responsible for the production of proteins of the complement system, which in turn are associated with Aβ deposits [106]. Additionally, complement receptor 1 (CR1) modulates the impact of the APOE ε4 allele on brain fibrillar amyloid burden [107]. Furthermore, there are other players with neuroinflammatory actions in AD, such as perivascular macrophages promoting Aβ clearance [108], endothelial cells contributing to the transport of Aβ species between the brain and the periphery [109, 110], oligodendrocytes [111] and neurons [112] that contribute to neuroinflammation by expressing complement components.

In the end, the recruited microglia and astrocytes fail to resolve the Aβ insult effectively, resulting in an excessive proinflammatory cytokine and chemokine production, as well as enhancing DAMPs secretion, ultimately leading to deleterious microglial and astrocytic reactivity [113]. This chronic neuroinflammatory environment thus starts a vicious cycle altering APP processing towards a further increase in Aβ production, culminating in neuronal loss and perpetuating inflammation, which with the advance of the disease compromises blood-brain barrier (BBB) permeability, allowing the invasion of peripheral inflammatory cells that exacerbate the deleterious neuroinflammation and facilitate neurodegeneration [114]. Therefore, neuroinflammation in AD was firstly attributed exclusively to these innate immune sensors of Aβ, contributing to the exacerbation of the disease and viewed only as a response, but in reality the pathway is much more complex.

A decade ago, a significant change in this thought was brought by Wyss-Coray who reviewed the hypothesis that inflammation may serve as a cause and driving force for AD [115]. As seen by the significant immune response later on in the disease and as a response to the Aβ accumulation, it is accurate to state that inflammatory pathways are a driving force in AD. However, for a causative role, inflammation should have an early impact or precede the pathogenesis of the disease [81]. In support of inflammation as a primary contributor for the disease, recent genome-wide association studies (GWASs) of sporadic AD cases (or LOAD—late-onset AD) have found associations between AD and genes that are involved in cholesterol metabolism and in innate immunity [116]. Surprisingly, even Selkoe and Hardy drew attention to the importance

of the innate immune system in AD on their update on the status of the amyloid hypothesis [74]. Accordingly, three risk genes have been highlighted: TREM2, CD33 and CR1, and all are involved in some way in microglial response, being upregulated during Aβ plaque development [117–119]. Another important aspect is the timeline involvement of the immune system response in AD's development. Analyses from both patients with early AD and mild cognitive impairment (MCI), which precedes AD stage, have identified a correlation between clinical symptoms and the presence of inflammatory markers in the cerebrospinal fluid (CSF), suggesting a much early involvement of the immune system in the disease [120, 121]. Noteworthy, a study in wild-type mice found that chronic inflammatory conditions triggered the development of AD-like neuropathology during aging, demonstrating a case where immune response not only precedes fibrillary Aβ plaque deposition and neurofibrillary tangle formations but also is responsible for their induction [122]. Thus, the possibility to manipulate inflammatory pathways, thereby changing the course of the disease, is yet another indication of the role of inflammation as a driving force of AD pathology. The questions we should make previously of that said manipulation are: Which cells and immune molecules should be modulated? And when should modulation occur? As the activation of microglia and the neuroinflammatory environment are constantly changing depending on the stage of the disease, the time window for modulation and for therapeutically potential is very important [81]. Inefficiency in clinical trials with nonsteroidal anti-inflammatory drugs (NSAIDs) in AD could be largely due to wrong timing of intervention [123], since epidemiological and preclinical studies show a reduction up to 80% in the risk of AD onset and decrease in microglial activation and amyloid burden with NSAID use [124, 125].

As aforementioned, there is an uncontrolled production of cytokines and chemokines that may be used as effective tools for inflammatory biomarkers in AD. Early assessment of neuroinflammation in the AD patients may be an important preventive strategy to act before the detrimental aspects of neuroinflammation, thus averting or delaying any cognitive decline [126]. Several studies have investigated the levels of proinflammatory and anti-inflammatory markers in the CSF, plasma and serum of AD patients. IL-1β, TNF-α and IL-6 have been observed to be altered in the three types of samples in AD, although the results vary according to the time point of sampling [126]. Once again, the stage of the disease is a crucial factor for any therapeutic intervention. Moreover, an increase in TGF-β [127] and S100B [128] levels in the CSF from AD compared to controls has also been reported. Regarding blood-based biomarkers of inflammation, α-1-antichymotrypsin (ACT) [129] and C-reactive protein (CRP) [130] have been shown to be increased in AD. Noteworthy, α-2-macroglobulin (α-2 M) [131] and clusterin (or apolipoprotein J) [132] have been implicated in the pathology of AD, with significant increases in patients, showing promising results as potential plasma biomarkers of AD. Interestingly, many of these inflammatory mediators are also altered in MCI subjects. The levels of IL-8, monocyte chemoattractant protein-1 and interferon-γ-inducible protein 10 are found to be increased in CSF, while IL-1β and TNF-α are increased and apolipoprotein A-1 and complement C1 inhibitor are decreased in blood [126]. Besides the detection of neuroinflammatory markers, inflammation may be also monitored through imaging methods. In patients with AD or MCI subjects, increased microglia activation has been detected by PET scans [133].

The induction of neuroinflammatory effects is not restricted to factors of the CNS and can result from systemic influences [125]. On the one hand, traumatic brain injury is an example of a CNS-intrinsic neuroinflammatory condition that facilitates the development of AD pathology [134]; on

the other hand,systemic inflammation may be induced from several chronic diseases [135], such as obesity and T2D, all characterized by CNS inflammation and microglia activation [136, 137]. Therefore, in AD, neuroinflammation can cause and drive pathogenesis [22].

3. Parkinson's disease hallmarks

PD is the most common movement neurodegenerative disorder characterized by numerous motor symptoms, including tremor, bradykinesia, rigidity and postural instability [138]. PD is twice as common in men than in women, and about 2% of the population above the age of 60 is affected by the disease [139]. PD is characterized by the severe loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and by the presence of intracytoplasmatic proteinaceous inclusions called Lewy bodies, which are primarily composed of fibrillary α-synuclein (SNCA), and ubiquitinated proteins within some remaining nigral neurons [140, 141].

Several evidences from autopsy studies showed that multiple processes are involved in cell death, including oxidative stress, mitochondrial dysfunction, neuroinflammation, excitotoxicity and accumulation of misfolded proteins due to proteasomal and autophagic impairment [142].

Data show that mitochondrial deficits occur in PD patient's brain neurons, platelets and lymphocytes [139],which play a critical role in the loss of dopaminergic neurons [143]. Furthermore, data suggest that mitochondrial dysfunction can be potentiated by defects in mitochondrial biogenesis caused by the deregulation of transcription factors, such as peroxisome proliferator-activated receptor gamma coactivator1-alpha (PGC-1α) [144], which levels are decreased in post-mortem brains of PD and in white blood cells [139]. Recent studies in post-mortem PD brain tissue showed that nigrostriatal axon terminals are dysfunctional, which can alter normal axonal transport. Also, the generation of ROS induces the damage of complexes I and III and protein oxidation in mitochondria and in cytoplasmic proteins, leading to mitochondrial dysfunction [145].

Several studies obtained in post-mortem PD brain tissue, human clinical imaging and fluid biomarker have demonstrated that neuroinflammation is a salient feature and probably an essential contributor to PD pathogenesis [145]. Inflammation associated with oxidative stress and cytokine-dependent toxicity has been described and can lead to both innate and adaptive immune responses. Immune responses can act a secondary response to cellular damage and/ or neuronal loss in the affected regions of the nervous system. These mechanisms imply not only a complex crosstalk between the CNS and the peripheral immune system but also interactions between the brain resident immune cells (microglial cells) and other brain cells (neurons, astrocytes, endothelial cells) [146]. Indeed, it has been described that PD brains show microglial activation and lymphocyte infiltration in the areas of degeneration and an increased expression of inflammatory cytokines with alterations in the composition of peripheral immune cells, suggesting the key role of neuroinflammation in PD.

3.1. The role of mitochondrial dysfunction in Parkinson's disease etiology

Mitochondrial dysfunction relevance in PD was first documented when 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was associated with parkinsonian syndrome in humans [147].

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MPTP is able to cross the blood-brain barrier, is metabolized to 1-methyl-4-phenylpyridinium (MPP^+) and is uptaken by dopaminergic neurons, inhibiting mitochondrial respiration at complex I [148]. Complex I activity was shown to be decreased in PD brain samples [149], in peripheral tissues namely platelets and lymphocytes [150] and in PD cybrids [151]. The inhibition of complex I, with MPTP and rotenone, is widely used as *in vitro* and *in vivo* models of PD since these recapitulate the main features of the disease [152–154]. Mitochondrial dysfunction in PD tissues and models is also characterized by a decrease in $\Delta\Psi$mit [52, 155, 156]. Accordingly, at a functional level, brain bioenergetics is compromised in PD where PET scans showed glucose utilization are decreased in PD individuals in the occipital cortex compared to control individuals [157].

Oxidative damage driven by mitochondria malfunctioning is a prominent aspect in PD [158]. Mitochondrial complex I is one of the most important sites of ROS production in the cell, primarily O_2^- [159]. The consequences of oxidative damage are such in PD that oxidative stress was proposed as the cause for dopaminergic neurons death in the SNpc [160, 161]. The same authors found in post-mortem samples from PD subjects increased lipid peroxidation whereas glutathione pathway, an antioxidant defense, is impaired [160]. Mitochondria are the main producers and are also the primary targets of ROS. PD brain biopsies revealed complex I itself is oxidatively damaged, which prevents its proper assembly and function [149]. Although it is incontestable that oxidative stress contributes to PD pathology, it is now generally accepted that ROS are a by-product of mitochondrial dysfunction that contributes to worsen cell demise [162].

Familial forms of PD bearing mutations in mitochondrial proteins reinforced the involvement of mitochondrial dysfunction in PD etiology and shed light into the mechanisms leading to neuronal death, unifying both familial and sporadic cases. Rare mutations causing juvenile PD are related to mitochondrial degradation by mitophagy created an opportunity for clarification of the disease mechanisms. The first identified mutation in *PARK2* (Parkin), an E3 ubiquitin ligase, cause early onset PD [163]. The second mutation was identified in *PARK6*, PTEN-induced kinase 1 (PINK1) and a mitochondrial kinase [164]. PINK1 and Parkin act together in a tightly regulated process to target dysfunctional mitochondria for degradation, named mitophagy. This process is crucial for the maintenance of a healthy pool of mitochondria, potentially protecting cells in early stages of mitochondrial dysfunction [165]. In healthy mitochondria, PINK1 levels are maintained low as this protein is degraded within mitochondrial matrix after its import from cytosol [166]. When mitochondria lose their membrane potential, PINK1 is stabilized at their surface recruiting Parkin that, in turn, ubiquitinates and targets mitochondria to undergo mitophagy [167–169]. PD caused by PINK1 and Parkin mutations is not clinically differentiated from idiopathic PD [170]. Morphologically, PINK1 mutations have drastic repercussions in mitochondria from *Drosophila melanogaster* to mouse models, with larger, swollen and disrupted cristae [171, 172]. In cybrids from sporadic PD subjects, mitochondria also present abnormal structure with enlarged and scarce cristae [52, 173]. Mitochondrial network images show that in PD models it presents a fragmented structure. From PD cybrids [174] to dopaminergic neurons treated with MPTP [175], a number of models show early mitochondrial fragmentation that precedes cell death. Although DRP1 has been implicated in the fragmentation of mitochondria in PD [174], studies point to SNCA directly interacting with mitochondria inducing fragmentation, in a process that does not require DRP1 [176]. Recently, it was found a common mechanism for mitophagy failure, besides Pink1-Parkin axis, that is shared by familial and sporadic PD, with potential

of an early biomarker [177]. In fibroblasts isolated from patients that carry PD mutations and idiopathic PD subjects, it was found an impairment in RHOT1 degradation that in turn delays mitochondria immobilization and consequent degradation [178]. RHOT1 is a mitochondrial kinesin adaptor protein that, upon mitochondrial damage, interacts with PINK1 and Parkin to target mitochondria for proteasomal degradation [179]. Consequently, abnormal levels of autophagy markers were found in brain tissue preparations from PD patients, both sporadic and early onset [180, 181]. This impairment in autophagy has been related to the decreased transport along microtubules and fusion of autophagic vesicles with the lysosomes rather than a defect in cell waste recognition by autophagy machinery [173]. Mitochondrial dysfunction is intimately connected to microtubule instability and, thus, autophagy impairment in PD models. In PD cybrids, intracellular transport of autophagosomes and mitochondria is compromised [173]. Accordingly, MPP^+-treated cells have disrupted microtubule network and a decrease in mitochondrial trafficking [182]. Also, there are some data pointing that Parkin can bind to microtubules contributing to their stabilization, whereas ablation of Parkin causes reduced microtubule mass [183, 184]. Accumulation of non-degraded mitochondria and other autophagic substrates, such as SNCA aggregates, increments cell demise and contributes to Lewy body-like structure formation. Oxidative stress provoked by mitochondrial malfunctioning is able to induce proteasomal subunit disassembly, leading to the accumulation of degrading substrates, such as ubiquitin [185], contributing to Lewy body formation and cell death. In fact, ubiquitin accumulation, impaired ubiquitin proteasome system (UPS) function and mitochondrial dysfunction have been proposed to be intimately associated [186].

3.2. Immune response in Parkinson's disease

Despite PD is characterized by a slow and progressive degeneration of dopaminergic neurons in the SNpc, the cause of this neuronal loss is still poorly understood. Nevertheless, neuroinflammatory mechanisms, such as microglial activation, astrogliosis and lymphocytic infiltration have been postulated to contribute to the cascade of events leading to neuronal degeneration [187].

A growing body of evidence suggests a role of autoimmune and neuroinflammatory mechanisms in the etiopathogenesis of PD [188]. Peripheral immune responses can trigger inflammation and exacerbate neurodegeneration in several neurodegenerative disorders including PD. Indeed, peripheral inflammation in early stages of disease appears to accompany the development of preclinical non-motor symptoms, including olfactory and gastrointestinal dysfunction, providing a possible association between autoimmunity and PD [189]. Strikingly, chronic constipation, which occurs many years before the first motor symptoms of PD, is casually linked to peripheral inflammation [190].

Inflammation is a defense mechanism aimed at counteracting with diverse insults. In neurodegenerative disorders, such as PD, inflammation could results from the activation of innate immunity by PAMPs; DAMPs or protein aggregates. Other than the activation of inflammatory responses, there is also the ability of the immune system to detect harmful agents. Mounting evidence indicates that dopaminergic cell death is influenced by the innate immune system and neuroinflammatory processes in PD. Soreq and coworkers described an altered expression of neuroimmune signaling-related transcripts in early stages of PD [191].

Remarkably, epidemiological studies showed that non-steroidal anti-inflammatory drugs, such as ibuprofen lowers the risk of PD further supporting the contribution of inflammation to disease process [192–194]. Interestingly, the SNpc (main area affected in PD) exhibit high sensitivity to proinflammatory compounds, whereas the hippocampus appears to be more resistant, which can be explained due to the differences in the number of microglial cells between both areas [195]. In fact, numerous evidences that came from experimental PD models suggest that dopaminergic neurons are extremely vulnerable to inflammatory challenge [196, 197]. Moreover, stereotaxic injection of lipopolysaccharide (LPS, a Gram-negative bacteriotoxin that activates microglial cells) into the SNpc induced degeneration of dopaminergic neurons while sparing GABAergic and serotonergic neurons, suggesting selective dopaminergic neurons vulnerability to PAMPs [198].

There are several factors that may be underlying this selectivity. Dying neurons release substances that are recognized by glial cells, activating them, such as dopamine, neuromelanin and SNCA [199]. Dopamine seems to play a role in the inflammatory response induced by LPS, since depletion of this neurotransmitter prevents gliosis and reduces peripheral macrophages infiltration and dopaminergic neuronal death induced by 6-hydroxydopamine (6-OHDA) [200]. Recently, Dominguez-Meijide and colleagues observed that the decrease in dopamine levels observed in early stages of PD promotes neuroinflammation and disease progression via glial renin-angiotensin system exacerbation [201]. Neuromelanin is able to activate microglia cells leading to neuroinflammatory processes and degeneration of dopaminergic neurons [202, 203]. Extracellular and misfolded SNCA prompts microglia activation and production of proinflammatory molecules [204–206].

Further support for a role of innate immunity activation in PD pathogenesis come from genetic studies showing that polymorphisms in some proinflammatory cytokines may influence the risk of developing PD. Indeed, there is an association between genetic variations in the human leukocyte antigen (HLA) region and sporadic PD [207, 208]. HLA isalso called human MHC molecules, which presentation activates CD+4 T cells and CD+8 cytotoxic lymphocytes. Remarkably, in a GWA study, several susceptibility loci have been identified as strong risk factors that are related to both innate and adaptive immune functions [209]. Moreover, PD-linked genes such as LRRK2 and SNCA are also known to stimulate inflammatory responses and immunological regulation [210]. In fact, Harms and colleagues reported that accumulation of pathological SNCA in PD brain leads to T cell infiltration, microglial activation and increased production of inflammatory cytokines and chemokines [211]. Furthermore, transgenic mice with overexpression of wild-type or mutated SNCA showed an early microglial activation [212, 213]. Beraud and colleagues demonstrated that misfolded SNCA directly activates microglia, inducing production and release of TNFα and increasing expression of Nfr2-dependent antioxidant enzymes [214]. Aggregated and nitrated SNCA also stimulates microglia activation triggering innate and adaptive immune responses [215]. Intranigral injection of SNCA resulted in the upregulation of mRNA expression of proinflammatory cytokines and the expression of endothelial markers of inflammation and microglial activation [216, 217]. Multiple immune cells show high levels of LRRK2 expression [218, 219]. R1441G LRRK2 mutation was shown to increase proinflammatory cytokine release from activated microglial cells [220, 221]. Moreover, LPS-mediated neuroinflammation is attenuated in murine *lrrk2*-knockdown brain microglia [222].

The first evidence for a neuroinflammatory processes in PD came in 1988 when McGeer and co-workers observed the presence of activated microglial cells and inflammatory macrophages, as well as, proinflammatory cytokines in post-mortem brain samples of the SNpc of PD patients [223]. Similarly, Langston and coworkers reported an accumulation of activated microglia around dopaminergic neurons in post-mortem human brains with MPTP-induced parkinsonism [224]. Later, several authors corroborated this result and further observed the presence of other markers such as HLA-DP, HLA-DQ, HLADR (CR3/43), CD68 (EBM11, a low-density lipoprotein binding glycoprotein, equivalent to macrosialin in mice) and ferritin in the SNpc and putamen [225–227]. In addition, intercellularadhesion molecule-1-positive glia levels are also increased in the SNpc of PD brains, indicating activation of cells of the innate immune system, in particular, in areas with neuronal loss and extracellular melanin accumulation [228]. Furthermore, Damien and colleagues used glutathione peroxidase as an astrocytic marker and observed that the density of astrocytes in the SNpc is low when compared to the ventral tegmental area. This indicates that vulnerable neurons in patients with PD have less surrounding astroglial cells and as a result reduced detoxification of oxygen-free radicals by glutathione peroxidase [229]. McGeer and colleagues described for the first time the presence of cytotoxic T lymphocytes (CD8+) in the substantia nigra from one patient with PD [223]. Moreover, several reports found alterations in the population of blood T lymphocytes in PD patients [230–232]. In addition, cytotoxic infiltration of CD8+ and CD4+ T cells into the brain parenchyma of both post-mortem human PD specimens and in the MPTP mouse model of PD was described during the course of neuronal degeneration [233, 234]. Interestingly, these markers were not detected in the red nucleus suggesting that this infiltration is selective for the injured brain areas. Furthermore, these cells were in close contact with blood vessels and near to melanized dopaminergic neurons. These data indicate that cells migrate from the bloodstream and suggest an interaction between the lymphocytes and the dopaminergic neurons during the neurodegenerative process. Hence, alterations in the BBB might occur in the brains of PD patients. Not only during aging but also in PD, a BBB disruption can occur, leading to an invasion of immune cells, peripheral mediators, toxins and elements of adaptive immunity to the brain parenchyma potentiating the degenerative process [235]. Additionally, PD patients have increased permeability of the intestinal epithelial barrier and a chronic gut inflammation characterized by increased expression levels of proinflammatory cytokines and inflammatory markers [236, 237]. Moreover, several studies reported increase in TNFα, β2-microglobulin, epidermal growth factor (EGF), transforming growth factor α (TGFα), TGFβ1 and interleukins 1β, 6 and 2 levels in the striatum of PD patients and increasein TNFα, interleukin 1β and interferon γ levels in the SN of PD patients [238–243]. Interestingly, dopaminergic neurons express the receptors for these cytokines, suggesting that they are sensitive to these cytokines [244, 245]. Proinflammatory cytokines, such as TNFα, interleukin 1β, and interferon γ, can induce the expression of the inducible form of nitric oxide synthase (iNOS) or cyclo-oxygenase 2 (COX2), which are known to produce toxic reactive species. To corroborate the previous studies, a CD23-mediated increase in iNOS in the SN of PD patients was found. Furthermore, enzymes that are involved in neuroinflammatory processes mediated by oxidative stress, such as NADPH oxidase, COX2 and myeloperoxidase, are also increased in PD patients [239, 246, 247]. This may indicate that the inflammation-derived oxidative stress could contribute to dopaminergic neuronal degeneration.

The results obtained in post-mortem studies were further corroborated by studies carried out in biological fluids (serum or CSF) of patients suffering from PD. Serum samples from PD patients indicated that the expression of certain cytokines such as IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12,

TNFα, TNFR1 and RANTES is increased [248–254]. Interestingly, RANTES levels were correlated with the severity and duration of the disease [255]. Additionally, studies analyzing CSF from PD patients reported proinflammatory changes such as the presence of TNFα [238] and interleukin 1β [225, 256, 257] and osteopontin (a member of the integrins family) [258]. Moreover, PET scan analysis also reported the presence of PK-11195 in PD samples, which is indicative of microglia activation [259, 260]. PET analysis using radioligand ^{11}C-PK-11195 corroborated these results in the SNpc of sporadic PD patients within a year from clinical onset [261]. More recently, microglial activation in PD has been observed with PET by using [18F]-FEPPA [262]. Moreover, it was found a significantly increase numbers of T-helper 17 cells and myeloid-derived suppressor cells in peripheral circulation in PD patients compared with controls [263]. This suggests that a microglial-mediated inflammatory process occurs early in PD process.

It has also been demonstrated that mitochondrial toxins, such as 6-OHDA, MPTP and rotenone, trigger an immune reaction in the striatum and SNpc suggesting that a primary damage to the mitochondrial respiratory chain represents, per se, a trigger for microglial activation and neuroinflammatory processes [264–267]. This reaction includes activation of microglia and infiltration of CD4+ and CD8+ T cells. Rotenone administration was shown to cause microglial activation not only in rodent models [268] but also in human microglial cell lines [269]. Similarly, a significant increase in the number of activated microglial cells was detected in the brain of 6-OHDA rats, at both nigral and striatal areas [233, 270]. Moreover, in the same model CD+3, CD+4 and CD+8 T cells were abundant and migrated from blood vessels into the SNpc [271]. Additionally, in the brains of both monkeys and mice after systemic injection of MPTP, an activated microglia and infiltration of T-lymphocytes has been observed [197]. Microglial activation was also observed in mice that overexpress SNCA [213], in the SNpc and striatum of rats exposed to 6-OHDA [272, 273] and to MPTP [274].

Interestingly, intranigral or systemic injection of LPS in animals can selectively kill dopaminergic neurons [200, 275–279]. Furthermore, injection of LPS into pregnant female rats led to offspring with less and abnormal dopaminergic neurons and increased levels of TNFα in the striatum when compared to the controls [280]. Remarkably, the offspring in adulthood were also more susceptible to the effects of parkinsonian toxins than were the controls [281, 282]. Furthermore, the injection of other proinflammatory compounds such as thrombin within the SNpc also induced the death of dopaminergic neurons [283, 284]. These studies suggest that microglia-mediated inflammation underlies the neuronal cell death in the SNpc.

As previously mentioned, microglial cells when activated produce and release toxic oxygen-derived and nitrogen-derived products, which rely on the regulated induction of several enzymatic systems such as NADPH oxidase and iNOS.Indeed, the expression of these biocatalytic systems within the SNpc is significantly increased in PD patient's post-mortem samples as well as in PD animal models [239, 247]. Oxygen and nitrogen-derived products such as NO, O_2^- and $ONOO^-$ can directly cross membranes and enter dopaminergic neurons, which can cause oxidative damage in tyrosine hydroxylase decreasing its enzymatic activity and in SNCA promoting its aggregation [285, 286]. Additionally, activated microglia can release inflammatory cytokines and chemokines, such as TNFα, interleukin 1β and interferon,whichcan induce neurotoxicity via a direct mechanism through receptor binding on dopaminergic neurons or an indirect mechanism through glial-cell activation and expression of inflammatory factors. In fact, chronic adenoviral expression of TNFα in the SNpc of rats can cause time-dependent dopaminergic cell death [287].

4. The interplay between mitochondria and innate immunity

In response to microbial infection, the mammalian innate immune system recognizes invading microorganisms and orchestrates a proinflammatory immune response to eliminate the undesired pathogens and infected cells. The sensing of the infection by the innate immune system is mediated by a variety of pattern recognition receptors (PRRs), which recognize molecular patterns conserved among microbial species known as PAMPs. For detailed information regarding the different families of receptors, respective PAMPs recognition, and the intracellular signaling cascades triggered, see reference [288]. Interestingly, even in the absence of microbial infection, PRRs sense and orchestrate inflammatory responses through recognition of intracellular molecules known as DAMPs. DAMPs are endogenous molecules sequestered within cellular compartments of healthy cells, which, upon injury or stress, are released to trigger sterile proinflammatory immune responses.

Recent insights revealed that mitochondria are an important source of DAMPs. Interestingly, upon injury, both mtDNA and N-formylated peptides can act as DAMPs. This is due to the fact that mitochondria and bacteria display some similarities in that both possess circular DNA, N-formylated proteins and are double-membrane structures—evidence used in support of the endosymbiotic theory. mtDNA is similar to bacterial DNA in that it contains CpG motifs, which activate the TLR9 [289, 290]. Moreover, mitochondrial protein synthesis is initiated with the residue N-formyl methionine, similar to bacterial protein synthesis [291]. The resulting bacterial N-formylated peptides are known to act as PAMPs by binding and activating G protein-coupled formyl peptide receptors (FPRs) [292], while the mitochondrial N-formylated peptides act as DAMPs through activation of the formyl peptide receptor 1 [290]. Therefore, upon injury, release of these mitochondrial DAMPs activates the innate immune system, much like bacterial PAMPs, to promote sterile inflammatory responses [290].

Several studies have now described a crucial role for mitochondria in the regulation and activation of the inflammasome, specifically the NLRP3 inflammasome [293]. The inflammasomes are intracellular molecular platforms activated upon cellular infection or sterile stressors, which activate the proinflammatory cytokines, interleukin-1β (IL-1β) and IL-18, to trigger pyroptotic cell death (reviewed in [294, 295]). A variety of insults, resulting from cellular infection or stress, can promote mitochondrial dysfunction and activate the NLRP3 inflammasome [293]; however, the molecular mechanisms underlying the contribution of mitochondria to the activation of the NLRP3 inflammasome have only recently been described. While initial studies showed that mitochondrial dysfunction and mtROS production are required for NLRP3 inflammasome activation [296, 297], further evidence has shown that mtDNA translocation to the cytosol plays an active role in this process [297, 298], where it can directly bind to and activate the NRLP3 inflammasome [298]. In addition, the mitochondrial lipid cardiolipin—a phospholipid located exclusively in mitochondrial inner and bacterial membranes, regarded as evidence for symbiogenesis [299, 300]—is also required for NLRP3 inflammasome activation, by directly binding to NLRP3, downstream of mitochondrial dysfunction [301]. Altogether, mitochondria and mitochondrial DAMPs (such as mtDNA and cardiolipin) play a critical role in NLRP3 inflammasome activation and regulation. Moreover, by sensing mitochondrial DAMPs, the NLRP3 inflammasome plays a critical role in integrating mitochondrial dysfunction in a proinflammatory signaling response, thus explaining the association of mitochondrial damage with inflammatory diseases.

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Despite the great number of studies describing mitochondria as a source of DAMPs during inflammation in the periphery, the potential for mitochondrial DAMPs to trigger, or exacerbate, inflammation in the brain is now being explored. In recent studies, this potential was tested by treating different brain cell types with mitochondrial components and measuring markers of inflammation afterwards. Neuronal and microglial cell lines exposed to mitochondrial lysates displayed increased markers of inflammation, with mtDNA being identified as the candidate DAMP responsible for the inflammatory changes [95]. While SH-SY5Y neuronal cells treated with mitochondrial lysates showed increased TNFα mRNA, decreased IκBα protein and increased NF-κB protein, microglial cells treated with mitochondrial lysates showed increased TNFα mRNA, increased IL-8 mRNA and redistribution of NF-κB to the nucleus [95]. In a different study, extracellular recombinant Tfam treatment of different models of human microglia, in combination with IFN-Υ, was shown to induce secretions that were toxic to SH-SY5Y neuronal cells [302]. Recombinant Tfam treatment induced the expression of proinflammatory cytokines, such as IL-1β, IL-6 and IL-18, supporting the hypothesis that Tfam may also act as a proinflammatory intercellular signaling molecule recognized by brain microglia [302]. Moreover, mice injected with isolated mitochondria into the brain also revealed increased markers of inflammation such as increased Tnfα, increased NF-κB phosphorylation, increased GFAP protein and decreased Trem2 mRNA [94]. Despite these novel findings describing a role for extracellular mitochondrial DAMPs as proinflammatory signaling molecules in the brain, little is known about the mechanisms by which mitochondria act as a transcellular signaling platforms in the CNS. Recent research revealed that neurons and astrocytes can exchange mitochondria as a potential mode of cell-to-cell signaling [303, 304]. Whilean initial study showed that retinal ganglion cell axons can transfer mitochondria to adjacent astrocytes for degradation [303], mitochondria can also be transferred from astrocytes to adjacent neurons during ischemia to amplify cell survival signals [304], thus representing a neuroprotective strategy or a more efficient way to dispose/recycle mitochondria. However, during neurodegeneration, increased disposal of damaged mitochondria by compromised neurons (e.g. due to compromised mitochondrial quality control mechanisms) or its inefficient uptake by the recipient astrocytes (e.g. due to the presence of extracellular protein aggregates) might result in extracellular accumulation of mitochondrial DAMPs and, as a result, exacerbating neuroinflammation. Further research is necessary to test this hypothesis and identify the PRRs in the brain that are responsible for recognizing extracellular mitochondrial DAMPs; nevertheless, these studies suggest that mitochondria play an active role in neuroglial crosstalk during cellular homeostasis and stress.

5. Concluding comments

Although the innate immune system has specialized in the recognition of molecular patterns foreign to the host cells, cellular injury or stress may result in the release of endogenous molecular patterns, which trigger sterile inflammatory responses. Given its bacterial origin, mitochondria display some similarities with bacteria and represent an important source of DAMPs (including lipids, nucleic acids and proteins) with immunostimulatory potential. While under healthy conditions these DAMPs are sequestered within mitochondria, pathological insults resulting in mitochondrial and cellular damage promote the release of these

danger signals to cause inflammation mediated by the innate immune system. Recent studies have shown that mitochondrial DAMPs have the potential to mediate inflammatory signaling in the brain; therefore, its contribution to the neuroinflammatory process in neurodegenerative disorders characterized by impaired mitochondrial function represents an emerging and promising field of research (**Figure 1**).

Further understanding of neuronal innate immunity-induced chronic mild neuroinflammation and its impact on age-related neurodegenerative disorders should focus on new studies addressing not only mitochondrial dysfunction and protein oligomerization but also mild inflammation, nutritional states, among others. The development of new biomarkers focusing on the inflammatory process and the identification of protective inflammatory processes should be pursuit. Additionally, exploiting the effect of mutations, epigenetic and the microbiome on immune-related modifications affecting the AD and PD phenotypes will be of paramount relevance to understand etiology of both diseases.

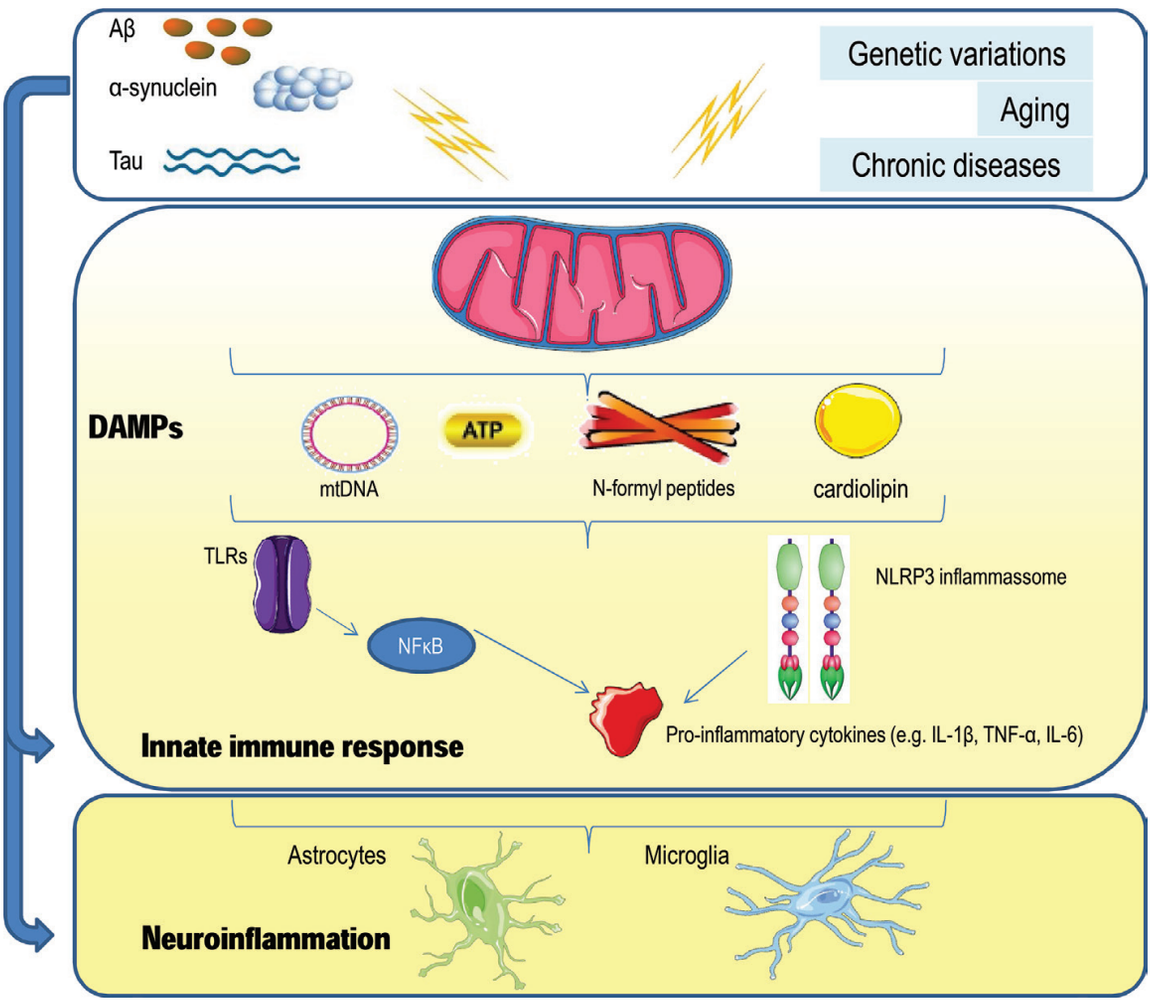

Figure 1. Mitochondria are primary targets of cellular peptides, such as Aβ, tau and SNCA, overproduced during AD and PD pathogenesis. Damaged mitochondria are a source of DAMPs that activate the NLRP3 inflammasome and TLRs leading to the intraneuronal production of cytokines. These proinflammatory cytokines are released and activate innate immune response through microglia and astrocytes. This chronic inflammation impacts neurons exacerbating peptides formation and mitochondrial damage.

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