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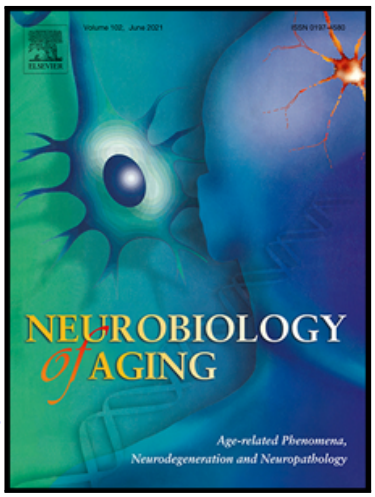

Fatal attraction – The role of hypoxia when alpha-synuclein gets intimate with mitochondria

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Fatal attraction – The role of hypoxia when alpha-synuclein gets intimate with mitochondria

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Authors' contributions

J.B.: conception and design, drafting and finalization of the manuscript and figures. M.M.K.S.: conception and design, finalization of the manuscript. M.A.K., H.A.L. & G.P.M.: finalization of the manuscript. All authors read and approved the final article.

Highlights

- Hypoxic stress influences alpha-synuclein aggregation and mitochondrial dysfunction
- Hypoxia and acidification may increase the toxicity of alpha-synuclein aggregates
- Hypoxia might drive Parkinson's disease pathogenesis

Abstract

Alpha-synuclein aggregation and mitochondrial dysfunction are main pathological hallmarks of Parkinson's disease (PD) and several other neurodegenerative diseases, collectively known as synucleinopathies. However, increasing evidence suggests that they may not be sufficient to cause PD. Here we propose the role of hypoxia as a missing link that connects the complex interplay between alpha-synuclein biochemistry and pathology, mitochondrial dysfunctions and neurodegeneration in PD. We review the partly conflicting literature on alpha-synuclein binding to membranes and mitochondria and its impact on mitochondrial functions. From there, we focus on adverse changes in cellular environments, revolving around hypoxic stress, that may trigger or facilitate PD progression. Inter-dependent structural re-arrangements of mitochondrial membranes, including increased cytoplasmic exposure of mitochondrial cardiolipins – and changes in alpha-synuclein localization and conformation are discussed consequences of such conditions. Enhancing cellular resilience could be an integral part of future combination-based therapies of PD. This may be achieved by boosting the capacity of

cellular – and specifically mitochondrial – processes to regulate and adapt to altered proteostasis, redox, and inflammatory conditions and by inducing protective molecular and tissue re-modelling.

1. Mitochondrial dysfunction and alpha-synuclein pathology in Parkinson's Disease

Parkinson`s Disease (PD) is the most common neurodegenerative motor disease. It is characterized mainly by motor - but also non-motor - symptoms and a selective loss of neurons, most notable dopaminergic neurons in the substantia nigra.

On the molecular level, two potentially inter-related pathological processes are of particular interest for a better understanding of PD disease progression: (1) mitochondrial dysfunction and (2) alpha-synuclein misfolding and aggregation, resulting in Lewy pathology in PD and Dementia with Lewy bodies (DLB). Aggregated alpha-synuclein in Multiple Systems Atrophy (MSA) is mainly found in oligodendrocytes and termed glial cytoplasmic inclusions there (Takeda et al., 1997; Tu et al., 1998; Wakabayashi et al., 1998). Undoubtedly, other, inter-dependent pathological processes, such as neuroinflammation (Hirsch and Standaert, 2020), impairment of protein clearance machineries (Bellomo et al., 2020), synaptic pathologies (Wong et al., 2019) and others influence the development and progression of PD. The disentanglement of the contributions and synergistic/antagonistic interplay between these factors represents a major challenge for research on PD. Detailed knowledge of the crosstalk between the involved pathways is necessary to improve PD models and to develop novel curative treatment strategies.

Here, we discuss the complex molecular interplays leading to Lewy pathology, mitochondrial dysfunction, and neurotoxicity, with a focus on the potentially central role of hypoxia. Despite emerging evidence on a disease-progression determining influence of cellular oxygen-levels (discussed in section 1.3), the effects of hypoxia on the interplay between mitochondrial and proteostatic dysfunctions in PD are poorly understood. The development of an integrated

model, therefore, is important to inspire new research on the role of brain hypoxia in PD that could ultimately result in improved translational efficiency of PD models.

1.1 Mitochondrial dysfunction in PD – cracks in the powerplant

Mitochondrial dysfunction is a common feature of neurodegenerative diseases and is particularly prominent in PD (for review see (Greenamyre, 2018)). Interest in the role of mitochondrial dysfunction in PD was kindled when Langston and colleagues (Langston et al., 1983) reported L-dopa responsive Parkinsonism in young men, who had injected themselves with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). MPTP is specifically taken up into dopaminergic neurons, where it is oxidized by monoamineoxidase to 1-methyl-4-phenylpyridinium (MPP+) (Storch et al., 2004), leading to inhibition of complexes I, III, and IV of the mitochondrial respiratory chain (Desai et al., 1996). MPTP-based approaches subsequently became standard preclinical models for the characterization of PD mechanisms and to test potential drugs for the treatment of PD (Tetrud and Langston, 1989). Other complex I inhibitors, such as the pesticide rotenone, were found to induce PD-like symptoms as well, although most of them do not specifically target dopaminergic neurons. Genetically disrupted mitochondrial function in the mouse substantia nigra also results in PD-like pathology (Ekstrand et al., 2007).

In human patients of sporadic PD, respiratory chain deficiencies (linked in particular to complex I of the electron transport chain) have been repeatedly reported in a wide array of tissues, including the substantia nigra, striatum, skeletal muscle, platelets, and lymphocytes, as recently summarized (Bose and Beal, 2016). Moreover, several of the genes linked to familial PD are associated with the maintenance of mitochondrial integrity (see reviews of (Cieri et al., 2017; Grünewald et al., 2019)). Besides electron transport chain deficits, several

other mitochondrial dysfunctions have been reported in PD patients' brains, such as deficiencies in mitochondrial dynamics and interactions with other cellular organelles that have previously been reviewed (Bose and Beal, 2016)).

Interestingly, many PD-related mitochondrial dysfunctions are related to the protein most tightly linked to PD pathology, alpha-synuclein.

1.2 Alpha-synuclein in PD – breaking bad

The association of misfolded and aggregated forms of alpha-synuclein with PD became very clear when mutations and multiplications of the gene *SNCA* (encoding alpha-synuclein) were observed to cause PD (for review see (Lashuel et al., 2013)). Subsequently, aggregates of the protein were reported to constitute the major part of Lewy Bodies and Lewy Neurites (Spillantini et al., 1997). Alpha-synuclein is an abundant protein in the mammalian brain and its abundance may even be increased after injury (Busch and Morgan, 2012; Kholodilov, Nikolai G et al., 1999; Kim et al., 2016; Mondello et al., 2013; Su et al., 2010; Unal-Cevik et al., 2011), likely related to consequences of resulting hypoxic conditions, as discussed in section 4.2.

Despite the presence of increasingly widespread alpha-synuclein pathology in PD-patient brains with advancing disease stage, only specific nuclei, among them most prominently the lateral substantia nigra pars compacta, succumb to neurodegeneration. High bioenergetic demand - and thus high reliance on oxygen - is a major suspected factor contributing to selective neuronal vulnerability in synucleinopathy, and has previously been reviewed (Pacelli et al., 2015).

2. From physiology to pathology: alpha-synuclein interactions with (mitochondrial) membranes

Although the physiological functions of alpha-synuclein are still debated (Sulzer and Edwards, 2019), its role in synaptic transmission (Abeliovich et al., 2000; Burre et al., 2010) and exocytosis (Logan et al., 2017) is well-documented in the literature. Alpha-synuclein also interacts with mitochondria but despite much research in this field, the effects of this interplay in physiology and pathology are poorly understood. Alpha-synuclein's attraction to membranes, however, is likely a key determinant of its interaction with mitochondria.

2.1 The attraction of alpha-synuclein to lipids and membranes

Alpha-synuclein – lipid binding and its interactions with membranes are well documented (Nakamura et al., 2008; Parihar et al., 2008; Pfefferkorn et al., 2012; Pirc and Ulrih, 2015) and have recently been reviewed in more detail than the scope of this review allows by Ugualde and coworkers (Ugalde et al., 2019) and by Iyer and Claessens (Iyer and Claessens, 2019). While increased misfolding and/or aggregation of alpha-synuclein is associated with lipid binding *in vitro*, the *in vivo* relevance is unclear. However, the presence of lipids and membranes in Lewy bodies or Lewy body-like inclusions (den Jager, 1969; Duffy and Tennyson, 1965; Forno and Norville, 1976; Gai et al., 2000; Shahmoradian et al., 2019; Wakabayashi et al., 1998) in neurons suggests a role of lipid-synuclein interactions in Lewy body formation *in vivo*. A recent study furthermore reports altered interactions of alpha-synuclein with plasma membranes upon changes in lipid compositions that are linked to neurodegenerative diseases (Man et al., 2021).

In neurons, alpha-synuclein is localized preferentially at presynaptic terminals, especially in proximity to lipid rafts (Fortin et al., 2004). Alpha-synuclein (having no transmembrane domains or lipid anchor) interaction with membranes is influenced by several factors, including lipid class preference (Bartels et al., 2010; Galvagnion et al., 2016) or membrane curvature (Nuscher et al., 2004), as recently reviewed (Ugalde et al., 2019). Upon association with membranes / lipid vesicles, alpha-synuclein adopts an alpha-helical conformation (Bussell Jr and Eliezer, 2003; Davidson et al., 1998). This conformational change concerns mainly the N-terminal domain of the protein (see Fig. 1A) (Jao et al., 2004; Jao et al., 2008; Perrin et al., 2000), and has been demonstrated to induce remodeling of the interacting membranes (Bodner et al., 2009). It is important to point out that most studies on alpha-synuclein-membrane interactions are based on using artificial small unilamellar vesicles (SUVs) or planar lipid bilayers as model systems. In the case of SUVs, composed of a mixed lipid composition, alpha-synuclein's first 12 residues anchor the protein to the SUV lipids (Fusco et al., 2016). Deletion of any of the three exons encoding the N-terminus of alpha-synuclein abolishes phosphatidylserine-containing vesicle binding and leads to a reduced membrane binding capacity (Perrin et al., 2000). Lipid composition, the protein to lipid ratio, alpha-synuclein conformation and other factors influence this interaction, as recently reviewed (Ugalde et al., 2019), limiting generalization to biological conditions.

The interaction of alpha-synuclein with lipid membranes has been suggested to facilitate amyloid fibril formation depending on the lipid type (Galvagnion et al., 2016) or by simply increasing local alpha-synuclein concentrations and inducing molecular crowding (Galvagnion et al., 2015; Uversky et al., 2002). On the other hand, the helical conformation of the membrane-bound alpha-synuclein has been proposed to prevent fibrillization, while dissociation of alpha-synuclein from membranes might initiate the aggregation process by

increasing cytosolic alpha-synuclein concentrations, thus favoring its aggregation (Zhu and Fink, 2003).

These seemingly contradictory observations could be attributed to differences in lipid composition, membrane types and *in vitro* and cellular models used by different laboratories.

2.2 Interaction of alpha-synuclein with mitochondria

Similar to vesicle trafficking defects, mitochondrial dysfunction may result from pathological interactions of alpha-synuclein with membranes. Although it is clear that alpha-synuclein can localize to mitochondria, as previously reviewed (Pozo Devoto and Falzone, 2017), how it mechanistically interacts with mitochondria is still debated. The N-terminus of alpha-synuclein (figure 1A) has been shown to play an important role in regulating alpha-synuclein interactions with mitochondrial membranes (Devi et al., 2008; Ulmer et al., 2005). In addition, both soluble and aggregated forms of alpha-synuclein have been reported to interact with mitochondrial proteins, predominantly mediated by the C-terminus of alpha-synuclein, as recently summarized (Vicario et al., 2018). Prominent examples of such mitochondrial proteins are the outer mitochondrial membrane proteins TOM20, TOM40, and VDAC; the latter is known to at least interact with overexpressed human A53T alpha-synuclein (Martin et al., 2014). Interaction of the 1-65 amino acid fragment of alpha-synuclein with adenine nucleotide translocator (ANT), an abundant protein of the inner mitochondrial membrane, has also been demonstrated (Shen et al., 2014). Furthermore, physical interaction of alpha-synuclein has been shown for ATP-synthase subunit alpha (Ludtmann et al., 2016), mitochondrial complexes I and IV (Vicario et al., 2018) of the electron transport chain, and other mitochondrial proteins.

Alpha-synuclein interactions with mitochondrial proteins as main drivers for binding of mitochondria *in vivo*, should be interpreted cautiously. In our opinion, the evidence for mitochondrial membrane binding, in particular, mediated by cardiolipins (see section 3.2) is stronger (figure 1B).

3. Consequences of the interaction of alpha-synuclein with mitochondria

Given the strong affinity of alpha-synuclein for mitochondria, the question arises: how do these interactions (or a lack thereof) contribute to alpha-synuclein pathology formation? In a model of aging yeast, the presence of functional mitochondria was strictly necessary for clustering of alpha-synuclein (which, however, may not consist of pathological aggregates and thus may not be relevant for PD) to be toxic for cells (Büttner et al., 2008). Importantly, synuclein proteins are relatively well conserved across vertebrates but appear to have no homologues in invertebrate model organisms, like yeast. While we are not aware of similar studies in more readily translatable models for PD, this observation may indicate a distinct role of the combination of mitochondria and abnormalities in alpha-synuclein biochemistry for toxicity. In line with these findings are observations of high concentrations of alpha-synuclein in mitochondrial fractions obtained from PD-patient post-mortem brain tissue (Devi et al., 2008). Given the importance of the combination of both mitochondrial dysfunction and alpha-synuclein pathology (Figure 2), the chicken-and-egg question in PD pathogenesis is: does alpha-synuclein pathology form due to mitochondrial dysfunction (Figure 2B), or is mitochondrial damage the consequence of alpha-synuclein aggregation and/or pathology formation (Figure 2C)? This dichotomous way of asking the question may, however, be limiting. We propose that other factors, in particular hypoxia and the capacity of the organism

to respond to it, determine the occurrence of reciprocal and concomitant pathological processes affecting both alpha-synuclein proteostasis and mitochondrial function as defining components of PD pathogenesis (Figure 2D). This concept is supported by modulating effects of metabolic deficits or inflammation on alpha-synuclein pathology toxicity and aggregation kinetics in synucleinopathy mouse models, as recently demonstrated (Peelaerts et al., 2020).

Although the causalities remain to be clarified, manifold mitochondrial dysfunctions have been linked to alpha-synuclein pathology and *vice versa*. A simplified summary is depicted in Figure 3 and discussed below. Of particular interest for the present review are the reciprocal effects of alpha-synuclein pathology on oxygen-dependent mitochondrial respiration and on cardiolipins.

3.1 Mitochondrial respiration and alpha-synuclein pathology

Given its reliance on oxygen, mitochondrial respiration could be impaired if hypoxia is a main component of alpha-synuclein pathology and PD pathogenesis. While in some PD models of mitochondrial respiration dysfunction alpha-synuclein pathology ensues (Betarbet et al., 2000; Nisticò et al., 2011; Tieu, 2011) (partially supporting the hypothesis depicted in Figure 2B), it is not clear whether the reverse happens; i.e., whether induction of alpha-synuclein pathology is sufficient to induce mitochondrial respiration deficits. However, alpha-synuclein upregulation (even in absence of oligomerization) has been reported to induce complex I inhibition (Loeb et al., 2010). As *vice versa* complex I inhibition, e.g. in models of chronic MPTP administration (Vila et al., 2000), can also upregulate alpha-synuclein levels. This interaction potentially represents a vicious cycle.

Physiological levels of alpha-synuclein have been suggested to be required for normal mitochondrial respiration (Devi et al., 2008; Ellis et al., 2005; Ludtmann et al., 2016) and

limited oxidative stress (Menges et al., 2017). Monomeric alpha-synuclein enhances ATP-synthase activity (Ludtmann et al., 2016), specifically if alpha-synuclein is localized in the mitochondrial matrix (Vicario et al., 2019). Conversely, oligomeric forms of alpha-synuclein have been demonstrated to impair complex-I linked respiration, leading to specific ATP-synthase oxidation and increased cell death probability (Ludtmann et al., 2018). While alpha-synuclein levels in the mitochondrial matrix physiologically are low - and the physiological relevance in mitochondria thus remains somewhat speculative - , they increase in response to various cellular stressors (ROS, inhibition of lysosome acidification, or electron transport chain) (Vicario et al., 2019). This suggests a potential compensatory mechanism by which alpha-synuclein is translocated to the mitochondrial matrix in order to boost respiration, e.g. to counteract insufficient oxygen supply.

Alpha-synuclein targeted to mitochondria in differentiated dopaminergic human neurons (LUHMES cells), however, compromises mitochondrial structure and function (Ganjam et al., 2019). This could reflect the vulnerability of human dopaminergic neurons; or the limitations of alpha-synuclein overexpression models; e.g., with regard to overexpression levels and precise localization of the transgene product. A suppression of mitochondrial ATP-dependent Clp protease (ClpP) by alpha-synuclein with detrimental effects on mitochondrial respiration constitutes one explanation of the harmful effects that alpha-synuclein may exert within mitochondria (Hu et al., 2019).

In the neuronal seeding model of alpha-synuclein pathology, impaired mitochondrial respiration has been demonstrated recently in different preparations of mouse primary neurons, in mouse cortical neurons (Wang et al., 2019), mouse hippocampal neurons (Mahul-Mellier et al., 2020) or rat midbrain neurons (Tapias et al., 2017). Importantly, deficits in mitochondrial respiration appear to require very high concentrations of exogenous alpha-synuclein fibrils (Tapias et al., 2017; Wang et al., 2019) or long culturing *in vitro* to

precipitate (Mahul-Mellier et al., 2020). Conversely, acute exposure of SH-SY5Y cells to misfolded alpha-synuclein causes increased mitochondrial respiration, without apparent dysfunction (Ugalde et al., 2020). SH-SY5Y, however, is a tumor-derived cell-line, the responses of which do not necessarily reflect the responses of neurons challenged with misfolded alpha-synuclein. Furthermore, early stage alpha-synuclein pathology in mouse striatum and amygdala was not sufficient to cause either respirational deficits or increased ROS production (Burtscher et al., 2020). In line with these pre-clinical findings, a lack of correlation between complex I deficits and neurodegeneration in PD patient brains has been reported (Flønes et al., 2018). It is important to note that in these latter studies, brain tissues consisting of mixed cell populations were investigated. How alterations of mitochondrial functions of different cell types in PD or PD-model brains, as well as of neurons affected or not affected by Lewy pathology, contribute to the overall bioenergetics status of the tissue, remain open questions.

Taken together, these findings are not yet sufficient to establish any direct causality between alpha-synuclein pathology and mitochondrial dysfunction.

3.2 The role of cardiolipins

Approximately 10-20% of mitochondrial membrane phospholipids are the non-lamellar phospholipids cardiolipins; they are phospholipids exclusive for mitochondria and especially enriched in the inner mitochondrial membrane, as previously reviewed (Horvath and Daum, 2013). In contrast to most other lipids, cardiolipins are glycerol-bridged dimers of two phosphatidyl moieties, generating a unique structure with four rather than only two fatty acyl side chains. The resulting combinatory diversity of possible molecular species is also responsible for the fact that cardiolipin - at least in theory - is one of the most variable lipid classes (Oemer et al., 2018). This diversification is however counteracted by the process of

cardiolipin remodeling, which iteratively exchanges acyl side chains to optimally match the respective circumstances and environment, as summarized elsewhere (Schlame, 2013). Cardiolipins are actively involved in a series of central mitochondrial functions (as previously reviewed (Paradies et al., 2019)), including the structural organisation of the inner mitochondrial membrane (reviewed elsewhere (Ren et al., 2014)), the stabilisation and assembly of protein complexes therein (including respiratory supercomplexes) (Pfeiffer et al., 2003; Senoo et al., 2020), the release of cytochrome C from mitochondria as part of the apoptotic signaling process (Ott et al., 2007), as well as by acting as potent ROS scavengers – as outlined in another review (Kagan et al., 2014).

Cardiolipins exhibit a particularly strong and specific affinity for alpha-synuclein (Cole et al., 2008; Ghio et al., 2016) especially in its oligomeric forms (Nakamura et al., 2011). Apart from a direct specificity for cardiolipins, alpha-synuclein binds mitochondrial cristae due to its high affinity for highly curved membranes (Middleton and Rhoades, 2010). Thus, the role of cardiolipins to effectuate the high curvature of mitochondrial cristae, based on cardiolipin structures (Elías-Wolff et al., 2019) is a further relevant feature for alpha-synuclein binding to mitochondrial membranes.

Cardiolipin-acyl substitution patterns are highly tissue-, cell type- and species-dependent (Oemer et al., 2018). In the mammalian brain they are particularly unusual and different from other tissues (Tyurina et al., 2014), due to the cell-specific phospholipid-bound acyl pool (Oemer et al., 2020b) and the associated strong responses to the local fatty acid availability (Oemer et al., 2020a). The linoleic acid-depleted lipid environment in the brain (Anderson and Connor, 1988) and a strong enrichment of arachidonic and docosahexaenoic acid (Oemer et al., 2020b) generate a highly unsaturated and long chained cardiolipin species that may further facilitate the interaction with alpha-synuclein.

The composition of the inner mitochondrial membrane, importantly based on cardiolipins (Paradies et al., 2019), allows the formation of a mitochondrial membrane potential, which maintains the proton-motive force generated by the electron transport chain to be used by ATP-synthase to generate ATP. The membrane potential and cardiolipins are also prerequisites for functional mitochondrial import (Paradies et al., 2019; Zorova et al., 2018). Conversely, aggregated alpha-synuclein in neurons has been shown to impair the mitochondrial membrane potential (Reeve et al., 2015) and alpha-synuclein oligomers (but not monomers or fibrils) have been reported to impair mitochondrial import (Di Maio et al., 2016). Accordingly, the recently reported neuroprotection by overexpression of TOM20 in a rat model of synucleinopathy seems also to be mediated by rescued mitochondrial import (De Miranda et al., 2020). Besides their involvement in mitochondrial membrane potential maintenance, cardiolipins also improve mitochondrial bioenergetics efficiency by stabilization of the electron transport chain complexes and their arrangement in respiratory super complexes (Pfeiffer et al., 2003) (see review by (Paradies et al., 2014)). Accordingly, supplementation of mitochondria with cardiolipin rescues complex I deficiencies in the Pink1 drosophila model of PD (Vos et al., 2017).

Cardiolipins in the outer mitochondrial membrane have been demonstrated to specifically bind alpha-synuclein fibrils leading to a reduction in their beta-sheet content, which may be indicative of a potential capability of cardiolipins to dis-aggregate alpha-synuclein fibrils (Ryan et al., 2018). Alpha-synuclein, however, has been demonstrated to disrupt cardiolipin containing artificial membranes (Nakamura et al., 2011) and overexpression of alpha-synuclein depleted cardiolipins in cells (Shen et al., 2014) and in isolated mitochondria from mouse brain (Gao et al., 2017). As no change in cardiolipin levels was observed in the substantia nigra of PD patients (Seyfried et al., 2018), the relevance of this effect for pathology formation and disease progression remains to be elucidated. Intriguingly, however,

it has been shown that alpha-synuclein is enriched in mitochondria in the substantia nigra and striatum of PD patients, which coincided with reduced complex I activity in these brain regions (Devi et al., 2008). Specifically, alpha-synuclein was located primarily at the inner mitochondrial membrane and thus at the membrane with the highest reported cardiolipin density.

In another study (Ugalde et al., 2020) cardiolipins were confirmed as binding partners for misfolded alpha-synuclein and this association accelerated alpha-synuclein fibrillization and possibly favored the generation of alpha-synuclein species that are more resistant to proteolytic cleavage. Mitochondrial cell death regulation by opening of the mitochondrial permeability transition pore (mPTP) and release of cytochrome c is influenced by the interaction of alpha-synuclein with mitochondria (Parihar et al., 2008). In particular oligomeric alpha-synuclein seems to induce mPTP opening (Ludtmann et al., 2018). Cardiolipins have been reported to be involved in alpha-synuclein oligomer mediated pore formation in mitochondria, also leading to release of cytochrome c and the induction of cell death pathways (Ghio et al., 2019).

Cardiolipin remodelling may furthermore influence alpha-synuclein aggregation and - *vice versa* - it may be influenced by alpha-synuclein levels. Depletion of the acyltransferase ALCAT1, which is involved in pathological remodeling of cardiolipins, has recently been demonstrated to prevent alpha-synuclein oligomerization as well as MPTP-induced neurotoxicity and mitochondrial and motor deficits in mice (Song et al., 2019). Accordingly, increased ALCAT1 expression was observed in a mouse MPTP-model and in a mouse alpha-synuclein overexpression model (Song et al., 2019).

Future studies to systematically address remaining knowledge gaps on the precise role of cardiolipins in synucleinopathy pathogenesis in well-defined models with high translational potential will be of great importance.

3.3 Interactions of alpha-synuclein with other mitochondrial functions

Some further important interdependences of alpha-synuclein and mitochondrial functions are very briefly discussed below.

First, mitochondrial ROS formation and resulting oxidative stress are positively correlated with alpha-synuclein aggregation (Hashimoto et al., 1999; Ostrerova-Golts et al., 2000) and oligomerization (Xiang et al., 2013). Also, overexpression (Hsu et al., 2000) or aggregation (Reeve et al., 2015) of alpha-synuclein in rat neuroblastoma cells as well as *in vivo* in mice (Bender et al., 2013) is associated with increased oxidative stress. The reciprocal effects of oxidative stress and alpha-synuclein aggregation with feed forward loop potential may represent a central feature of PD pathology formation but require better understanding. Although the importance of oxidative stress in PD has been long acknowledged, translatability of this knowledge to clinic advances has proved difficult, as highlighted by multiple reviews (Filograna et al., 2016; Grunewald et al., 2018).

The pronounced interdependence between mitochondrial dynamics (changes in mitochondrial morphology by fusion and fission events) and alpha-synuclein pathology and the roles of mitophagy in PD have recently been reviewed (Grunewald et al., 2018; Pozo Devoto and Falzone, 2017). Due to the complex regulation and consequences of changes in mitochondrial dynamics (see the recent review of (Giacomello et al., 2020)), the interaction of alpha-synuclein pathology and mitochondrial dynamics is not yet well understood. Similarly, reports on intra-cellular transport (trafficking) of mitochondria are conflicting: pathological alpha-

synuclein has been linked to downregulated (Melo et al., 2017; Pozo Devoto et al., 2017) but also to pathologically upregulated (Shaltouki et al., 2018) mitochondrial motility.

Another important emerging aspect of alpha-synuclein pathology relates to its impact on mitochondria-associated membranes (MAM) (Guardia-Laguarta et al., 2014), including endoplasmic reticulum -mitochondria associations. These have been demonstrated to be disrupted by overexpression of wild-type and mutated (A53T and A30) alpha-synuclein, perturbing inter-organellar calcium homeostasis and reducing ATP-production by inhibition of the tricarboxylic acid cycle (TCA) (Paillusson et al., 2017). The effect of alpha-synuclein on MAMs has been reviewed elsewhere (Guardia-Laguarta et al., 2015; Vicario et al., 2018).

4. Modulation of alpha-synuclein pathology and mitochondrial dysfunction by hypoxic stress

Given the pronounced interaction of alpha-synuclein and mitochondria and the potential damage it can cause, the question arises, under which circumstances is this harmful and contributes to PD disease progression? The central hypothesis of this review is that hypoxic stress and the capability to adapt to it are crucial determinants of that interaction.

4.1 Physiological responses of alpha-synuclein to cellular stress and injury

Alpha-synuclein is thought to fulfill several roles to maintain mitochondrial function and integrity, including bioenergetics, calcium homeostasis etc. Upon cellular injury, usually involving hypoxia, alpha-synuclein levels have been reported to be altered. While monomeric alpha-synuclein levels have been observed to be reduced in the hippocampus and – less

severely – in cortex and striatum after controlled cortical injury in rats (Carlson et al., 2021), most studies support increased alpha-synuclein levels after injury; such an upregulation has been reported in "poor survivor" reticulospinal neurons in lamprey brain after spinal cord injury (Busch and Morgan, 2012), in rat substantia nigra (Kholodilov, N. G. et al., 1999) and in mouse cortex after ischemic insult (Unal-Cevik et al., 2011) that was also associated with increased nuclear localization of alpha-synuclein (Kim et al., 2016). Total and phosphorylated (pS129) alpha-synuclein levels are also elevated in plasma of obstructive sleep apnea (OSA) patients (Sun et al., 2019), as is monomeric alpha-synuclein in the cerebrospinal fluid of children (Su et al., 2010) and adults (Mondello et al., 2013) after traumatic brain injury. Neuronal upregulation of alpha-synuclein results in nuclear and mitochondrial localization of alpha-synuclein (Vicario et al., 2019), where it possibly exerts reparative tasks, such as enhancing DNA-repair in the nucleus (Paiva et al., 2017; Schaser et al., 2019; Vasquez et al., 2020), boosting oxidative phosphorylation in the mitochondria and regulating mitochondrial dynamics, trafficking, and inter-organellar communication.

These beneficial functions may be lost when alpha-synuclein misfolds and aggregates, events that are usually prevented by the protein quality control in mitochondria (Ruan et al., 2017) (see also review of (Lautenschäger and Schierle, 2019)). Mitochondrial chaperones and proteases such as high temperature requirement protein A2 (HtrA2), Lon protease (Lautenschläger et al., 2020) or ClpP (Hu et al., 2019) are major contributors to the alleviation of proteostatic stress and alpha-synuclein pathology seeding. Their dependence on the mitochondrial import system (Ruan et al., 2017) and on the mitochondrial membrane potential, next to the ATP-dependent enzymatic activity of the proteases themselves, demonstrate the importance of adequate oxygen supply for proper mitochondrial functioning in cellular proteostatic stress handling. A number of cytosolic chaperones bind alpha-synuclein (Burmann et al., 2020), and the disruption of this binding – for instance, in response

to hypoxia – could result in re-localization of alpha-synuclein to mitochondria and may promote aggregation.

4.2 Hypoxic stress in the brain and its potential role in PD pathogenesis

Neurons crucially rely on oxygen, particularly for mitochondrial oxidative phosphorylation, the primary cellular sink of oxygen and primary source of molecular energy in the form of ATP. In oxygen-limited conditions (hypoxia), physiological adaptive responses to counteract hypoxia are key for cells, as previously reviewed (Kaelin Jr and Ratcliffe, 2008), and in particular for neuronal function maintenance and survival, as overviewed for example in (Lourenço et al., 2017; Toth et al., 2017). Many brain pathologies are characterized by hypoxia and can be caused by impaired blood flow, for example due to hemorrhage, stroke or cardiopulmonary failure, by respiratory diseases or by low ambient oxygen, such as in high altitude – see (Terraneo and Samaja, 2017) for a review. Hypoxia is also integrally linked to inflammation, cancer, trauma, seizures (Rheims et al., 2019) and other cellular injuries, as recently outlined (McGettrick and O'Neill, 2020). In addition, a role of physiologic hypoxic cues in the brain have recently been proposed to be involved in neuronal plasticity (Butt et al., 2021).

At the molecular level, responses to hypoxia are orchestrated by a number of molecular pathways revolving notably – but not exclusively – around reactive oxygen species (ROS) (as recently reviewed (Sies and Jones, 2020)), as well as the transcription factors hypoxia-inducible factors (HIFs) (see (Lee et al., 2020) for a recent review on molecular adaptation to hypoxia) and nuclear factor erythroid 2-related factor 2 (Nrf2) (Leonard et al., 2006). The role of HIFs thereby is mainly the induction of molecular adaptations to preserve oxygen supply and energy metabolism in response to reduced oxygen levels. HIF-1 is the primary inducer of

adaptations in response to acute hypoxia. HIF-1 consists of 2 subunits; the β-subunit is stably expressed, while the α-subunit is continuously degraded in normoxia (Bruick and McKnight, 2001; Epstein et al., 2001; Ivan et al., 2001; Jaakkola et al., 2001). HIF-1α in normoxia gets hydroxylated by prolyl hydroxylases, recognized by Van Hippel-Lindau proteins, poly-ubiquitinylated and proteasomally degraded (for review see (Kaelin Jr and Ratcliffe, 2008)). In hypoxia, HIF-1α stabilizes and dimerizes with the β-subunit, which enables the transactivation of hypoxia responsive elements (HREs). The HIF-2 isoform shares structural, functional and regulatory features with HIF-1, while the HIF-3 isoform lacks a transactivation domain and represses activation of HREs by HIF-1 and HIF-2 (Makino et al., 2001). HIFs regulate for example erythropoiesis, angiogenesis and the balance between glycolysis and oxidative phosphorylation as means of cellular ATP production (for an overview see (Almohanna and Wray, 2018)). Nrf2 is a key mediator of responses to re-oxygenation after hypoxia and regulates a wide array of anti-oxidant and anti-inflammatory adaptations, which has recently been reviewed (Baird and Yamamoto, 2020). The physiological adaptations to hypoxia - including bolstering of mitochondrial functions, protection from oxidative stress and inflammation and thus general neuroprotection (summarized in more detail elsewhere (Mallet et al., 2020)) have been suggested to be compromised in brains affected by neurodegeneration (Lourenço et al., 2017; Steinert et al., 2010). Unsurprisingly, both HIF (see previous reviews (Correia et al., 2013; Correia and Moreira, 2010)) and Nrf2 (reviewed elsewhere (Sharma et al., 2020; Vasconcelos et al., 2019; Yang and Zhang, 2020)) pathways are therefore currently in the focus of much research as potential therapeutic targets for neurological diseases, including neurodegenerative diseases. In addition, the enhancement of cellular and systemic adaptations to hypoxia by the controlled exposure to hypoxic conditions gains increasing interest as a novel therapeutic approach against neurodegeneration, as highlighted in several recent reviews (Baillieul et al., 2017; Burtscher et al., 2021a; Speer and

Ratan, 2016). Termed hypoxia conditioning, this approach takes advantage of the capability of cells and tissues to harness hypoxia-inducible molecular pathways (such as HIFs and Nrf2) to react to mild hypoxic stress by enhancing the resistance to subsequent hypoxic injuries, as outlined elsewhere (Almohanna and Wray, 2018).

With regard to the pathogenesis of PD and other synucleinopathies, a central role of hypoxia, and thus a high potential of hypoxia conditioning and of targeting related molecular pathways, could be hypothesized based on several observations. First, a high incidence of general ventilatory dysfunction in PD (as discussed in a recent review (Vijayan et al., 2020)) and related alpha-synucleinopathies, such as MSA (Flabeau et al., 2014), is well known. In MSA (Benarroch et al., 2007; Schwarzacher et al., 2011) and DLB (Presti et al., 2014) a reduced sensing of oxygen levels may also occur due to the degeneration of potentially chemosensitive respiratory neurons. Second, an abnormal hypoxic ventilatory response (Serebrovskaya et al., 1998) and chemosensitivity to hypoxia (Onodera et al., 2000) of PD and MSA (Tsuda et al., 2002) patients have also been reported. Similarly, an impaired respiratory response to hypercapnia has been reported for patients with DLB (Mizukami et al., 2009). Still, the role of potential respiratory abnormalities in alpha-synucleinopathy pathogenesis is insufficiently investigated. It is thus also unclear, whether the detection of key molecular markers of hypoxia, such as HIFs in alpha-synucleinopathy (MSA and PD) patient brains (Heras-Garvin et al., 2020), and of markers of re-oxygenation after hypoxia, such as Nrf2 (as previously reviewed (Toth and Warfel, 2017)) in PD-patient blood leukocytes (Petrillo et al., 2020), are causally involved in pathogenesis of PD. Although the importance of these hypoxia-associated molecules in neurodegenerative diseases are increasingly supported by literature (for reviews, see (Correia et al., 2013; Correia and Moreira, 2010; Fão et al., 2019)), evidence on the direct role of hypoxia in PD remains scarce. However, supporting a potential drugability of molecular adaptations to hypoxia, targeting the HIF-1 pathway has been

repeatedly shown to be beneficial in preclinical models of PD. Early results have been summarized by Youdim and colleagues (Youdim et al., 2014), and since then much more research has demonstrated beneficial effects of HIF-1 modulation in PD-models. For example, the pharmacological upregulation of glycolysis by terazosin was protective in toxin and genetic models in mice, rats, flies, and induced pluripotent stem cells (Cai et al., 2019). Albendazole was effective in a rat PD model (Kandil et al., 2019), agmantin in a cellular PD-model (Ferlazzo et al., 2019), lactoferrin (Xu et al., 2019) and deferoxamine in mouses model of PD (Guo et al., 2016); all enhancing HIF-1 signalling. Furthermore, inhibition of prolyl hydroxylases (that degrade HIF-1a under normoxic conditions) was shown to be beneficial in cellular and rodent PD models (Li et al., 2018). Despite these promising findings, translation to clinics has not yet been achieved. This is particularly disappointing in light of the recent suggestion of polymorphisms in HIF-1 as risk factors for PD (Qin et al., 2019).

A better understanding of the consequences of hypoxia on PD etiology and disease progression could, open up new possibilities to find therapeutic approaches to alter the disease course of PD. Early studies on PD patients applying hypoxia conditioning indeed already demonstrated benefits of hypoxia conditioning on ventilation parameters (Russian original papers summarized elsewhere (Kolesnikova and Serebrovskaya, 2009)). We also recently provided a perspective on the potential of hypoxia conditioning in PD (Burtscher et al., 2021b).

4.3 Modulation of alpha-synuclein aggregation by hypoxic stress and its consequences

There are several indications of a regulatory link between hypoxia and alpha-synuclein and its aggregation even if better understanding of these effects requires more research. In rodents, hypoxia seems to upregulate alpha-synuclein expression levels in the brain (Kim et al., 2016;

Yu et al., 2004) and may affect its aggregation (Kim et al., 2016). The mentioned elevated alpha-synuclein levels in OSA patients (Sun et al., 2019) may also be due to the hypoxic episodes the patients experience during their sleep.

In contrast, enhancing the tolerance to hypoxic insults may be beneficial. For example, in mice hypoxia conditioning halted alpha-synuclein upregulation in response to acute hypoxia (Yu et al., 2004). The activation of the delta opioid receptors and the consequential improved response to hypoxia also restricted alpha-synuclein expression and oligomerization after the application of hypoxic insults or in the MPTP-model of PD (Chen et al., 2014; Chen et al., 2019).

Hypoxia, both on the systemic and on the cellular level, is associated with changes in pH, as outlined elsewhere (Swenson, 2016). Severe hypoxia can substantially reduce the pH of the cellular milieu by lactate accumulation (summarized in recent reviews (Ivashkiv, 2020; Swenson, 2016)). Low pH is associated with increased alpha-synuclein aggregation by promoting alpha-synuclein liquid-liquid phase separation (Ray et al., 2020) but cellular pH also promotes alpha-synuclein – mitochondria interactions (Cole et al., 2008; Nakamura et al., 2008). Low pH furthermore leads to a structural re-arrangement of cardiolipins resulting in their increased cytoplasmic exposure (Cole et al., 2008), possibly facilitating alpha-synuclein aggregation (McClendon et al., 2009). Early findings of lactate accumulation in brains of DLB patients (Bowen et al., 1995), however, have not yet been confirmed.

The link between hypoxia and pH regulation with inflammation is a further aspect with relevance for PD. Increased infection susceptibility is a characteristic of PD (Bu et al., 2015). Despite the downregulation of innate immune responses in presence of high levels lactate, pro-inflammatory processes are still triggered in a hypoxia-induced glycolytic cellular environment (Ivashkiv, 2020). Inflammation in turn has been shown to inhibit lysosome

acidification, which results in reduced autophagic alpha-synuclein clearance (Wang et al., 2015). In line with these results, influenza virus infection via autophagy inhibition can trigger alpha-synuclein aggregation (Marreiros et al., 2020).

4.3 Aging

Inflammation, oxidative stress and mitochondrial dysfunction (Campisi et al., 2019) are all increased with aging and are also all features of age-related neurodegenerative diseases. Unsurprisingly, age therefore is the highest risk factor for the development of many neurodegenerative diseases, including sporadic PD (for reviews, see (Collier et al., 2017; Hou et al., 2019; Reeve et al., 2014)) (figure 4). The consequential impairment of numerous cellular functions with aging and a potential change of alpha-synuclein levels with age are expected to contribute to a facilitation of adverse alpha-synuclein and mitochondria interactions. Regarding alpha-synuclein levels, both increased levels in brain (Chu and Kordower, 2007) and in lymphocytes (Brighina et al., 2010) as well as reduced levels in plasma (Koehler et al., 2015) have been reported at higher age. This apparent discrepancy has been suggested to indicate an intracellular accumulation of alpha-synuclein that translates into lower plasma levels (Koehler et al., 2015).

In addition, lysosome function is crucially involved in aging and obviously in protein aggregation diseases (reviewed elsewhere (Carmona-Gutierrez et al., 2016)). Lysosomal dysfunction is particularly central in PD, as recently summarized (Minakaki et al., 2020; Muñoz et al., 2020). Mitochondrial damage is detrimental for lysosomal function and, conversely, lysosomal damage also exerts adverse effects on mitochondria; e.g., by impairing mitophagy and mitochondria biogenesis (Bellomo et al., 2020; Deus et al., 2020). An example of a lysosomal enzyme affected by age is glucocerebrosidase. Glucocerebrosidase activity is

reduced with aging and in PD and has been shown to decrease with alpha-synuclein aggregation (Gegg et al., 2020). Glucocerebrosidase deficiency may furthermore increase cell-to-cell transmission and release of alpha-synuclein fibrils from neurons (Gegg et al., 2020).

Notably, increased cellular acidification with higher age due to lysosomal membrane damage has recently been reported in human senescent cells (Johmura et al., 2021). Intriguingly, cellular mechanisms in the (non-neuronal) senescent cells tended to rescue the intracellular pH (Johmura et al., 2021), contributing to cellular survival of the unhealthy cells with adverse consequences on aging. This observation may be of particularly high relevance for PD. It would be interesting to see future studies on this phenomenon on brain-related cell types and in particular in a brain(-like) environment (e.g., *in vivo* or in organoids).

5. Towards an integrated model of the interplay of alpha-synuclein and mitochondria

Recent findings have significantly advanced our understanding of how alpha-synuclein might interact with mitochondria and provided some clues as to how changes in oxygen levels contribute to the pathogenesis of PD. Molecular chaperones normally seem to be involved in limiting alpha-synuclein – mitochondria interactions (Burmann et al., 2020), which may not be the case following cellular injuries, particularly due to severe hypoxia. Possibly the subsequent increasing localization of alpha-synuclein to mitochondria in conjunction with its hypoxia-dependent expression upregulation may be a cellular attempt to boost mitochondrial efficiency. A dropping pH, such as in cellular hypoxia, further triggers a mitochondrial membrane remodelling leading to more cardiolipins facing the cytosol and enabling the interaction with alpha-synuclein. This could be a reason for detrimental consequences of

alpha-synuclein – mitochondria interactions and may lead to potentially more toxic aggregations, forming the characteristic inclusions of PD and PD-models consisting of membranous (mitochondrial) components and aggregated alpha-synuclein, as reviewed recently (Fares et al., 2021). Whether enhanced binding of alpha-synuclein to cardiolipins results in a higher toxicity of alpha-synuclein containing inclusions or in aggravated mitochondrial dysfunction, however, remains to be experimentally investigated. But it is possible that it prevents regeneration of mitochondria after hypoxic periods, negatively affecting mitochondrial membranes and membrane potential, as well as mitochondrial import, ion homeostasis and ROS- and ATP-generation. That alpha-synuclein can compromise mitochondrial quality control has already been demonstrated (Hu et al., 2019; Lautenschäger and Schierle, 2019). The largely speculative model described in this section is summarized in Figure 5.

6. Conclusions

There is an enormous wealth of preclinical trials successfully treating PD-like pathology and symptoms. But successful translation to clinical settings is extremely rare. The reason may be that our models do not sufficiently take the most relevant factors of PD-pathogenesis into account, of which for example hypoxic insult may be one. We argue that a particular constellation of factors is necessary to initiate mechanisms of toxic alpha-synuclein pathology formation in the context of PD and occurs preferentially in vulnerable brain regions. Among the modulating factors are age, genetic predisposition, the type of neuron (depending on metabolic demand, basal redox levels, alpha-synuclein expression levels, etc.), embedding in neuronal systems, acquired resilience (for example, with hypoxia conditioning), pre-existing

acquired vulnerabilities that are often related to hypoxic conditions (e.g., infections, ischemic injuries, seizures or exposure to toxins) and the occurrence of neuronal insults and inflammation, which are also associated with hypoxia. Variation of these parameters in models of PD and the rigorous assessment of oxygen levels, molecular markers and physiological effects of hypoxia adaptations, as well as intra- and extracellular pH will advance the understanding of hypoxia in PD pathogenesis and the evaluation of the potential of modulating hypoxia adaptations as treatment strategies in PD.

Although several recent experimental results corroborate a role of hypoxia, its importance in PD pathogenesis and disease progression remains speculative. More research is necessary to confirm causality and to determine the efficacy of related approaches for PD.

One approach of increasing popularity in neurodegeneration research is hypoxia conditioning (Burtscher et al., 2021a; Mallet et al., 2020; Manukhina et al., 2016). In hypoxia conditioning, mild hypoxia stimuli trigger processes that confer resilience to subsequent hypoxic insults (hormesis). Besides this, hypoxia conditioning can boost cellular mitochondrial, anti-oxidative and anti-inflammatory capacities (Burtscher et al., 2021a; Mallet et al., 2020).

The rapidly expanding understanding of involved signaling pathways – most notably HIF – will enable thorough mechanistic investigation of hypoxia conditioning potentials for PD. It will also allow the combination or replacement of hypoxia conditioning by pharmacological means that may be more practical in clinical applications.

Other strategies against neurodegeneration that - similar to hypoxia conditioning - act by increasing the resilience of cellular systems, by improving oxygen and nutrient supply and by boosting mitochondrial, anti-oxidative and anti-inflammatory capacities include for example (for more information refer to the referenced reviews) hyperoxic approaches (van Vliet et al., 2021), healthy lifestyles like regular exercise (Speelman et al., 2011; Valenzuela et al., 2020)

or dietary restriction approaches (Fontana et al., 2021). In addition, brain stimulation techniques, like for example photobiomodulation, are emerging as potential strategies to improve mitochondrial function and the health of cellular environments, (as recently reviewed (Santos, L. et al., 2019; Yang et al., 2020)), and may be effective in PD (Maloney et al., 2010; Santos, Luis et al., 2019).

We hope that this review will inspire future studies to address the highlighted knowledge gaps on the role of hypoxia in PD pathogenesis and to explore the therapeutic potential of associated approaches.

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Figure legends

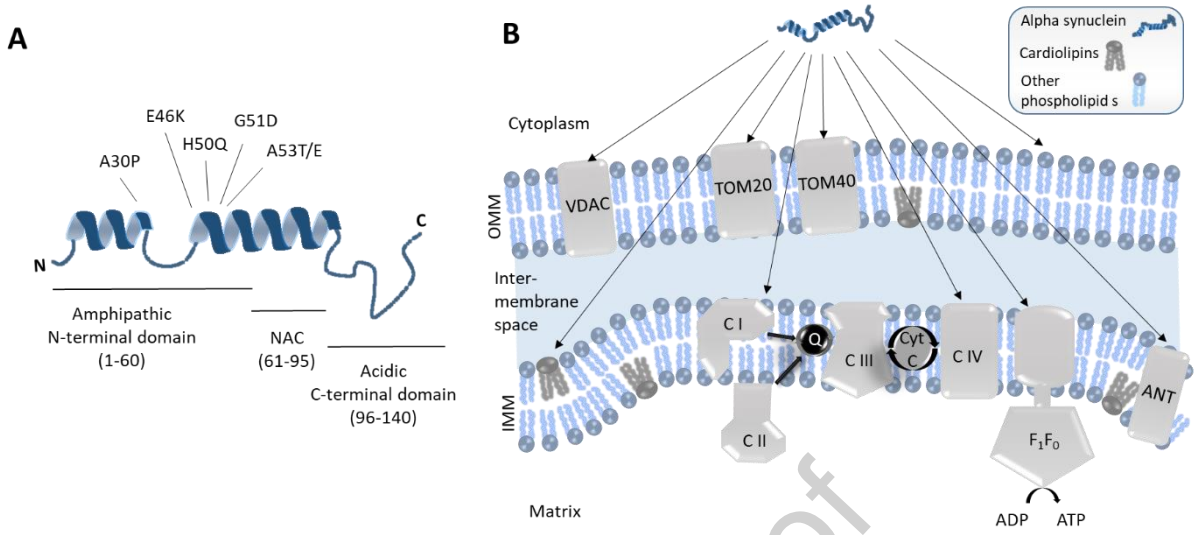

Figure 1 - Molecules implicated in alpha-synuclein – mitochondria interaction. A. Structure and PD-related mutations of alpha-synuclein; familial PD mutations are indicated. B. Components of inner (IMM) and outer (OMM) mitochondrial membranes binding alpha-synuclein.

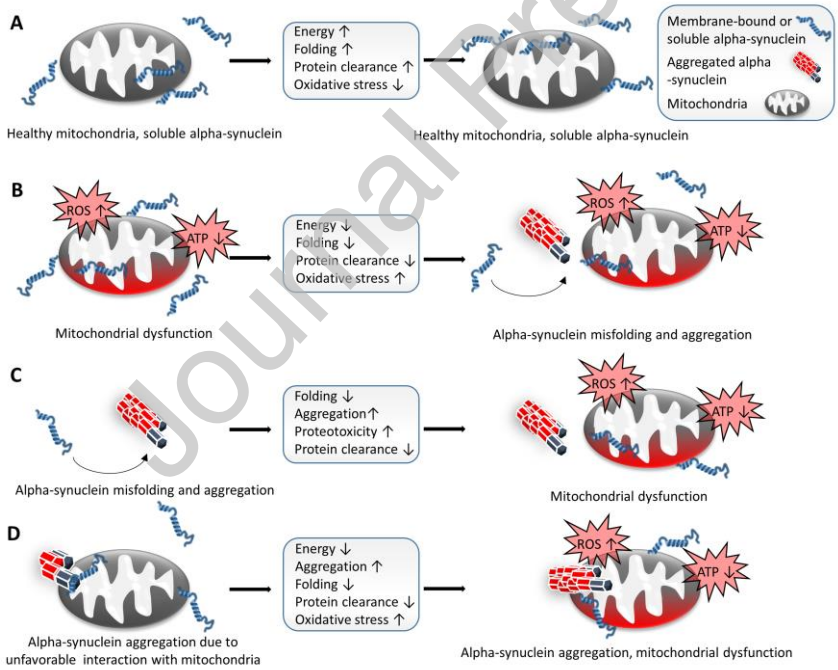

Figure 2 – Possibilities of interactions between alpha-synuclein and mitochondria leading to alpha-synuclein pathology and/or mitochondrial dysfunction.

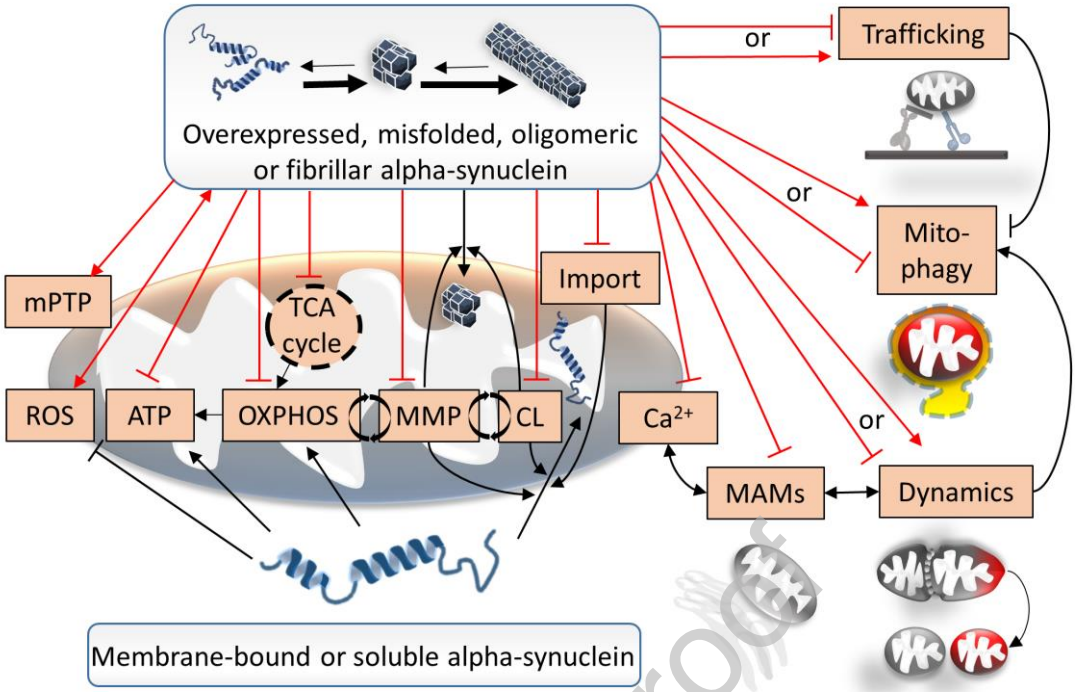

Figure 3 – Alpha-synuclein regulates mitochondrial functions.
Soluble, monomeric alpha-synuclein may enhance oxidative phosphorylation (OXPHOS) and decrease reactive oxygen species (ROS) mediated oxidative stress and thus enhance mitochondrial function. In contrast, pathological alpha-synuclein has been suggested to interfere with many mitochondrial functions, including tricarboxylic acid (TCA) cycle function, OXPHOS, ROS and Ca^{2+} homeostasis, regulation of mitochondrial import, membrane potential (MMP) and permeability transition pore (mPTP), trafficking and dynamics, as well as with mitochondrial quality control (the lightning symbol indicates that the directionality of these effects is unclear) and membrane architecture by interaction with cardiolipin (CL). In turn, several mitochondrial factors may influence alpha-synuclein pathology formation or the import of aggregated alpha-synuclein (e.g., ROS, MMP and CL-binding).

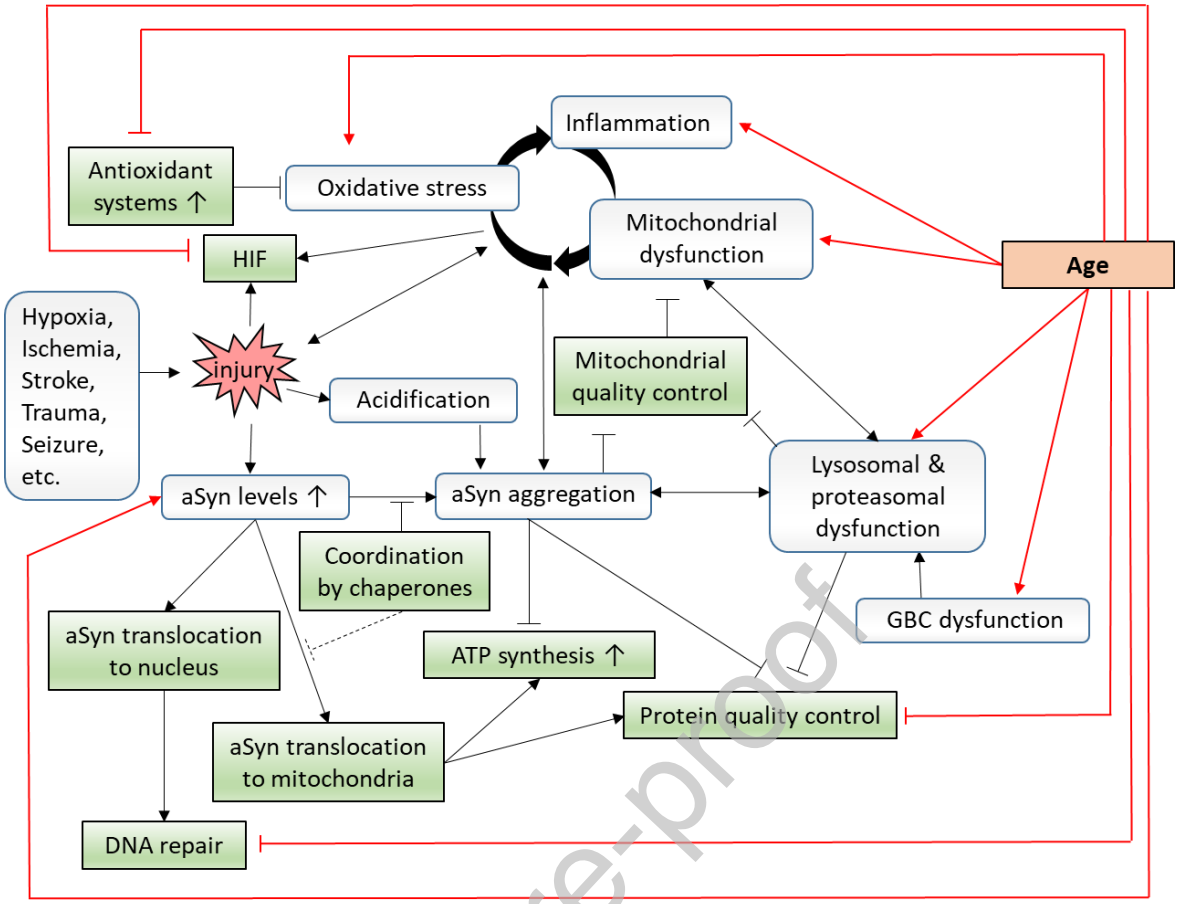

Figure 4 – Repair mechanisms, aging and alpha-synuclein aggregation.
Induction of alpha-synuclein (aSyn) pathology may be induced by brain insults. It is counteracted on multiple levels by different cellular systems and promoted by aging, oxidative stress, mitochondrial dysfunction and inflammation. HIF – hypoxia inducible factor, GBC - Glucocerebrosidase

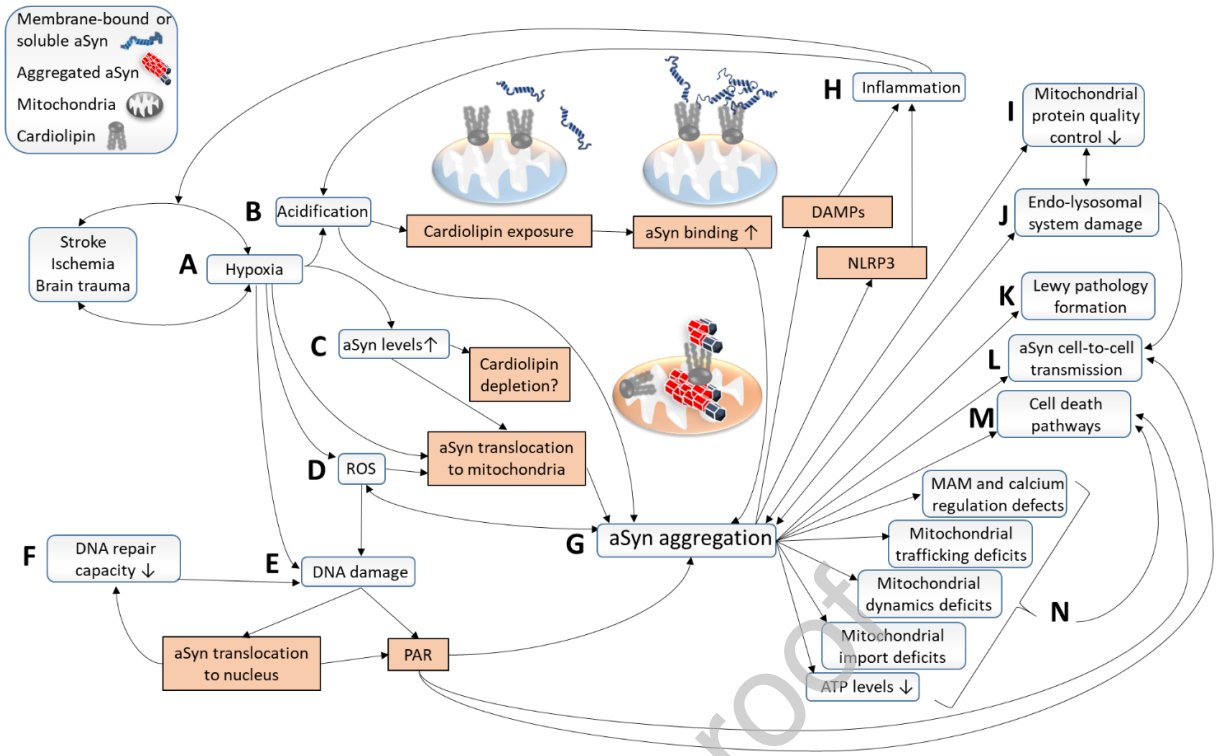

Figure 5 – Alpha-synuclein aggregation in mitochondrial membranes.
Brain insults leading to hypoxic conditions (A) cause intracellular acidification that may promote cardiolipin exposure and alpha-synuclein (aSyn) – mitochondria interaction (B). (A) may also elevate aSyn levels (C). In addition, reactive oxygen species (ROS) result in oxidative stress (D) and promote DNA-damage (E). Pathological translocation of aSyn may reduce DNA repair capacities (F). (A) – (F) facilitate aSyn aggregation (G) and may promote inflammation (H), the breakdown of several cellular and mitochondrial systems and induction of robust aSyn pathology (I) – (N). PAR - poly (ADP ribose), DAMP - damage associated molecular patterns, NLRP3 - NLR Family Pyrin Domain Containing 3, MAM –mitochondrial associated membranes.