



The gut-brain axis in Parkinson's disease: A macrophage perspective

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Abstract

Parkinson's disease (PD) is defined by the progressive accumulation of misfolded α -synuclein (α Syn) across the gut-brain axis, yet the cellular systems that normally contain this burden are only beginning to be understood. Among them, tissue-resident macrophages (RTM) occupy strategically positioned niches and functionally interact with their microenvironment. In this Perspective, we examine how muscularis externa macrophages in the enteric nervous system, parenchymal microglia, and border-associated macrophages in the central nervous system respond to α Syn and shape disease progression. We argue that these RTM serve as early sentinels of synucleinopathy by taking up extracellular α Syn and attempting to degrade it through lysosomal pathways. However, with ageing and in the context of genetic or environmental stress, this protective function may break down. As degradative capacity declines, RTM may enter dysfunctional states marked by cellular stress, incomplete processing of α Syn, propagation of pathogenic species, and enhanced antigen presentation. In this way, RTM may influence not only the local handling of α Syn, but also the emergence of adaptive immune responses and neuroinflammation across the enteric nervous system (ENS)-central nervous system (CNS) axis. We further discuss how anatomical niche, ontogeny, and α Syn conformational diversity may shape these responses, and how restoring macrophage proteostatic function could offer therapeutic opportunities to limit disease progression.

Keywords: Parkinson's disease, tissue-resident macrophages, neuroimmunology, gut-brain axis

1. Introduction

Parkinson's disease (PD), first described as "shaking palsy" by James Parkinson in 1817^[1], is a synucleinopathy characterized by the misfolding and aggregation of α -synuclein (α Syn) into Lewy bodies and Lewy neurites, accompanied by the neurodegeneration of dopaminergic neurons in the basal ganglia of the central nervous system (CNS)^[2,3] (A full list of abbreviated molecules and terms is provided in [Table 1](#)). In addition to the classical motor symptoms of tremor, bradykinesia, and rigidity, PD is characterised by a spectrum of *prodromal* manifestations; for example, constipation, which could reflect enteric nervous system (ENS) dysfunction^[4,5]. In 2003, Braak and colleagues proposed a pathological staging scheme in which α Syn aggregation follows a caudo-rostral progression; from the dorsal motor nucleus of the vagus in the brainstem, through pontine and midbrain nuclei to limbic and neocortical regions^[6]. The early involvement of the vagal system, together with the observation of α Syn aggregation in the submucosal and myenteric plexuses of the ENS of patients, led to the hypothesis that α Syn pathology could originate in the intestine, from where it could spread, via the vagus nerve, to the CNS, potentially in a cell-to-cell transsynaptic manner^[5]. This concept is supported by animal studies showing gut-to-brain transmission of α Syn that is attenuated by vagotomy^[7-9], and by human epidemiological data suggesting a reduced PD risk following truncal vagotomy^[10], although this association remains debated. However, accumulating evidence supports substantial clinical and pathological heterogeneity in PD. Proposed disease trajectories include "body-first" PD, in which α Syn pathology may arise in peripheral autonomic or enteric structures before spreading to the CNS, and "brain-first" PD, in which pathology may originate within the CNS and subsequently involve peripheral autonomic pathways^[11]. Consistently, early brain-first cases may show little or no peripheral Lewy pathology, indicating that ENS involvement and gut-to-brain propagation are not universal features of PD. Although strict dichotomisation of patients into "body-first" and "brain-first" categories remains challenging and controversial^[12], the ENS-CNS axis may nevertheless represent an important route of α Syn propagation in a subset of patients.

Alongside the growing recognition of the gut-brain axis in PD, the immune system has also emerged as an important contributor to



its pathogenesis^[13,14]. Initial postmortem studies in the late 1980s reported the presence of *reactive* microglia, the major tissue-resident macrophages (RTM) of the CNS, in areas of gliosis adjacent to Lewy body pathology and degenerating neurons in the substantia nigra^[15]. Subsequent positron emission tomography scan studies using translocator protein (TSPO) ligands suggested increased microglial *activity* early in the disease^[16,17], although the specificity of TSPO as a marker and the concept of an “*activated*” microglial state in general remain debated^[18]. While most PD cases appear to be sporadic and influenced by a complex interplay of genetic and environmental factors, studies have identified genes of the endolysosomal and autophagic pathways as risk factors, including glucocerebrosidase 1 (*GBA1*), vacuolar protein sorting-associated protein 35 (*VPS35*), galactocerebrosidase (*GALC*), sphingomyelin phosphodiesterase 1 (*SMPD1*), and cathepsin D (*CTSD*) among others^[4,19]. Other risk genes include *PINK1* and parkin RBR E3 ubiquitin protein ligase (*PRKN*), which function in mitochondrial quality control, and the multifunctional kinase leucine-rich repeat kinase 2 (*LRKK2*), the most frequent genetic cause of familial PD^[4]. Of note, these genes are expressed at moderate to high levels in RTM, in some cases at higher levels than in neurons, suggesting that PD-associated pathways are active in these cells^[20,21]. It also suggests that the interactions of RTM with α Syn, for example through uptake and lysosomal clearance, may contribute to PD pathogenesis.

Table 1. Key molecules and pathways cited in the text.

Molecule/pathway	Function
α Syn; s129p α Syn	Core pathological protein and phosphorylated pathology-associated form used as a readout.
A β ; tau	Comparator proteopathic proteins discussed in relation to age-related clearance burden.
GBA1; VPS35; GALC; SMPD1; CTSD; CTSB; GRN; LAMP1; p62	Endolysosomal/autophagy and lysosomal cargo-handling pathways relevant to α Syn processing.
PINK1; PRKN; NADH-ubiquinone oxidoreductase; ROS	Mitochondrial quality-control and oxidative-stress-related genes and molecules linked to macrophage vulnerability.
LRKK2; Rab10	Pathway implicated in lysosomal stress and α Syn release from macrophage-lineage cells.
MerTK; TLR2; TLR4; LAG3; FAM171A2	Candidate α Syn uptake or sensing receptors with context-dependent evidence.
NF- κ B; TNF; JAK-STAT; HSPA1A; HSPA1B; HSPA5; HSPA9	Inflammatory and cellular-stress programmes induced by α Syn exposure.
C1q; complement	Engulfment-related pathway implicated in α Syn handling and synaptic/protein-associated clearance.
MHC-II; HLA-DQB1; HLA-DRB5; HLA-DRB1*15:01	Antigen-presentation molecules linking α Syn processing to adaptive immune recognition.
TGF β 1; CCR2; CD163; CD206; LYVE1; CD22; CD68	Macrophage subset, trafficking, scavenger, phagocytic and regulatory markers discussed across ENS and CNS niches.

α Syn: α -synuclein; s129p α Syn: serine-129-phosphorylated α -synuclein; A β : amyloid-beta; ROS: reactive oxygen species; NF- κ B: nuclear factor kappa-light-chain-enhancer of activated B cells; TNF: tumor necrosis factor; JAK-STAT: Janus kinase-signal transducer and activator of transcription; MHC-II: major histocompatibility complex class II; ENS: enteric nervous system; CNS: central nervous system.

In this Perspective, we explore the concept that RTM across the ENS–CNS interface are not mere bystanders in synucleinopathy, but active participants and potential modulators of disease. We frame impaired RTM-mediated α Syn clearance as a plausible vulnerability that may amplify and accelerate existing pathology. We discuss how the interaction of α Syn with RTM could modulate its aggregation, and how their engagement with the adaptive immune system may link synucleinopathy to disease progression. Although a myriad of RTM are present along the ENS–CNS axis, we focus on *muscularis externa* macrophages (ME-Macs) in the ENS, and on parenchymal microglia and border-associated macrophages in the CNS, given the mounting experimental evidence of their importance in PD pathogenesis.

The mechanistic evidence discussed here comes primarily from rodent models of synucleinopathy and *in vitro* systems involving genetic or pharmacological manipulation, while available human tissue evidence is largely correlative. We therefore distinguish model-system observations from the broader pathogenic framework proposed for PD.

2. Tissue-Resident Macrophages in the ENS and CNS: Mechanisms of Neuronal Clearance

Across the ENS and CNS, RTM occupy functionally analogous niches and maintain long-term relationships with neuronal tissues. In the ENS, ME-Macs represent the dominant RTM population and are primarily associated with the myenteric plexus, the major

ganglion network governing intestinal motility, secretion, and blood flow^[22]. They differ transcriptionally and regionally from submucosal RTM that are localized in the submucosal plexus and regulate vasculature permeability and epithelial homeostasis^[23,24]. In the CNS, microglia are the main phagocyte population residing in the parenchyma. A second macrophage population, collectively termed border-associated macrophages (BAMs), occupies CNS-body interfaces at the brain border regions. These include the perivascular spaces, meninges (dura mater, arachnoid, and pia mater), and the choroid plexus (apical ependymal cells and stromal BAMs)^[25,26]. Despite these anatomical differences, both systems are populated by long-lived macrophages of embryonic origin. In mice, microglia derive from yolk-sac progenitors from E7.25-E7.5 onwards, seed the brain by E9.5, and are maintained largely by self-renewal, although niche disruption or severe inflammation can permit limited engraftment by monocyte-derived macrophages^[27,28]. ME-Macs are also established during embryogenesis and are partially self-maintaining, but, in contrast to microglia, they undergo substantial age-dependent replacement by C-C motif chemokine receptor 2 (CCR2)⁺ monocytes, reaching approximately 70% renewal by eight months of age^[24]. BAMs receive a similar monocytic input to ME-Macs, depending on their anatomical location; for example, dural macrophages are 80% replenished in the first year of murine life^[29].

Both ME-Macs and microglia closely interact with neurons and contribute to neural circuit homeostasis, in part through clearance functions. During murine early postnatal development, ME-Macs localize to enteric ganglia and dynamically extend processes towards neurons, engulfing synapses and other neuronal material to refine ENS circuits^[30]. This functional interaction with neurons persists into adulthood, where ME-Macs are proposed to continuously phagocytose dying myenteric neurons and neuronal debris in the healthy mouse gut, consistent with their ongoing role in ENS maintenance and potentially neurogenesis^[31]. Similarly, in the murine brain, microglia shape developing neuronal circuits through complement C1q-mediated synaptic engulfment of less-active synapses^[32]. Beyond synaptic engulfment, microglia phagocytose apoptotic newborn oligodendrocytes in neurogenic regions^[33], whereas in the developing cortex, interferon-responsive microglia can also engulf whole neurons, linking microglial phagocytosis to neuronal sculpting during circuit maturation^[34]. In adulthood, murine microglia continuously engulf myelin to prevent hypermyelination^[35] and, in zebrafish, clear cellular remnants after traumatic brain injury via efferocytosis^[36]. TAM receptor signalling, particularly through Mer and Axl, allows microglia to phagocytose apoptotic cells during adult neurogenesis, whereas loss of these receptors on microglia results in the accumulation of apoptotic cells in the subventricular zone^[37]. In conclusion, microglia and ME-Macs continuously balance clearance and remodelling of surrounding neurons to maintain neuronal homeostasis, at least in mice. Whether human RTM exhibit similar roles in neuronal clearance remains to be elucidated.

With ageing, however, protein clearance appears to decline in these RTM^[38]. A recent proteomic study on nascent proteomes showed prolonged half-lives of synaptic proteins in aged murine microglia, particularly in the hippocampus and hypothalamus, with many of these proteins also displaying increased aggregation propensity^[39]. This suggests that protein aggregates may directly impair the clearing capacity of microglia, or alternatively, that protein aggregation arises from a progressive failure of degradative pathways in microglia, potentially related to lifelong exposure to microbial signals and misfolded proteins such as amyloid-beta ($A\beta$), tau, and α Syn. In line with this, as myelin fragmentation increases with age, microglia accumulate insoluble myelin aggregates and exhibit increased lysosomal volume together with the upregulation of antigen-presentation molecules^[38]. In the ENS, murine ME-Macs adopt an age-associated CLEC7A⁺CD11c⁺ phenotype and show reduced phagocytic activity^[40]. At the same time, α Syn, a physiological regulator of enteric neurotransmission^[41], progressively accumulates in enteric neuronal axons and terminal varicosities with age, and is detected within ME-Macs^[40,42]. This suggests that the clearance capacity of ME-Macs might become gradually outpaced by the rising burden of neuronal α Syn pathology.

At CNS-peripheral interfaces, BAMs restrict the entry and accumulation of peripheral signals, pathogens, and cellular debris^[25,26]. They express scavenger receptors such as CD163 and CD206 and are enriched in antigen-presentation pathways compared to microglia. In highly permeable regions, including the area postrema and choroid plexus, CD163⁺ macrophages rapidly capture circulating serum proteins, thereby limiting their access to the parenchyma^[43,44]. BAMs also continuously sample antigens present in the cerebrospinal fluid (CSF): after intra-ventricular or intra-cisterna magna tracer delivery, labelled antigens are detected in ependymal macrophages and in meningeal BAMs across the pia and subarachnoid space^[45,46]. Along venous and sinus-associated drainage routes, CD163⁺LYVE1⁺ macrophages further sample CSF contents while supporting CSF efflux through extracellular matrix remodelling^[45]. Because CSF flow declines with ageing and in Alzheimer's disease^[47,48], impaired clearance at these interfaces may promote retention of disease-associated proteins. Given that $A\beta$ accumulates in meningeal and vascular deposits^[49] and misfolded α Syn is detectable in the CSF of PD patients^[50], BAMs are strategically positioned to capture such CNS-derived proteins and potentially shape their clearance and immune presentation^[51].

3. Tissue-Resident Macrophages into the Spotlight in Parkinson's Disease

We propose that declining RTM clearance capacity with age may increase susceptibility to synucleinopathy. PD, whose strongest risk factor is ageing^[4], is characterized by the accumulation of misfolded α Syn in the ENS and CNS. In this Perspective, we suggest that RTM across these compartments respond to extracellular α Syn in broadly similar ways (Figure 1). Following uptake, RTM may undergo one or more of three pathological trajectories: 1) induction of cellular stress due to incomplete digestion; 2) propagation of pathology through transport or release of partially processed α Syn species; and/or 3) antigen presentation following processing of

α Syn-derived peptides. These RTM outcomes should be viewed as parallel, potentially reversible states that can coexist rather than as a fixed progression from protection to dysfunction. Their balance is shaped by the tissue niche, RTM ontogeny, host genetics, environmental exposures, α Syn conformer, and disease stage.

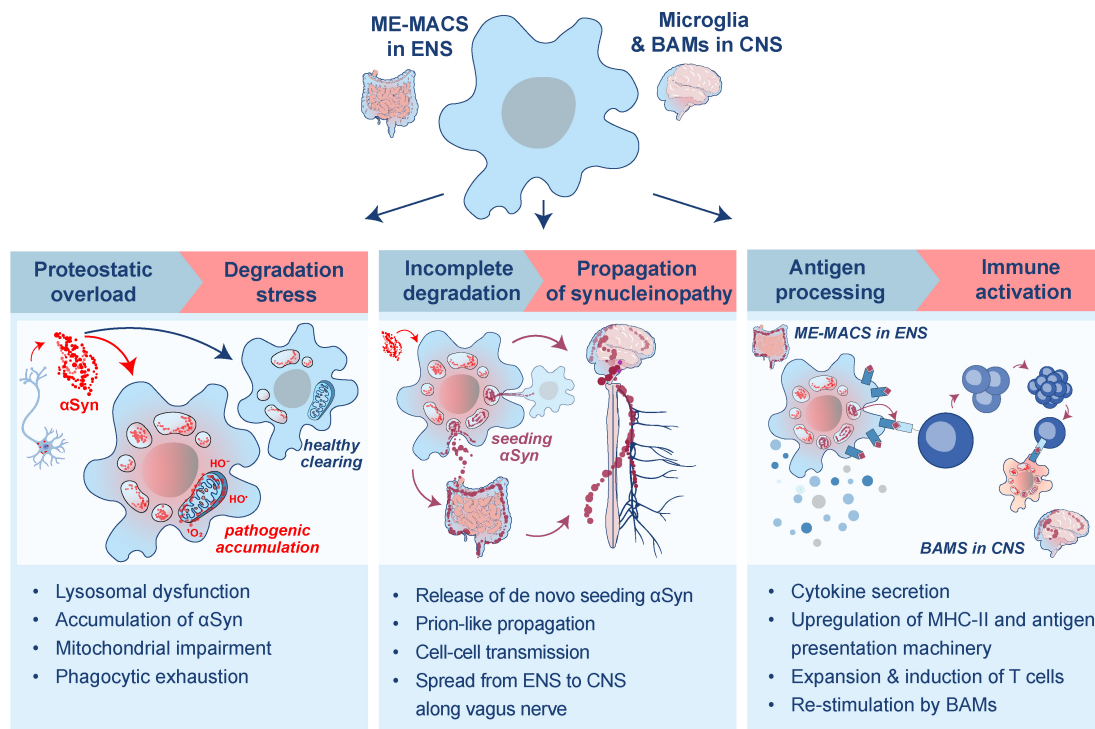


Figure 1. Pathological trajectories of tissue-resident macrophages following α Syn uptake. The schematic depicts parallel/coexisting outcomes after α Syn uptake rather than a required deterministic sequence. ME-Macs: *muscularis externa* macrophages; ENS: enteric nervous system; α Syn: α -synuclein; CNS: central nervous system; BAMs: border-associated macrophages.

In interpreting the evidence reviewed below, we distinguish between three levels of inference: findings from direct experimental manipulation in animal models, including genetic deletion and cell-type-specific depletion models; mechanistic data from *in vitro* or *ex vivo* systems, which illuminate molecular pathways but may not fully recapitulate *in vivo* conditions; and observations from human postmortem tissue or patient cohorts, which are largely correlative with disease state.

4. Cellular Stress Responses

While neurons can internalize and degrade extracellular α Syn, *in vitro* studies indicate that microglia have a greater capacity to do so^[48]. This is consistent with a division of labour in which neurons may rely in part on RTM, as professional phagocytes, to limit extracellular proteopathic burden^[49]. However, the relative contributions of these cell types *in vivo* remain to be established. In the homeostatic murine brain, microglia sequester extracellular α Syn, accumulate it in ubiquitin-positive puncta, and degrade it through p62- and TLR4-dependent autophagy^[52]. In microglia-specific *Atg7*-deficient mice expressing human α Syn, disruption of autophagy caused α Syn accumulation and increased insoluble α Syn pathology in whole-brain lysates, demonstrating that intact microglial degradative pathways are required to limit α Syn buildup through efficient clearance^[52].

Uptake of α Syn aggregates partly occurs through receptor-mediated pathways, although the dominant receptor depends on both cell type and α Syn conformer. In neurons, early studies implicated lymphocyte-activation gene 3 (LAG3) in α Syn uptake^[53], but this has been challenged by more recent evidence showing minimal neuronal expression and no survival benefit of LAG3 deletion in A53T α Syn mice^[54]. Attention has therefore shifted towards alternative receptors, including FAM171A2, which was recently identified as a neuronal receptor for fibrillar, but not monomeric, α Syn in mice and humans^[55]. Consistent with this, adeno-associated virus (AAV)-driven FAM171A2 overexpression increased serine-129-phosphorylated α Syn, a widely used marker of pathological α Syn^[56,57], in striatal and substantia nigral neurons of mice^[55]. Notably, *in vitro* experiments support alternative mechanisms of α Syn transport in neurons, including axonal transport^[58], transfer via tubular structures that connect donor and recipient cells^[59], or exosome-mediated uptake of α Syn^[60], although their contribution *in vivo* and relevance to humans remain to be investigated.

In microglia, mechanistic studies in primary human cells and induced pluripotent stem cell (iPSC)-derived models indicate that mer tyrosine kinase (MerTK) is a major contributor to α Syn fibril internalisation^[61]. In parallel, pattern-recognition pathways influence

both uptake and inflammatory sensing: TLR2 binds aggregated α Syn in a conformation-dependent manner, whereas TLR4 links extracellular α Syn exposure to nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) activation in microglia^[62-64]. In murine primary microglia, exposure to extracellular α Syn activates inflammatory programmes including NF- κ B, tumor necrosis factor (TNF), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signalling, together with heat-shock proteins such as HSPA1A, HSPA1B, HSPA5, and HSPA9, consistent with a cellular stress response to internalized α Syn aggregates^[65,66]. These findings support the idea that pathological α Syn triggers innate receptor signalling and inflammasome-linked cascades rather than the immunologically silent pathways related to efferocytosis^[67]. Instead, the response resembles activation by pathogen-associated stimuli such as lipopolysaccharide (LPS)^[68]. In line with this, fibrillar α Syn induces high levels of reactive oxygen species (ROS) in microglia *in vitro*^[69,65]. Similarly, selective overexpression of human A53T α Syn in microglia *in vivo* drives accumulation of serine-129-phosphorylated α -synuclein (s129p α Syn), increased ROS production, and upregulation of CD22^[70]. As CD22 has also been identified as a negative regulator of phagocytosis in aged microglia, this may point to a negative feedback response to intrinsic α Syn burden^[71]. In line with impaired homeostatic function, microglia exposed to fibrillar α Syn acquire an amoeboid morphology with retracted processes^[52,62,63], yet simultaneously upregulate pathways linked to microtubule assembly and polymerisation^[65]. These coinciding features suggest attempted but ineffective engagement of the phagocytic machinery, reminiscent of “frustrated phagocytosis” described during the incomplete clearance of persistent particles, such as microplastics^[65,72,73]. Nevertheless, because these models artificially overload microglia with fibrillar α Syn, they may overestimate the extent to which α Syn uptake drives inflammatory activation under physiological disease conditions.

A similar pattern appears to emerge in the ENS. In the 3KL transgenic mouse model, which expresses aggregation-prone human α Syn carrying three lysine substitutions^[74], ME-Macs show increased lysosomal lysosome-associated membrane protein 1 (LAMP1) volume together with the appearance of s129p⁺ α Syn within lysosomes^[75]. Proteomic profiling further revealed upregulation of lysosomal and phagosome-associated proteins, including GRN, cathepsin B (CTSB) and CD68. Simultaneously, the mitochondrial nicotinamide adenine dinucleotide (reduced form) (NADH)-ubiquinone oxidoreductase complex was downregulated in ME-Macs, pointing to concurrent activation of degradative pathways and mitochondrial vulnerability^[75]. We further found that injection of brain-derived fibrillar α Syn from PD postmortem donors into the muscularis externa of wildtype mice increased enteric s129p pathology and promoted its uptake by ME-Macs. Similar findings were reported by Mackie et al. using intestinal injection of endotoxin-free, *Escherichia coli*-derived murine α Syn preformed fibrils^[76]. In that study, ME-Macs initially upregulated complement-associated engulfment pathways, and C1q-dependent clearance transiently constrained enteric synucleinopathy. However, this protective response appeared to decline over time, suggesting a state in which sustained α Syn uptake exceeds degradative capacity and progressively impairs phagocytic function^[76]. Mechanistically, the involvement of C1q aligns with a broader theme in neurodegeneration, whereby complement tags synaptic or protein-associated targets for removal by microglia^[77]. Together, these observations suggest that ME-Macs, like microglia, initially mount a degradative response to extracellular α Syn but may be progressively overwhelmed and can exhibit features associated with endolysosomal stress and impaired phagocytic function as pathological burden accumulates. This response is likely heterogeneous across RTM populations: some subsets may retain efficient α Syn clearance and degradation, whereas others may fail to resolve α Syn burden and transition toward cellular stress and inflammatory activation. The mechanisms governing this functional divergence remain to be elucidated.

5. Propagation of Synucleinopathy

When lysosomal degradation is incomplete, the sequestration of α Syn may generate an intracellular reservoir of pathogenic species, while lysosomal stress or rupture could allow seeding-competent material to escape into the cytosol and further influence α Syn aggregation^[78,79]. In a catecholaminergic neuronal cell line, *de novo* aggregation between exogenous fibrillar and endogenous α Syn largely colocalized with LAMP1⁺ lysosomes, indicating that the lysosome may present a favourable environment to facilitate aggregation^[79]. By contrast, studies in macrophage-like RAW264.7 cells show that exogenous fibrillar α Syn initially localizes to lysosomes but is subsequently exported in exosomes through LRRK2–Rab10 signalling, indicating that undigested α Syn can be released back into the extracellular space^[80]. Retained α Syn can also be transferred between neighbouring microglia through F-actin-dependent intercellular “nanotubes”, although this has so far only been shown in primary microglia and interpreted as a cooperative clearance mechanism rather than direct evidence of pathological propagation^[65]. Consistent with the idea that RTM in the ENS and CNS could modulate α Syn propagation, we found that depletion of ME-Macs via anti-CSF1R blockade prior to administration of patient-derived α Syn fibrils reduced local enteric neuronal s129p⁺ α Syn pathology and limited its spread along the ENS^[75]. Whether this propagation occurs trans-synaptically via the vagus nerve, as suggested by previous studies^[8], remains to be determined. By analogy, microglial depletion following the injection of murine α Syn preformed fibrils (PFF) in the striatum of mice reduced the presence of s129p⁺ α Syn in the striatum and amygdala, and attenuated dopaminergic neuron loss in the striatum and substantia nigra^[62]. Another study similarly found that microglial depletion was beneficial in an rAAV-hSYN mouse model, in which neuronal overexpression of human α Syn in the substantia nigra induces progressive dopaminergic neuron loss and motor deficits^[81]. Together, these findings from rodent models suggest that RTM can shift from a transiently protective role towards one that facilitates the persistence and dissemination of pathogenic α Syn species. Whether this transition occurs in (a fraction of) human PD patients, at which stage, and to what extent it is reversible, remains open questions.

Notably, distinct α Syn polymorphs differentially engage receptors such as TLR2 and elicit divergent transcriptional and cytokine programs in human iPSC-derived microglia^[62]. The uptake of α Syn is size- and species-dependent, with smaller prefibrillar or oligomeric assemblies entering cells more efficiently than longer fibrils and potentially exerting distinct downstream effects^[82]. Mackie *et al.* observed that ME-Mac depletion increased neuronal pathology following murine α Syn PFF administration, in contrast to our findings with human fibrils, suggesting that both neuronal and macrophage responses are shaped by strain-specific properties^[76]. More broadly, this fits with the concept that α Syn strain identity emerges from the interplay between the seed and the host-cell environment, raising the possibility that RTM might actively shape the fate, conformation, and downstream toxicity of internalized α Syn assemblies^[83]. These apparently divergent depletion and uptake studies are important because they argue against a single unified macrophage function in synucleinopathy. Depending on the route of administration, timing of depletion, tissue niche and readout, macrophages or microglia may appear protective and/or pathogenic. Whether targeting macrophage uptake or survival would be beneficial in human PD remains to be determined.

6. Antigen Presentation

We hypothesise that antigen-presenting cells, including RTM, may provide a mechanistic link between α Syn processing and the adaptive immune activation observed in PD. In humans, this is supported by a genome-wide association study (GWAS) identifying human leukocyte antigen (HLA) class II alleles, including HLA-DQB1 and HLA-DRB5, as genetic risk factors for PD^[84]. Experimental evidence comes from a landmark study by Sulzer *et al.*, which showed that T cells from PD patients recognise defined α Syn epitopes, with immunoreactivity concentrated in discrete regions of the protein^[85]. Notably, an N-terminal epitope within the Y39 region (aa32-46; KTEGVLYVGSKTKE) binds with high affinity to PD-associated HLA class II alleles, including the abovementioned *HLA-DRB1*15:01* and *HLA-DRB5*01:01*. A second antigenic region localises to the C-terminus and includes epitopes surrounding s129, linking immune recognition to a disease-relevant post-translational modification state^[85]. Importantly, α Syn-specific T cell responses are enriched in prodromal and early-stage PD and can be detected before motor symptom onset, indicating that adaptive immune activation may contribute to early disease mechanisms rather than simply reflecting inflammatory responses to central neurodegeneration^[86]. Consistently, work by Garretti *et al.* showed that, in *HLA-DRB1*15:01* humanized mice, immunization with the α Syn-derived epitope α Syn^[32-46] triggers intestinal inflammation, enteric neurodegeneration, delayed gastrointestinal transit, and weight loss, supporting a potential role for α Syn-specific adaptive immunity in prodromal enteric PD-like pathology^[87]. Because single-nucleotide substitutions in HLA-DQ and HLA-DR can alter peptide binding affinity and major histocompatibility complex class II (MHC-II) complex stability^[88], this raises the possibility that RTM and other antigen-presenting cells might generate and present disease-relevant α Syn-derived epitopes in the context of synucleinopathy.

In mice, enteric injection of PD patient-derived α Syn fibrils induced surface MHC-II upregulation on ME-Macs following α Syn engulfment and coincided with local T-cell expansion. Compared with neurologically healthy control-derived extracts, mice injected with PD-derived α Syn fibrils showed increased numbers of CD3⁺ T cells, predominantly CD4⁺ T cells, within myenteric ganglia^[75]. These expanded T cells subsequently migrated from the ENS to the dura mater and brain during disease progression, whereas targeted depletion of ME-Macs attenuated T cell expansion and ameliorated neurodegeneration and motor deficits. Importantly, ME-Macs may also promote T cell expansion through cytokine signalling. Single-cell RNA-seq analysis of ME-Macs and T cells in α Syn mouse models identified distinct macrophage subsets, including CCR2⁺ and CD163⁺ populations, that express high levels of transforming growth factor beta 1 (TGF β 1), together with corresponding receptor expression on gut CD4⁺ T cells^[75]. Moreover, deletion of TGF β 1 in ME-Macs abrogated α Syn-induced T cell expansion in the ENS, demonstrating a functional requirement for macrophage-derived TGF β 1 in this process. Together, these data position ME-Macs as local immune instructors that couple α Syn handling to T cell expansion and differentiation within the ENS.

In the murine CNS, antigen presentation in α Syn-driven pathology appears to be organized primarily at the brain borders rather than within the parenchyma. Although murine and human microglia are able to express MHC-II^[15,89], microglia-specific MHC-II deletion does not significantly alter peripheral immune cell infiltration in an AAV2-SYN induced mouse model of nigral human α Syn overexpression^[90]. Instead, BAMS appear to act as the dominant antigen-presenting cells: α Syn induces their expansion into a disease-activated state marked by the upregulation of antigen-presentation, chemotactic, and matrix-remodelling programmes, and BAM depletion markedly reduces CD4⁺ T cell recruitment and neuroinflammation^[90]. Together, these findings from experimental models support a model in which BAMS at vascular and meningeal interfaces may orchestrate T cell entry and restimulation, whereas parenchymal microglia primarily execute downstream inflammatory and phagocytic responses. Perivascular BAMS and T cells are also found in close proximity in the human PD midbrain, although the directionality and functional significance of this spatial relationship in human disease remain to be determined^[75].

7. Outlook: From Clearance Failure to Therapeutic Opportunities

We hypothesize that RTM dysfunction may constitute an underlying vulnerability factor in PD, one that could contribute to and amplify α Syn pathology rather than being solely a secondary response to neuronal loss. With ageing, genetic predisposition, environmental insults, or their combined effects, α Syn uptake by RTM may shift the distribution of RTM states: some cells may retain efficient degradative clearance, whereas others may accumulate incompletely processed or immunogenic α Syn cargo. Familial PD

genetics support this idea, as risk variants are enriched in pathways regulating endolysosomal and mitochondrial homeostasis, processes that are also relevant to RTM^[19]. Environmental exposures may further exacerbate RTM stress, including pesticides such as paraquat and rotenone, which impair lysosomal and mitochondrial function, as well as indigestible contaminants such as microplastics^[73,91]. This is supported by epidemiological studies linking environmental toxins to increased risk of developing PD^[92]. It will be important to experimentally define the thresholds that distinguish age-associated decline, reversible stress responses, and loss of phagocytic performance within α Syn-challenged RTM compartments.

An important consideration is that pathological α Syn is unlikely to behave as a single ligand. Instead, increasing evidence suggests that misfolded α Syn comprises a structurally heterogeneous family of assemblies with distinct biochemical and immunological properties^[62,83]. Conformation-specific epitopes can be differentially recognised by antibodies^[93], and distinct α Syn conformations have been shown to trigger divergent inflammatory programmes in macrophages^[62]. Although some studies implicate specific TLRs in the recognition of different α Syn structures, the precise epitopes that drive pro-inflammatory responses remain unclear. Future work is therefore needed to determine how α Syn strain diversity might impact RTM phenotypes, and in turn, how the RTM response could shape α Syn strain identity^[83] across the ENS and CNS. An additional consideration regarding α Syn strain identity is that fibril-injection systems likely do not fully recapitulate idiopathic PD. Although studies injecting fibrils commonly perform endotoxin testing to rule out adjuvant-like immunological effects, pre-formed aggregates may activate RTMs differently compared to endogenously derived aggregates. Therefore, incorporating genetic mouse models with fibril injection systems will be beneficial to future studies.

It remains to be determined to what extent RTM responses are shaped by cell-intrinsic programming, for example ontogeny, in addition to local tissue cues and α Syn burden. Although microglia and ME-Macs are largely self-maintained in homeostasis, monocyte-derived macrophages can enter the CNS under pathological conditions and may remain transcriptionally and functionally distinct from embryonically derived resident cells^[28,94]. In neurodegenerative settings, these recruited populations often show increased expression of inflammatory cytokines, chemokines, and antigen-presentation machinery compared with resident microglia^[94]. In an AAV2-SYN mouse model of PD, in which full-length human α Syn is virally overexpressed in dopaminergic neurons of the substantia nigra pars compacta, peripheral monocytes infiltrate the ventral midbrain and contribute to dopaminergic neurodegeneration^[95]. In the ENS, monocyte-derived macrophage subsets with stronger antigen-presentation signatures appear to show enhanced α Syn uptake relative to more trophic populations^[75]. In line with these findings, monocytes from individuals at prodromal disease stages display heightened cytokine responsiveness compared with controls^[96]. Together, these observations suggest that RTM ontogeny may critically shape responses to α Syn pathology. Furthermore, although core microglia programmes are conserved across species^[97], primate- and human-specific states are not fully captured in mice, highlighting the need for validation in human tissues.

Beyond ontogeny and tissue-specific signals, the microbiota may further modulate RTM activation thresholds in synucleinopathy. This is supported by germ-free and antibiotic-treatment studies showing that microbial signals regulate microglial maturation, morphology, and inflammatory responsiveness, with short-chain fatty acids such as acetate, propionate, and butyrate acting as microbiota-derived metabolites that can restore several microglial defects^[98]. In α Syn-overexpressing mice, microbiota depletion attenuates microglial activation, α Syn pathology, and motor deficits, whereas short-chain fatty acid supplementation and transfer of PD patient-derived microbiota worsen disease-associated phenotypes^[99]. These data suggest that microbial metabolites and pattern-recognition receptor ligands can modulate how resident macrophages respond to α Syn. A key unresolved question is whether such signals act similarly on ME-Macs, microglia, and BAMS, or whether each compartment interprets microbiota-derived cues according to its local niche and ontogeny.

Finally, any RTM-based therapeutic strategy will need to account for the functional heterogeneity of these cells across subsets and disease stages, rather than treating macrophages as a single uniform target. In the ENS, ME-Macs may act as early regulators of α Syn handling and as coordinators of adaptive immune activation, suggesting that enhancing α Syn clearance, preserving lysosomal competence, or limiting inappropriate antigen presentation in the gut could represent upstream intervention strategies. In the CNS, by contrast, promoting efficient but non-inflammatory clearance by microglia or BAMS may become more relevant once brain α Syn accumulation is established^[100]. This implies that targeting uptake alone is unlikely to be sufficient and may even prove counterproductive unless coupled to reinforcement of degradative capacity. Approaches that enhance lysosomal biogenesis, stabilize lysosomal membranes, improve hydrolase activity, or restore autophagic flux are especially attractive, as they address a convergent vulnerability linking intracellular stress, seed persistence, and antigen generation. More broadly, reprogramming RTM towards states marked by enhanced proteostatic resilience, restrained inflammatory output, and efficient, non-propagative cargo disposal may offer a more plausible translational strategy than indiscriminate depletion.

Declarations

Authors contribution

Konstantellos V: Conceptualisation, writing-original draft, writing-review & editing.

Van De Walle P: Writing-original draft, visualisation, writing-review & editing.

De Schepper S: Conceptualisation, writing-original draft, supervision.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

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