Astrocytes and α-Syn in Parkinson’s Disease

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The α-syn protein is a 140-amino-acid protein that comprises an N-terminal region that assumes an α-helical secondary structure upon membrane binding, a non-amyloid-component hydrophobic domain that can adopt a β-sheet conformation, promoting protein aggregation in its monomeric form, and a negatively charged C-terminal domain. Astrocytes greatly contribute to neuronal survival through numerous mechanisms, such as the secretion of neurotrophins and antioxidants, the clearance of α-synuclein, glutamate metabolism, fatty acid metabolism, and the transfer of healthy mitochondria to neurons.

astrocytes Parkinson’s disease α-syn neurodegeneration

1. Alpha-Synuclein

In the mid-1990s, Polymeropoulos and colleagues identified the gene responsible for PD through a linkage analysis and association analysis for familial and sporadic PD, respectively [1][2]. The *SNCA* gene, which encodes the alpha-synuclein (α-syn) protein, was the first gene identified in familial PD, and subsequently, the presence of aggregates of this protein was described for different forms of the disease, including sporadic and autosomal dominant PD [1][3].

The α-syn protein is a 140-amino-acid protein that comprises an N-terminal region that assumes an α-helical secondary structure upon membrane binding, a non-amyloid-component hydrophobic domain that can adopt a β-sheet conformation, promoting protein aggregation in its monomeric form, and a negatively charged C-terminal domain [4]. This protein is abundant in the CNS and is primarily localized in presynaptic terminals [5].

The physiological function of α-syn remains unclear. Some evidence suggests that physiological levels of this protein play a role in regulating the presynaptic function of the SNARE complex, which is responsible for neurotransmitter release [6]. Additionally, α-syn is known to have functions associated with regulating vesicular and membrane dynamics [7][8]. Conversely, the excessive accumulation of α-syn has been linked to PD.

The triplication of the *SNCA* gene locus leads to increased α-syn levels, which has been associated with a higher risk of developing PD [9]. The mutations in α-syn (A53T, A30P, and E46K) also increase the probability of developing PD since they alter the secondary structure of this protein, promoting its neuronal and astrocytic aggregation [10]. Furthermore, alleles within a *Rep1* polymorphic region, 10 kB upstream of the *α-synuclein* gene promoter [11], have been associated with increased *α-syn* mRNA expression in human and mouse neurons [12][13]

as well as in the substantia nigra in humans [14]. These findings suggest that increased *α-syn* mRNA concentrations and α-syn protein levels are triggering factors for the development and progression of PD [15].

Under physiological conditions, α-syn can bind to the lipid membrane to promote the assembly of the SNARE complex and the formation of stable tetramers resistant to physiological aggregation processes [16]. When the balance between α-syn production and clearance is disrupted, this protein aggregates and unfolds into oligomers, then amyloid fibrils, and finally into LBs [15]. The α-syn aggregates exhibit diverse structures, ranging from soluble oligomeric ring-shaped, rope-shaped, or spherical forms (protofibrils) to insoluble fibrils [17][18][19]. These fibrils are thought to form the basis of Lewy bodies, although it is controversial whether the smaller protofibrils or the larger amyloid fibrils are the toxic α-syn species that cause neuronal cell death [20][21]. Among the multiple ways by which α-syn oligomers can induce cytotoxicity are mitochondrial damage, endoplasmic reticulum stress, synaptic impairment, excitotoxicity, neuroinflammation, proteostasis loss, and cell apoptosis [22].

The ubiquitin–proteasome system (UPS) and the lysosomal autophagy pathway (ALP) are the main pathways for eliminating overexpressed or misfolded proteins in cells to maintain protein homeostasis. It has been reported that the UPS is the primary pathway for degrading α-syn, although once saturated, the ALP also participates in the degradation process [23].

The reciprocal interaction between α-syn and the proteasome function suggests a self-perpetuating process in which permanently elevated levels of α-syn impair the UPS, which in turn may lead to the increased accumulation of α-syn. The detailed molecular mechanism by which α-syn is degraded by the proteasome is still not known. There is evidence in cell cultures that degradation can occur through a proteasome-dependent, ubiquitin-independent pathway [24][25][26].

In 2011, in a human α-syn WT transgenic mouse model, it was found that the UPS degrades α-syn under conditions with an increased endogenous α-syn load and that in contrast, autophagy is used to degrade α-syn only when intracellular levels of α-syn are elevated, providing a link between the proteasome, autophagy, and synucleopathies, being one of the first pieces of evidence in an *in vivo* model of protein loading and the pathways recruited to maintain homeostasis [23].

Recently, it has been reported that the down-regulation of the UPS and ALP leads to the accumulation of α-syn oligomers, which in turn inhibit the protein elimination process. By promoting the removal of α-syn oligomers, several research groups agree that targeting the signaling pathways involved in both systems can be an efficient way to restore proteostasis, becoming a potential and promising therapeutic target for PD [22][23][27][28][29].

Collectively, the evidence suggests that all misfolded proteins in neurodegenerative diseases show prion-like seed effects, including α-syn. Findings have shown the detection of α-syn-positive LBs in grafts from PD patients who received a transplant of embryonic midbrain cells, indicating the existence of the host-to-graft transfer of α-syn pathology and prion-like behavior [22].

Alpha-Syn: Its Prion-like Spreading and Presence in the Peripheral and Enteric Nervous System

The discovery that misfolded α-syn exhibits properties similar to those of prions has attracted interest in the understanding the progression of PD according to the Braak staging system [30], which classifies the progression of PD into six stages. The first stages (one and two) are pre-symptomatic, characterized by the loss of non-motor functions, such as the loss of one's sense of smell. At these stages, there may be more prevalent Lewy neurites than LBs, and the brain stem is the most affected. In the intermediate stages (three and four), patients lose motor functions and develop bradykinesia and rigidity. At this point, the disease passes to the striatum and LBs are formed. In the final stages (five and six), patients have all the other symptoms, the disease progresses to other parts of the brain, and there may be neuronal losses [31].

These findings suggest the propagation of α-syn from one brain region to another, a conclusion that is supported by studies in which fetal mesencephalic neurons transplanted into PD patients also developed a Lewy pathology [32][33]. Additionally, the administration of exogenous preformed fibrils of α-syn (PFF) to cultured neurons and intracerebral injections in wild-type (WT) mice led to the aggregation of endogenous α-syn and the subsequent propagation of this pathology [34][35][36].

Particularly, using aggregates isolated from brains of LB and PD patients, Recasens and coworkers seeded LB-enriched fractions containing α-syn. The result was the initiation of progressive neurodegeneration following a pattern similar to the Braak staging system, in both mice and primates [37]. On the other hand, by injecting PFF into WT mice or *SNCA*$^{-/-}$ mice, it was evaluated whether pathological α-syn can be transported through the vagus nerve and if endogenous α-syn is required for the propagation of pathological α-syn. It was found that α-syn can propagate from the gastrointestinal tract through the vagus nerve to the brain, supporting the Braak staging hypothesis [38].

These findings have led to the conclusion that α-syn pathology in PD is not limited to the CNS but also involves the peripheral and enteric nervous systems [39]. Over the past two decades, largely based on Braak and colleagues' findings, it has been proposed that PD may be caused by a pathogen that enters the body through the nasal cavity, is subsequently swallowed, and reaches the intestine, initiating Lewy pathology in the olfactory bulb and the digestive tract, explaining the simultaneous occurrence of the disease in both regions, as per the Braak staging system [31][40].

Despite the fact that Braak's staging hypothesis in PD has been clinically validated both *in vivo* and *in vitro*, there is still a lack of understanding regarding its underlying molecular mechanisms. Furthermore, it is necessary to consider some documented inconsistencies [41]. For example, in the study published by Braak and colleagues in 2002, only 30 of 413 cases of Lewy neurites in the dorsal motor nucleus of the vagus nerve were used to provide the basis of the stratification scheme. Likewise, no Lewy bodies were found in the SNpc of 30 of the sporadic PD patients [41]. Another study suggests that the Braak system does not allow for the classification of nearly 50% of PD cases. Zaccai and collaborators reported that only 51% of the 208 cases of autopsies in patients with a diagnosis

of PD followed the Braak pattern [42]. Other reports have provided evidence invalidating a smooth and predictable rostro-caudal progression of the synucleinopathy abnormality in the brains of people with PD [43].

Although the aforementioned are studies that cast doubt on the Braak staging system, there is evidence with important case statistics that allow to elucidate patterns of disease development, although more clinical, molecular, and pathological studies are required to strengthen this hypothesis

2. Astrocytes and α-Syn

Astrocytes greatly contribute to neuronal survival through numerous mechanisms, such as the secretion of neurotrophins and antioxidants, the clearance of α-synuclein, glutamate metabolism, fatty acid metabolism, and the transfer of healthy mitochondria to neurons [44]. However, the effects of astrocytic protection can be heterogeneous and depend on the brain region in which they are located and the loss of homeostatic balance of the CNS [45]. In contrast, reactive astrocytes are those that have undergone various cellular, molecular, and functional changes in response to injury or neurodegenerative diseases [44].

One of the hallmarks of PD is the formation of α-syn deposits. Several studies have demonstrated that astrocytes promote the formation and propagation of these protein deposits [46][47][48][49][50]. The first piece of evidence of the close relationship between α-syn pathology and astrocytes was through the analysis of post mortem brain tissue from patients with PD. Particularly, Wakabayashi et al. revealed that α-syn immunoreactive inclusions are frequently found in SNpc astrocytes of PD patients [47].

α-synuclein aggregates are primarily found in astrocytes [46][47], and the accumulation of α-syn in these cells occurs through intercellular transfer [51] as the astrocytes capture α-syn released by axonal terminals [52]. *In vitro* and *ex vivo* studies have shown that α-syn can be transmitted from neuron to neuron, astrocyte to astrocyte, and bidirectionally between neurons and astrocytes, although transmission from neurons to astrocytes or between astrocytes is much more efficient [53]. Extensive uptake leads to the incomplete and inefficient degradation of α-syn oligomers due to overloading the lysosomal degradation pathway, resulting in the formation of intracellular astrocytic protein deposits and mitochondrial damage [54].

Toxic α-syn has been shown to induce mitochondrial damage and increased mitochondrial fragmentation, as well as affect mitophagy in neuronal cells [54][55][56][57]. Also, in human primary astrocytes, α-syn has been suggested to locate to the mitochondria and cause reduced oxygen consumption [58]. In a study of primary astrocytes from mice infected with α-syn oligomers, mitochondrial damage with fragmentation patterns was confirmed, coupled with reduced mitochondrial functionality with abnormally high levels of reactive oxygen species (ROS), generating oxidative stress and neuronal death [54].

It has been reported that neuronal loss and the presence of cytoplasmic inclusions in neuronal cells are accompanied by astrogliosis [59]. In 2007, Braak and his team reported that many α-syn-positive astrocytes

appeared in stages 4 to 6 of the Braak PD stages, concentrating in the prosencephalon, specifically in the amygdala, thalamus, septum, striatum, claustrum, and cerebral cortex [46].

The overexpression of the mutant *SNCA* gene in primary astrocytes from a mouse model disrupted the normal functioning of these cells, impaired BBB permeability, and disrupted the homeostasis of glutamate uptake by astrocytic transporters (GLAST and GLT-1) [60]. On the other hand, a study using human brain homogenates from PD and LB patients demonstrated that α-syn is captured and propagated from astrocytes to neurons, causing neuronal death [61].

Studies on astrocytes derived from induced pluripotent stem cells (iPSCs) of familial PD patients have demonstrated that α-syn accumulation in astrocytes directly correlates with its toxicity to neurons [60][62]. Pathological α-syn contributes to the formation of A1 astrocytes, which prevent microglia-induced activation mediated by α-syn. In a sporadic PD mouse model, it was demonstrated that using agonists of GLP-1R (glucagon-like peptide) expressed on astrocytic membranes to prevent the conversion of astrocytes to a neurotoxic A1 phenotype mediated by microglia reduced the disease's progression [63].

The transmission of α-syn from neuron to astrocyte, followed by its accumulation and the formation of intra-astrocytic deposits, generates neuroinflammation and contributes to PD neurodegeneration. Astrocytes with accumulated α-syn produce pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, as well as chemokines CXCL1 and CX3CL1 [52]. Additionally, a 2010 study showed that the expression of the α-syn A53T mutation related to PD, selectively in astrocytes, disrupted astrocytic functions related to glutamate uptake and BBB regulation, leading to microglial activation, inflammatory responses, and dopaminergic neurodegeneration in mice [60].

Recently, a report identified a link between the molecular circadian axis (BMAL1-BAG3 axis) in astrocytes and α-syn aggregation. It has been shown that the silencing of the *Bmal1*$^{-/-}$ clock gene in astrocytes was enough to prevent α-syn pathology *in vivo* and induce the activation of these cells. This response was associated with the increased astrocytic phagocytosis of α-syn by BAG3 (a macroautophagy chaperone) [64].

The mechanisms underlying α-syn internalization by astrocytes are thought to be different from neuronal mechanisms. In neurons, such internalization can occur in different ways, such as the interaction with heparin sulfates on the cell surface [65], Lag3 receptors [66], or the sodium–potassium transport subunit ATPase β3 [67]. However, in astrocytes, it remains unclear, largely because they possess a unique interactome. Since astrocytic receptors that specifically bind to α-syn oligomers have not been identified so far, the development of therapeutic targets based on blocking astrocytic receptors continues to be studied [68].

Although the findings mentioned above demonstrate that both dysfunctional astrocytes and reactive astrogliosis contribute to PD pathogenesis and progression, it has been reported that in the early stages of the disease, astrocytes play a protective role in clearing α-syn deposits. However, this mechanism becomes compromised and

inefficient as α-syn deposition persists [69]. Therefore, a dual role of astrocytic dysfunction in PD pathophysiology is currently proposed with a potential therapeutic role for these cells in PD and synucleopathies.

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