Alpha-Synuclein

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Alpha-Synuclein (α-syn) has strong connection with Parkinson's disease. Parkinson's disease (PD) is considered the most common disorder of synucleinopathy, which is characterised by intracellular inclusions of aggregated and misfolded α-syn protein in various brain regions, and the loss of dopaminergic neurons. During the early prodromal phase of PD, synaptic alterations happen before cell death, which is linked to the synaptic accumulation of toxic α-syn specifically in the presynaptic terminals, affecting neurotransmitter release. The oligomers and protofibrils of α-syn are the most toxic species, and their overexpression impairs the distribution and activation of synaptic proteins, such as the SNARE complex, preventing neurotransmitter exocytosis and neuronal synaptic communication. In the last few years, the role of the immune system in PD has been increasingly considered. Microglial and astrocyte activation, the gene expression of proinflammatory factors, and the infiltration of immune cells from the periphery to the central nervous system (CNS) represent the main features of the inflammatory response. One of the actors of these processes is α-syn accumulation.

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1. Introduction

The reduction of striatal dopaminergic neurons triggers motor symptoms that include bradykinesia, uncontrollable tremor at rest, postural impairment, and rigidity, which together characterise Parkinson's disease (PD) as a movement disorder [1][2]. Neurodegeneration in the *Substantia Nigra pars compacta* (SNpc) leads to a marked decrease of dopamine (DA) levels in the synaptic terminals of the dorsal striatum and the consequent loss of nigrostriatal pathway, which allows PD to be described as a synaptopathy [3][4]. Synaptopathy is linked to α-synuclein (α-syn), a small, soluble protein encoded by the *SNCA* gene on human chromosome 4 [5][6], which is physiologically mainly localised in the presynaptic nerve terminals [7], the mitochondrial-associated membrane (MAM) [8], in which its overexpression increases the extent of contact sites and downregulates MAM activity [9][10][11][12], and in the nucleus [13][14][15][16].

α-syn accumulation compromises the fusion and clustering activity of the synaptic vesicles [17] and then influences neurotransmitter release, inducing the death of nigrostriatal neurons [18]. The transmission of α-syn pathology crosses different brain regions [19], though the impacts of extracellular α-syn on synaptic activity remains largely unknown [20][21]. Pacheco and colleagues [22] showed that extracellular α-syn oligomers facilitate the perforation of the neuronal plasma membrane, increasing its conductance and the influx of both calcium (Ca^{2+}) and glucose, explaining in part the synaptotoxicity observed in PD. α-syn occurs in a dynamic balance between the monomeric and oligomeric forms, which are not easily prone to form fibrils under physiological conditions. Identifying the most

toxic species, between fibrils and oligomers, has been difficult. There is evidence that the formation of fibrils mediates α-syn toxicity [23]. On the contrary, oligomeric forms are considered the most toxic species at the synapses [24], where they impair long term potentiation (LTP) and increase basal synaptic transmission through a mechanism dependent on N-Methyl-D-Aspartate (NMDA) receptor activation [25][26][27][28].

PD has a multifactorial aetiology. Indeed, the possible causes depend both on genetic and environmental factors that engage several biological mechanisms and processes, such as the cited α-syn misfolding, mitochondrial dysfunction, oxidative stress, synaptic plasticity, and neuroinflammation. Neuroinflammation, in recent years, has assumed a central role in the pathophysiology of PD and other neurodegenerative diseases. Evidence from post-mortem brains of PD patients, as well as in in vitro and in in vivo models, has highlighted the inflammatory contribution to the disease's neuropathology [29][30][31][32][33]. In 1988, McGeer and collaborators disclosed the presence of HLA-DR$^+$ microglia (macrophages) in the SN of idiopathic PD patients through immunohistochemical staining [34]. This finding proved the existence of the reactive microglia state around dead and dying dopaminergic neurons. Moreover, these macrophages exhibited phagocytic activity, as demonstrated by the presence of melanin detritus inside them [34]. This study, like others in the recent literature, suggested the involvement of immune system alteration in PD. Moreover, GWAS (genome-wide associations studies) analyses have unveiled the contribution of both innate and adaptive immune responses [35][36][37][38]. Furthermore, data support that oligomeric and fibrillary α-syn forms can activate microglial cells [39][40], suggesting a clear role for this protein in the central inflammation in PD affecting neuronal homeostasis through the modulation of microglia function, which could be either protective or detrimental in PD.

2. α-Synuclein and Its Role in Neuroinflammation in Parkinson's Disease

As mentioned above, α-syn represents a pathological hallmark of PD, in particular intraneuronal inclusions known as LBs and/or LNs [41]. During brain physiological activity, α-syn is specially found within the presynaptic terminal of neurons belonging to the neocortex, striatum, hippocampus, thalamus, and cerebellum [42][43][44], whose cellular function has not yet been clarified, even if its involvement in synaptic plasticity and in the release of neurotransmitters and synaptic vesicles has been recognised, as extensively discussed in the previous section of this review.

The *SNCA* gene encodes α-syn, and can undergo missense mutations (A53T, A30T and E46K) and multiplication (duplications and triplications), which demonstrates the key role of this protein in PD [6][45][46][47][48][49][50][51]. As previously mentioned, under such pathological conditions, α-syn can be overexpressed and acquire a misfolded conformation. These misfolding species can accumulate, because of impaired autophagy or reduced phagocytic clearance [42][52][53], and could assume aggregated forms, such as oligomers or protofibrils, that cause acute toxicity in the brains of PD patients [54][55]. α-syn aggregates to resist degradation and to prompt, as shown in in vitro experiments, the impairment of macroautophagy, reducing autophasome clearance and promoting dopaminergic neuron death [56]. Moreover, post-translational modifications (ubiquitination, nitration, and phosphorylation) facilitate the formation of these aggregate species, increasing the disease process [42][53][57][58].

However, α-syn is not only a citoplasmatic protein, but can also be found in the extracellular space [59]. Neuronal cells normally throw out α-syn in the extracellular space, which impairs biological processes, such as oxidative stress or mitochondrial and lysosomal dysfunction, amplifying its release [60][61][62][63][64][65]. Thus, extracellular α-syn, probably secreted through exosomes and exocytotic vesicles [60][61][62][63][64][65], could act as damaged-associated molecular patterns (DAMPs), triggering the immune system and neuroinflammation processes [37][66]. As previously indicated, PFF aggregates could activate endogenous α-syn, triggering inflammatory and neurodegenerative responses and, in the final instance, PD pathology [27][67][68][69][70][71]. Thus, in the context of nigrostriatal degeneration in PD, misfolded α-syn species could be considered as being strictly associated with neuroinflammatory events, acting as an antigen capable of activating immune molecules.

3. Neuroinflammation as a Therapeutic Target in Parkinson's Disease

Neuroinflammation is considered an early event in the pathophysiology of PD, or a driving mechanism of its progression. Thus, it could be an early therapeutic target to counteract PD. Many recent studies have described the use of different agents that act on inflammatory species [54][72]. In the past few years, it has been hypothesized that there is a correlation between the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) and reduced risk of developing PD [29][73]. Different meta-analyses have presented conflicting data. In particular, some studies did not find any correlation between the use of anti-inflammatory drugs and PD risk [74][75]. Other research studies showed a beneficial outcome for the use of non-aspirin NSAIDs [76][77], or aspirin in females [78]. Growing evidence supports the importance of neuroinflammation as a therapeutic target, with the aim of limiting disease progression.

Several clinical trials have been conducted in the last few years in this field (https://clinicaltrials.gov (accessed on 10 May 2021)). Immunotherapies against α-syn have been developed to reduce extracellular α-syn levels, which are responsible for triggering neuroinflammation, and its spread. There are two types of immunotherapies: active and passive [79][80].

Active immunotherapy, or vaccination, involves the production of antibodies against α-syn through the patient's immune system. AFFITOPE® AFF1 belongs to this category, and is characterised by administration of small fragments of α-syn. This immunotherapy has successfully reduced neurodegeneration and increased anti-inflammatory factors in two animal models [72]. AFFITOPE® AFF1 is currently being considered in a phase I clinical study (NCT02267434) [72][81].

Passive immunisation involves the administration of antibodies against α-syn, and has achieved good results in pre-clinical studies by increasing the clearance of α-syn [81]. A phase 2 clinical trial that uses PRX002 as a passive immunotherapy [72][81] is currently underway.

Immunotherapies could be a valid target for therapeutic approaches, either used in combination with current medications or even as an alternative treatment in the future.

4. Conclusions

Synaptic damage and neuronal loss are major neuropathological features of PD. Misfolded α-syn aggregates are associated with disease progression; this is known as synucleinopathy. In the non-pathological brain, α-syn is not toxic and participates in several functions associated with neurotransmission and synaptic plasticity, including synaptic vesicle recycling and neurotransmitter synthesis and release. Alterations to the conformity of α-syn lead to the beginning of pathological processes in synucleinopathies. To date, many studies have identified the functions of α-syn in the regulation of neurotransmission and synaptic plasticity, but further insights are needed to outline its pathological roles. Synaptopathy, α-syn misfolding/aggregation, and neuroinflammation processes seem to interact and contribute to PD pathogenesis. As demonstrated by many of the studies cited above, these mechanisms affect each other, creating a vicious circle in which it is difficult to establish the first pathology trigger. The involvement of α-syn pathology and an altered immune response point to potential new immunomodulatory targets to slow down the progression of the disease, and/or improve its outcome.

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