Relationship among α-synuclein, aging and inflammation in Parkinson's disease (Review)

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Abstract. Parkinson's disease (PD) is a common neurodegenerative pathology whose major clinical symptoms are movement disorders. The main pathological characteristics of PD are the selective death of dopaminergic (DA) neurons in the pars compacta of the substantia nigra and the presence of Lewy bodies containing α-synuclein (α-Syn) within these neurons. PD is associated with numerous risk factors, including environmental factors, genetic mutations and aging. In many cases, the complex interplay of numerous risk factors leads to the onset of PD. The mutated α-Syn gene, which expresses pathologicalα-Syn protein, can cause PD. Another important feature of PD is neuroinflammation, which is conducive to neuronal death. α-Syn is able to interact with certain cell types in the brain, including through phagocytosis and degradation of α-Syn by glial cells, activation of inflammatory pathways by α-Syn in glial cells, transmission of α-Syn between glial cells and neurons, and interactions between peripheral immune cells and α-Syn. In addition to the aforementioned risk factors, PD may also be associated with aging, as the prevalence of PD increases with advancing age. The aging process impairs the cellular clearance mechanism, which leads to chronic inflammation and the accumulation of intracellular α-Syn, which results in DA neuronal death. In the present review, the age-associated α-Syn pathogenicity and the interactions between α-Syn and certain types of cells within the brain are discussed to facilitate understanding of the mechanisms of PD pathogenesis, which may potentially provide insight for the future clinical treatment of PD.

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Contents

1. Introduction

Parkinson's disease (PD), which affects 6.1 million individuals globally, is a common neurodegenerative disorder (1). The pathological features of this disease include aggregation of synuclein α [SNCA, also termed α-synuclein (α-Syn)], resulting in the formation of inclusions called Lewy neurites (LNs) and Lewy bodies (LBs), apoptosis of dopaminergic (DA) neurons in the pars compacta of the substantia nigra (SN) and high levels of neuroinflammation (2,3). The main clinical manifestations of PD consist of movement disorders, such as bradykinesia, postural instability, myotonia and static tremor (2). Furthermore, patients with PD may have nonmotor symptoms, including mood disorders, hyposmia, autonomic nervous dysfunction, rapid eye movement sleep behavior disorder and cognitive decline (3-5). Notably, some of the aforementioned nonmotor disorders may develop several years before the appearance of motor complications (6).

It has previously been reported that the pathogenesis of PD involves multiple risk factors, such as environmental factors [for example, drugs and pesticides such as rotenone, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and paraquat], aging and genetic factors (such as SNCA, leucine-rich repeat kinase 2 and PTEN-induced kinase 1) (7). Through genetic testing of patients with early-onset PD, missense mutations of SNCA genes have been reported (such as, A53T, A53E, H50Q, G51D, E46K and A30P) (Fig. 1C), which suggested that α-Syn may be involved in the development of familial PD (8-10). Two possible α-Syn pathogenic substitutions, A18T and A29S (Fig. 1C), have also been previously reported; however, their potential pathogenicity remains to be further investigated (11). Previous studies on patients with PD with triplication or duplication of the SNCA gene have reported that overexpression of α-Syn is causally involved in PD, which leads to rapid progression of the disease (9,10,12). SNCA gene mutations may cause pathological aggregation of α-Syn, resulting in the formation of insoluble amyloidogenic fibrils (13). Furthermore, pathological α-Syn can be endocytosed by other neurons and then misfold normal α-Syn proteins in these cells, which leads to the propagation of misfolded α-Syn from cell to cell in a 'prion-like' fashion (13). Previous studies have reported that pathological α-Syn produces a variety of neurotoxic effects, such as impairing mitochondrial function, producing reactive oxygen species (ROS) (14), affecting neuronal membrane function (15,16), inducing glial cells to release inflammatory factors (17-20), interfering with iron metabolism (21,22) and causing neuronal presynaptic terminal function loss and dopaminergic depletion (9,23,24), which ultimately lead to DA neuronal death and the pathogenesis of PD. Of note, patients with identical gene mutations generally do not exhibit similar clinical manifestations, which indicates that the etiology of PD is caused by complex interactions among genetic factors, environmental influences and aging processes (25).

Neuroinflammation is an important hallmark of the pathogenesis and development of neurodegenerative disorders, including PD (26). There is growing evidence that both innate and acquired immunity contribute to the onset of PD (27,28). The innate immune reaction elicited by microglia can lead to neuronal apoptosis and disease progression (1). T cell infiltration has been reported in the brain tissues of both patients with PD and a mouse PD model (28), which suggests the involvement of acquired immunity in PD pathogenesis (1). In PD, α-Syn interacts with glial cells and peripheral immune cells. Microglia and astrocytes are able to phagocytose α-Syn (29,30) and various forms of α-Syn can activate microglia and astrocytes, which cause a neuroinflammatory reaction (31). Nitrated α-Syn contributes to harmful T helper cell maturation, which leads to severe neural damage (32). Additionally, astrocytes and oligodendrocytes are closely associated with the inflammatory response. It has previously been reported that the severity of neuronal loss in the SN may be related to the number of oligodendrocytes and astrocytes with α-Syn inclusions in the brains of patients with PD (5).

Aging is considered a major risk factor for the onset of PD and the PD incidence rises with advancing age (26). During aging, the brain undergoes structural and functional alterations and can suffer from chronic low-grade neuroinflammation (33). Neuroinflammation is also one of the features of the aging brain (34). The aging immune system interacts with environmental and genetic factors, resulting in an acceleration of PD pathology (25). In the aging brain, the intracellular clearance mechanism is impaired (35), thus, glial cells have a reduced ability to phagocytose and degrade α-Syn (36). In SN neurons, there is an age-associated increase in intracellular levels of α-Syn (23). Large toxic α-Syn aggregates cannot be metabolized during aging because of the impaired autophagy-lysosomal function, leading to chronic inflammation and neuronal death (37). Animal experiments have shown that aging increases the probability of α-Syn propagation, which results in a predisposition to α-Syn pathology (38,39). In addition, recombinant α-Syn can induce glial cell senescence and change the expression of cellular aging markers, such as by decreasing the expression levels of high mobility group box 1 (HMGB1) and Lamin B1, and increasing the expression level of p21 (40).

In this review, the structure and toxicity of α-Syn, age-related α-Syn pathogenicity in PD, the effects of α-Syn on glial cells and peripheral immune cells and the interaction of aging and α-Syn in glial cells are discussed. Elucidating the relationship between α-Syn, aging and neuroinflammation is essential for understanding the pathogenesis of PD.

2. α-synuclein structure

α-Syn, encoded by the SNCA gene on human chromosome 4q21, is a small soluble acidic protein with an average molecular weight of 14 kDa (16,41). The full-length α-Syn protein contains 140 amino acids (aa) and comprises three main distinct domains, namely, the N-terminal domain (aa, 1-60), the middle domain (aa, 61-95) and the C-terminal domain (aa, 96-140) (Fig. 1A) (17,42,43).

A total of seven imperfect 11-aa-residue repeats can be observed in α-Syn (44), of which four repeats are in the N-terminal domain (23,42,43,45,46). Each 11-aa-residue repeat (XKTKEGVXXXX) in the N-terminus contains a highly conserved hexameric motif (KTKEGV) (9,40,42,46-48), although certain aa sites of the hexameric motif are sometimes replaced (Fig. 1B) (47). It has previously been reported that the N-terminal domain, consisting almost exclusively of this 11-aa-residue repeat, is prone to form an amphipathic α-helical structure resembling the lipid-binding domain of the exchangeable apolipoprotein (9,10,46). The N-terminal domain is associated with lipid membrane binding, which may be a synergistic effect of the 11-aa-residue repeats. Lipid binding is significantly reduced when the N-terminal domain is truncated (10). Furthermore, the truncation of N-terminal repeats increases the production of β-sheet-enriched structures, while adding extra repeats results in the opposite effect (12). Additionally, the N-terminal domain carries an excess of seven positive charges, which may interact with the negatively charged C-terminal domain (49-51).

In human α-Syn, the middle domain with three additional 11-aa-residue repeats is a highly amyloidogenic and relatively hydrophobic region, which is also known as a non-A-β-amyloid component (NAC) domain (23,42,43,45,46). The NAC domain contains one extra positive charge and is

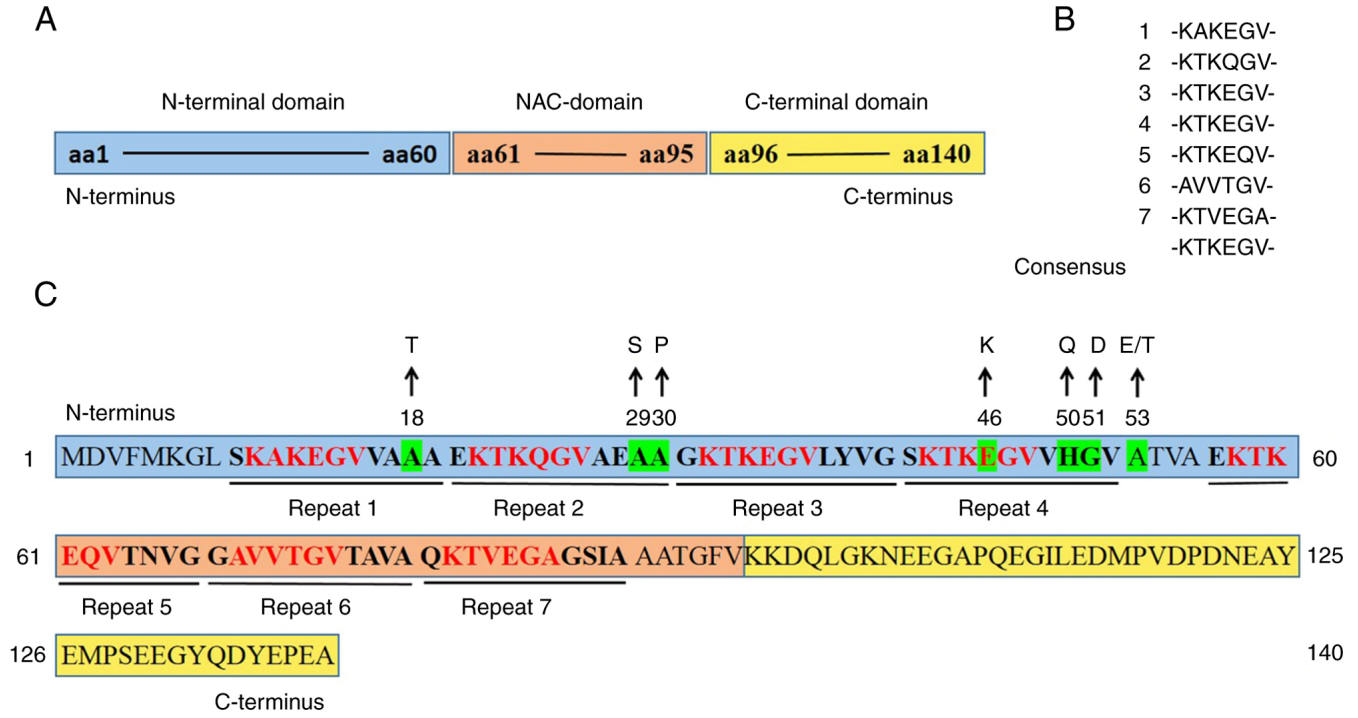

Figure 1. α-Syn structure. The α-Syn protein contains (A) three distinct domains represented by different colors and (B) include seven highly conserved hexameric motifs, with the consensus for the hexameric motifs being-KTKEGV-. (C) Amino acid sequence of the α-Syn protein. A total of seven imperfect 11-amino-acid-residue repeats are underlined. The highly conserved hexameric motif in each repeat is indicated in red. The arrows and green highlighting indicate missense mutations. α-Syn, α-synuclein; NAC, non-A-β-amyloid component.

slightly electropositive (49). It has been reported that the NAC domain serves a crucial role in α-Syn aggregation and fibrillogenesis. The residues (aa, 71-82) in the NAC domain, together with residues (aa, 36-42) in the N-terminal domain, contribute to the aggregation of α-Syn (31). It has been reported that the NAC domain can form a cross β-sheet structure (40); however, the glycosylated NAC region may suppress the aggregation of α-Syn (10). Moreover, the NAC domain may be involved in α-Syn aggregation, sensing membrane properties and interactions with metal ions, proteins and vesicles (9,52).

The C-terminal domain, a highly acidic area, includes 15 carboxylic acid groups and is rich in proline (42,53). Due to the large numbers of acidic groups and proline residues, the C-terminal domain has no propensity to form a specific structure; however, it randomly forms turns and loops in solution (9,42,53). There are certain binding sites in the C-terminal domain that are responsible for interactions with ligands, ions and small molecules (17,49,50). In addition, it has previously been reported that the C-terminal domain, enriched in negative charges, may protect the NAC domain from aggregation by interacting with the positively charged N-terminal domain to form an antiaggregating structure (49-51). C-terminal truncation greatly promotes fibrillization of α-Syn due to the charge imbalance of the N-/C-terminal domain (8,10). The multiple posttranslational modifications in the C-terminus may disturb long-range interactions between the N- and C-termini, leading to exposure of the hydrophobic NAC region and subsequent adoption of the β-sheet conformation (9). C-terminal truncation, as well as N-terminal truncation, occur in both patients with PD and healthy individuals (8,10).

3. α-synuclein toxicity

The physiological role of α-Syn protein has not been fully identified in normal neurons, but α-Syn may be involved in the regulation of DA biosynthesis, neurotransmitter release, synaptic plasticity, synaptic vesicle maintenance, axon regeneration and mitochondrial function (1,9,10,31). There are several possible mechanisms by which α-Syn is transferred between neurons. As α-Syn lacks sequences needed for secretion, α-Syn is released through a nonclassical mechanism involving tunneling nanotubes (TNTs) and exosomes (54). Another possible mechanism for α-Syn release is through the leakage of small amounts of the protein between pre- and post-synapses (Fig. 2) (54).

Unfolded α-Syn monomers undergo a structural change during PD-associated pathology, sequentially forming partially folded monomers, transient small soluble oligomers, structured oligomers (later β-sheet structures), β-sheet-structure protofibrillar oligomers and fibrils which accumulate in LBs (55). A previous study reported that soluble transient intermediate oligomers may be the critical form that causes cytotoxicity, including mitochondrial dysfunction, abnormal Ca^{2+} signaling, ROS production and neuronal death (14). A number of recombinant α-Syn fragments (aa, 1-95 and 61-140) have been reported to promote the formation of aggregates from cellular full-length α-Syn, inducing microglial toxicity and increasing the release of inflammatory factors (17). The α-Syn protein is almost exclusively localized to the presynaptic terminals of neurons (3,56,57), regulating the biosynthesis of DA (9). However, α-Syn aggregation in DA neurons results in the depletion of soluble α-Syn, which

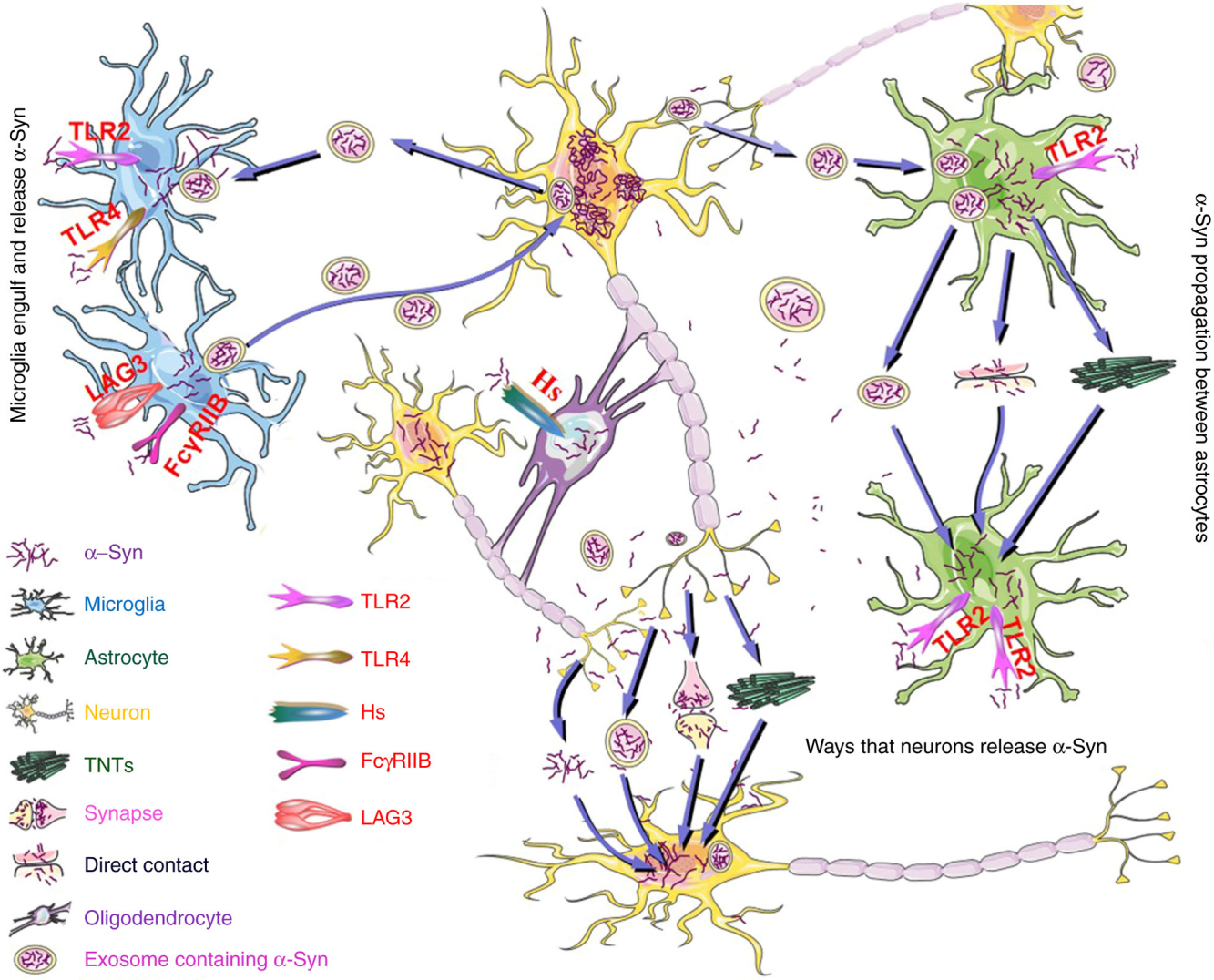

Figure 2. Possible mechanisms for intercellular transmission of α-Syn. α-Syn is released by neurons through TNTs and exosomes, as well as through a leaking process between pre- and post-synapses. α-Syn also spreads to nearby neuronal cells in a free-floating manner. Astrocytes engulf extracellular α-Syn and transfer it to other astrocytes through direct contact between cells, extracellular exosomes, vesicles and TNTs. The phagocytosis of extracellular α-Syn by astrocytes depends on TLR2, while the uptake of α-Syn by microglia is dependent on TLR2, TLR4, LAG3 and FcγRIIB. Microglia can also endocytose exosomes containing α-Syn and promote the transfer of α-Syn to neurons by releasing exosomal α-Syn. Hs is implicated in oligodendroglial uptake of extracellular α-Syn. α-Syn can be transferred from neurons to astrocytes, microglia and oligodendrocytes and can also be transferred from microglia to neurons, astrocytes to astrocytes and neurons to neurons. Astrocyte to neuron transfer is rare. α-Syn, α-synuclein; TNTs, tunneling nanotubes; TLR, Toll-like receptor; Hs, heparan sulfate; LAG3, lymphocyte-activation gene 3; FcγRIIB, Fc gamma receptor IIB.

subsequently causes a loss of the presynaptic terminal function of neurons and decreases DA levels in neurons in the SN-striatal system (9,24). The aberrant accumulation of α-Syn reduces the aggregation and fusion activity of synaptic vesicles, which subsequently affects the release of neurotransmitters (such as dopamine), resulting in neuronal death in the SN and movement dysfunction (16,58). α-Syn is also reported to be found extracellularly, which indicates that α-Syn may induce cytotoxic effects in the extracellular space (15). Extracellular α-Syn oligomers associate with the neuronal membrane, forming pore-like structures and leading to enhancement of the influx of both glucose and Ca^{2+} as well as membrane conductance (15,16). This may partly explain the synaptic toxicity of α-Syn. There is a marked increase in iron deposition in the SN of patients with PD (21,22), which indicates that iron serves a role in the pathology of PD. It has previously been reported that α-Syn exerts cytotoxic effects by regulating iron metabolism. Aggregated α-Syn inhibits ferritin release of iron and disturbs the autophagy of iron (22). In certain cases, such as in the presence of Cu^{2+}, α-Syn may perform the same function as the enzyme ferrireductase, which is involved in the reduction of Fe^{3+} to Fe^{2+}, Fe^{2+}/Fe^{3+} imbalance in PD and iron-mediated neuronal death. The imbalance of Fe^{2+}/Fe^{3+} may interfere with mitochondrial function (21). Since DA neurons consume large amounts of ATP, mitochondrial dysfunction may lead to their death (23). It has previously been reported that α-Syn overexpression disrupts the fusion of mitochondrial membranes, leading to mitochondrial fragmentation. Overexpression of α-Syn, which reduces the contacts between the endoplasmic reticulum and the mitochondria and interferes with Ca^{2+} transfer, can lead to impaired autophagic mechanisms, defects in mitochondrial fission and an increase in the

number of damaged mitochondria (23). The mutant forms of α-Syn or α-Syn overexpression suppress complex I activity in mitochondria, enhancing the generation of ROS. Furthermore, α-Syn also disrupts the intracellular transport of mitochondria in PD (23).

α-Syn preformed fibrils (PFFs) form from recombinant α-Syn *in vitro*. The α-Syn PFFs formed by aggregation *in vitro* are structurally similar to the pathological α-Syn found *in vivo*. α-Syn PFFs can also spread like prions between neurons both *in vivo* and *in vitro* (59). When α-Syn PFF is injected into a mouse brain, the serine 129 site of α-Syn PFF can be phosphorylated, forming p-α-Syn, which is a marker of α-Syn neurotoxicity (59).

To date, the initial trigger mechanism for the transformation of α-Syn into pathological α-Syn is still being explored. Different forms of α-Syn exist and the toxic mechanisms of each α-Syn form in the pathogenesis of PD remain poorly understood. Notably, the conformation of α-Syn may be highly correlated with its pathological toxicity. The toxic effects of α-Syn are multifaceted and can be severe, serving an important role in the pathogenesis of PD. In view of this, drugs that suppress α-Syn aggregation or promote pathological α-Syn degradation may be a key future PD treatment.

4. Age-related α-Syn pathogenicity

The intercellular transmission of α-Syn is widely accepted as a potential mechanism for the progression of PD (60). Previous studies have reported that several years before the diagnosis of PD, pathological α-Syn is present in both the brain and many peripheral organs, such as the skin, submandibular gland, heart, stomach and intestines (38,61-63). Braak *et al* (64,65) reported that the α-Syn protein may originate in the peripheral nervous system, specifically in the enteric nervous system (ENS) (66). Afterward, α-Syn spreads to the brain tissue through prion-like mechanisms via the autonomic nervous system (66). Other studies have also reported that various forms of α-Syn, including monomers, oligomers and fibrils, can be transferred from the ENS to the brain via the vagus nerve (Fig. 3) (23,38). Upon entering the brain, α-Syn spreads to the midbrain via interconnected neurons, leading to PD-associated motor disorders, such as bradykinesia, postural instability, myotonia and static tremor (Fig. 3) (39). α-Syn can also spread to nearby neurons through extracellular vesicles (EVs) or in a free-floating manner (Fig. 2) (67). Unlike prions, however, there is no evidence that pathological α-Syn is infectious (68).

Van Den Berge *et al* (38) injected recombinant human α-Syn PFFs (hPFFs) or mouse α-Syn PFFs (mPFFs) into the intestinal wall of the duodenum and pylorus in wild-type rats and demonstrated that age is a key factor in efficient α-Syn propagation along the intestine-brain axis (Fig. 3). In older mice, when compared with younger mice, after inoculation of α-Syn PFFs, α-Syn pathology is transmitted from the ENS to the brain stem and this transmission is accompanied by a decreased dopamine level in the striatum (Fig. 3) (39). Van Den Berge *et al* (38) also reported that: i) Sympathetic denervation in the heart and vagal denervation in the stomach are age-related and associated with the amount of α-Syn derived from α-Syn PFF after injection into wild-type rats; ii) deposits of phosphorylated α-Syn in aged rats are much denser and more resistant to proteinase K, a nonspecific serine protease used for protein digestion, compared with those in younger rats; iii) mPFFs are more efficient than hPFFs at inducing α-Syn transmission from the intestine to the brain in young rats, which suggests that a species barrier does exist; and iv) the pathological outcomes of old rats treated with hPFFs closely resemble, or are worse than, those of young rats treated with mPFFs, which indicates that aging lowers the species barrier (Fig. 3). Glucocerebrosidase (GCase) is a lysosomal enzyme and impairment of GCase function leads to aberrant accumulation of α-Syn. Injection of α-Syn PFFs into the mouse duodenum can activate inflammation, decrease GCase production and impair GCase function and ENS physiology. However, upregulation of the production of GCase alleviates the ENS functional deficit and α-Syn-associated pathology. The expression of GCase is markedly decreased in the duodenum in older mice compared with younger mice and this decrease is correlated with an increase in p-α-Syn, which indicates that aged mice are more vulnerable to α-Syn pathology in the intestinal tract. During aging, intestinal protein homeostasis (including maintenance of the function of GCase) and the ability to eliminate α-Syn aggregates decline (39). This negative variation leads to an increased vulnerability to α-Syn pathology and dysfunction of the sensorimotor system (Fig. 3) (39). Conversely, overexpression of α-Syn can lead to an imbalance in intestinal homeostasis and accelerate the occurrence of intestinal aging (13).

Iba *et al* (69) explored the role of aging and the inflammatory response in synucleinopathies by injecting α-Syn PFFs into the striata of young or aged mice. It was observed that aged mice showed enhanced α-Syn accumulation in specific brain regions and had more pronounced behavioral deficits compared with young mice. The loss of DA neurons and DA nerve endings in the striata of mice inoculated with α-Syn PFFs increased with aging. Compared with young mice inoculated with α-Syn PFFs, aged mice injected with α-Syn PFFs showed enhanced T cell infiltration and sustained active microglia in the brain tissue. Transcriptome analysis suggested that inflammation in the brain was greater in aged mice when compared with young mice inoculated with α-Syn PFFs. Rauschenberger *et al* (70) employed hm^{2}α-Syn-39 mice, a PD mouse model carrying a double-mutant human α-Syn gene (A30P/A53T), to explore the effects of the inflammatory response and aging on DA neurons. The aforementioned study reported that the striatal DA terminals, striatal dopamine levels and SN DA neurons were reduced in hm^{2}α-Syn-39 PD mice at the age of 16-17 months compared with age-matched control mice. In the striata of hm^{2}α-Syn-39 PD mice, there was an age-related association between striatal DA terminal loss and the number of infiltrating clusters of differentiation 4$^+$ (CD4$^+$) and CD8$^+$ T cells. Such a correlation, however, was not observed in the wild-type mice. No meaningful age-dependent changes in the numbers of CD8$^+$ T cells, CD4$^+$ T cells or B220$^+$ B cells were reported in the nigrostriatal tracts of the wild-type group of mice. By comparison, in the SN of hm^{2}α-Syn-39 PD mice, marked age-dependent increases in the number of CD8$^+$ T cells, glial fibrillary acidic protein (GFAP)$^+$ astrocytes and CD11b$^+$ microglia were observed. Furthermore, age-dependent impairment of motor function was also observed in hm^{2}α-Syn-39 PD mice.

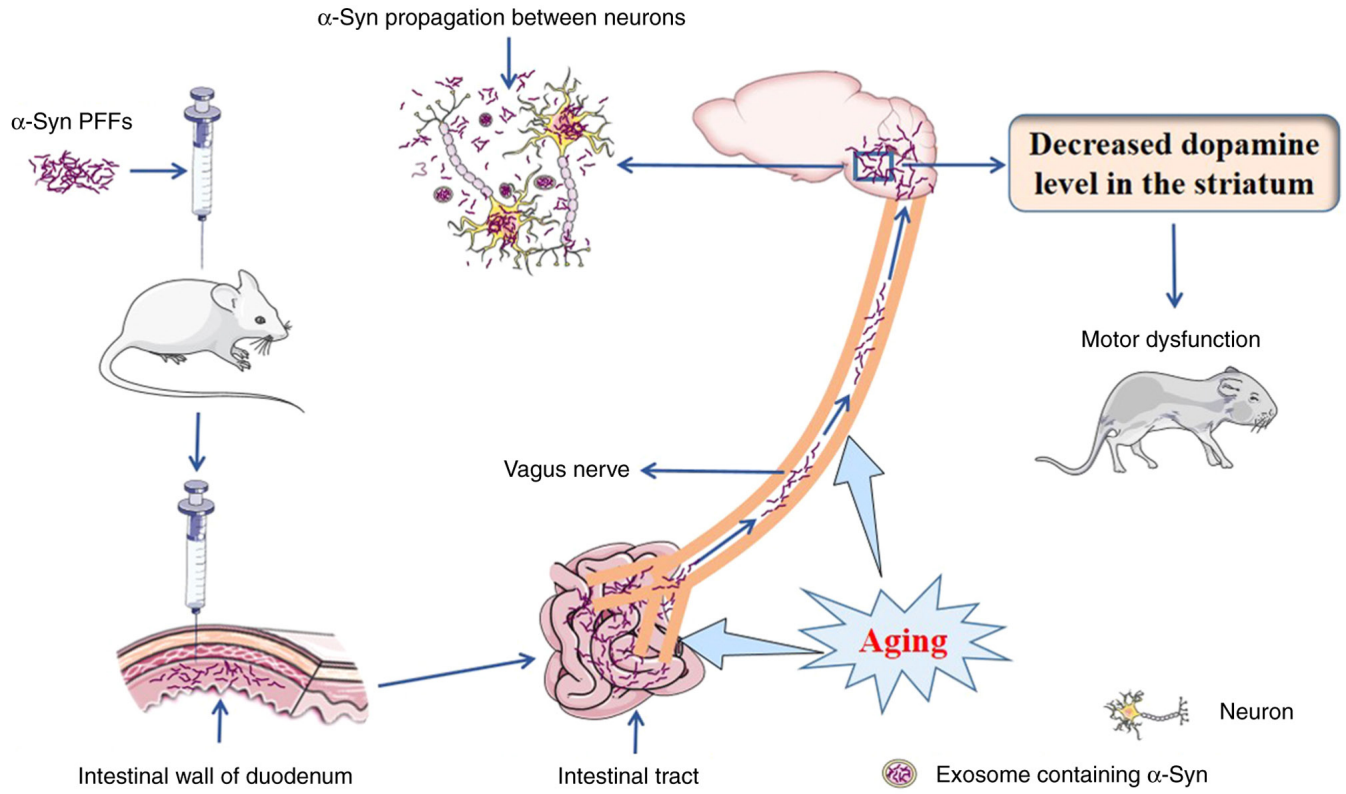

Figure 3. Aging promotes the development of α-Syn pathology in the intestinal tract and α-Syn PFF transmission along the intestine-brain axis. The murine duodenal intestinal wall is inoculated with α-Syn PFFs and α-Syn is transferred to the brain through the vagus nerve, which causes α-Syn propagation between neurons. α-Syn pathology reduces the dopamine level in the striatum, resulting in movement dysfunction. Aged rats and mice are more likely to be vulnerable to α-Syn pathology in the intestinal tract compared with young rats and mice. Aging promotes α-Syn transmission along the intestine-brain axis. α-Syn, α-synuclein; PFFs, preformed fibrils.

In addition, a previous study reported that the expression levels of the α-Syn-related complex were correlated with age. Nerve globins are O_2-binding proteins that participate in the etiopathogenesis of neurodegenerative disorders. The levels of neuronal hemoglobin (nHb), a member of the nerve globin protein family, are decreased in α-Syn deposits, DA neurons and LBs of patients with PD. In the brain tissue of elderly individuals, a complex consisting of Hb and α-Syn ($nHb^{α\text{-}Syn}$) has been reported. In the human striatum, the $nHb^{α\text{-}Syn}$ complex level in mitochondria decreases with age, while in the cytoplasm, the $nHb^{α\text{-}Syn}$ level increases with age (71). In the SN, a similar expression pattern of $nHb^{α\text{-}Syn}$ is observed (71). Of note, the $nHb^{α\text{-}Syn}$ complex also exists in red blood cells (RBCs). The levels of $nHb^{α\text{-}Syn}$ in RBCs significantly increase with age and significantly increase in patients with PD (71). However, the specific mechanism by which $nHb^{α\text{-}Syn}$ or $pHb^{α\text{-}Syn}$ expression changes with age remains to be further investigated.

The aforementioned studies indicate that the pathogenicity of α-Syn may be age-related. Aging promotes the development of α-Syn pathology in the intestinal tract and α-Syn PFF transmission along the intestine-brain axis. The pathological changes caused by α-Syn, including the loss of DA nerve endings, behavioral defects and inflammation in the brain, are aggravated with age. This may explain the susceptibility of elderly individuals to PD. Furthermore, maintaining normal intestinal function may be beneficial for PD patients. Therefore, the effects of diet and the gastrointestinal microbiome on PD should be evaluated.

5. α-synuclein and astrocytes

In the central nervous system (CNS), astrocytes are the most numerous non-nerve cell population, serving important roles in neurotrophic support, neurotransmitter transmission, synaptic development and neuroinflammation (16,18,57). There are two different phenotypes of astrocytes, namely, the A1 phenotype (proinflammatory phenotype) and the A2 phenotype (anti-inflammatory phenotype) (72). A1 astrocytes can release neurotoxic cytokines, such as complement C3, which are harmful to oligodendrocytes and neurons (19,73-75); hence, A1 astrocytes are considered a characteristic of normal aging and neurodegenerative diseases (16). In contrast to A1 astrocytes, A2 astrocytes are reported to be neuroprotective and capable of producing neurotrophic cytokines, including nerve growth factor and brain-derived neurotrophic factor (BDNF), to promote neuronal growth and survival (16,73). Depending on the changes taking place in the brain environment, astrocytes may shift between A1 and A2 types in a stimulus-specific manner (18,72,75). For example, A1 astrocytes can be induced by TNF, complement component 1q and IL-1α, which are secreted by activated microglia (76). Notably, in another previous study, the numbers of astrocytes of both phenotypes were increased in animal models of PD (77); however, no or only slight increases in the numbers of astroglial cells were observed in the brain tissues of patients with PD (16).

In astrocytes, α-Syn expression levels are normally low (29,78), whereas α-Syn accumulates within astrocytes of

patients with PD (20). Thus, it is reported that α-Syn in astrocytes may originate from neurons (57). Neurons release α-Syn in a variety of conformations, such as monomers, oligomers and fibril species (30). Previous studies have reported that astrocytes engulf extracellular α-Syn released by neurons and are involved in α-Syn transmission (16,29,74). Astrocytes take up α-Syn and transfer it to other astrocytes through direct contact between cells, extracellular exosomes and vesicles (Fig. 2) (16,57,79). In addition, TNTs are considered an important pathway for α-Syn transmission. TNTs are transient tubular structures used for long-distance cell-to-cell communication (79). Through TNTs, astrocytes transfer excessive α-Syn oligomers to other astrocytes (Fig. 2) (57). α-Syn can be transferred from neurons to neurons, neurons to astrocytes and astrocytes to astrocytes (79) but is rarely transferred from astrocytes to neurons (Fig. 2) (18).

Astrocytes express Toll-like receptors (TLRs), which are involved in astrocyte activation, neuroinflammation and α-Syn uptake (18,29,75). In astrocytes, the uptake of extracellular α-Syn relies on TLR2 rather than TLR4 (Fig. 2) (18), while intracellular α-Syn relies on TLR2, TLR3 and TLR4 to induce inflammatory responses in astrocytes (18,80). Notably, α-Syn entry into microglia is dependent on TLR2 and TLR4 (78). Astrocytes can degrade α-Syn fibrils more efficiently compared with neurons (79). Neurons and microglia can also degrade α-Syn fibrils. TLR2 stimulation accelerates the phagocytosis of α-Syn fibrils by neurons, astrocytes and microglia (30,78) and TLR2 stimulation, rather than TLR4 stimulation, significantly inhibits intracellular α-Syn fibril degradation in astrocytes and neurons (30). However, with or without stimulation of TLR2, α-Syn fibrils are degraded efficiently in microglia (30). It has also been reported that astrocytes phagocytose and eliminate extracellular recombinant human α-Syn through the autophagy and ubiquitin-proteasome pathways *in vitro* (81). Overexpression of wild-type α-Syn and expression of mutated forms of α-Syn can impair autophagy and the ubiquitin-proteasome system (23).

α-Syn can potentiate the activation of astrocytes and trigger their inflammatory response (18). Previous studies have reported that monomeric α-Syn, oligomeric α-Syn and fibrillar α-Syn can activate astrocytes, which leads to neuronal death (78,82). However, these α-Syn forms differ in their capacity for the activation and induction of cytotoxicity in astrocytes. In astrocytes, α-Syn oligomers can cause significant mitochondrial dysfunction, whereas the effects of monomers and fibrils on mitochondria are mild. Fibrillary, oligomeric and monomeric forms of α-Syn can all markedly increase IL-1β and TNF-α mRNA expression levels in astrocytes, while only oligomers induce an increase in extracellular hydrogen peroxide (82). Intracellular α-Syn induces neurotoxic proinflammatory responses, including expression of IL-6, C-X3-C motif chemokine ligand 1 (CX3CL1), chemokine (C-C motif) ligand 5 (CCL5) and TNF-α in astrocytes via the p38 MAPK and NF-κB signaling pathways (Fig. 4) (18,20).

Wild-type or A53T mutated α-Syn markedly enhances the expression of TLR2 and TLR3 in astrocytes and TLR2 or TLR3 may mediate extracellular inflammatory pathways and intracellular inflammatory pathways, respectively (80). A53T mutant α-Syn aggregates activate astrocytes and triggers neuroinflammation through the JNK and NF-κB signaling pathways. Subsequently, astrocytes express cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF-α and IL-1β (Fig. 4) (19). Heat shock protein 70, a molecular chaperone, has been reported to be an important modulator that suppresses the JNK and NF-κB signaling pathways in astrocytes and inhibits inflammation induced by α-Syn, exhibiting an anti-inflammatory effect (19). A previous study reported that co-expression of α-Syn and IFN-γ may be one of the mechanisms leading to the pathogenesis of PD (83). In astrocytes, IFN-γ alone increases TNF-α and TLR3 mRNA expression levels. Wild-type or A53T-mutant α-Syn alone enhances the expression levels of TNF-α, NF-κB, IL-1β, TLR2 and TLR3. Further mechanistic study confirmed that IFN-γ amplifies the wild-type or A53T mutant α-Syn-inducing effect, except in the case of IL-1β in astrocytes (84). IFN-γ enhances the stimulation of α-Syn and the inflammation of astrocytes through TNF-α, TLR2 and TLR3, which indicates that the participation of IFN-γ in the innate immunity, induced by α-Syn, is necessary to initiate and maintain astrocyte activation (84).

Astrocytes are not a type of immune cells, but they are involved in brain inflammation. α-Syn can trigger an inflammatory response in astrocytes and the inflammatory factors released by astrocytes can have a toxic effect on neurons. In addition, α-Syn oligomers cause mitochondrial dysfunction in astrocytes. Astrocytes that undergo inflammatory responses and astrocytes with mitochondrial dysfunction may reduce neurotrophic and metabolic support for neurons, exacerbating neurodegeneration. Inhibiting the inflammatory response of astrocytes and enhancing their neurotrophic and metabolic support for neurons may contribute to neuronal survival and alleviate PD symptoms.

6. α-synuclein and microglia

Microglia are a type of tissue-specific macrophages that reside in the CNS (57). Microglia are implicated in brain development, protein aggregate elimination, neuronal survival, neuronal apoptosis, immunosurveillance, synaptic plasticity maintenance, synaptic pruning, neural circuit shaping and injury repair (16,57,85,86). In numerous neurodegenerative diseases (including PD, Alzheimer's disease and amyotrophic lateral sclerosis), microglia can be polarized into two major functional subtypes, including the M1 (proinflammatory) phenotype and the M2 (anti-inflammatory) phenotype (37,73,87). M1 microglia mediate brain immunological reactions by secreting proinflammatory substances, including TNF-α, IL-12, IFN-γ, IL-1β and IL-6, which contribute to neuronal death (73,85). In addition, M1 microglia also express major histocompatibility complex class (MHC)-I and MHC-II molecules, which are associated with antigen presentation (16,88-90). Unlike the M1 phenotype, M2 microglia exert neuroprotective effects (37). Neurotrophic factors, such as insulin-like growth factor-1 (IGF-1) and BDNF and anti-inflammatory cytokines, such as IL-13, IL-4, TGF-β and IL-10 are released by M2 microglia, promoting neuronal survival (37,73,85). It has been previously reported that some microglial regulatory mediators, such as triggering receptors expressed on myeloid cells 2 (TREM2), TGF-β1, IFN-β and IL-10, have the potential to convert microglia from the M1 state to the M2 state (85), which may delay PD progression (37,91). During chronic inflammation,

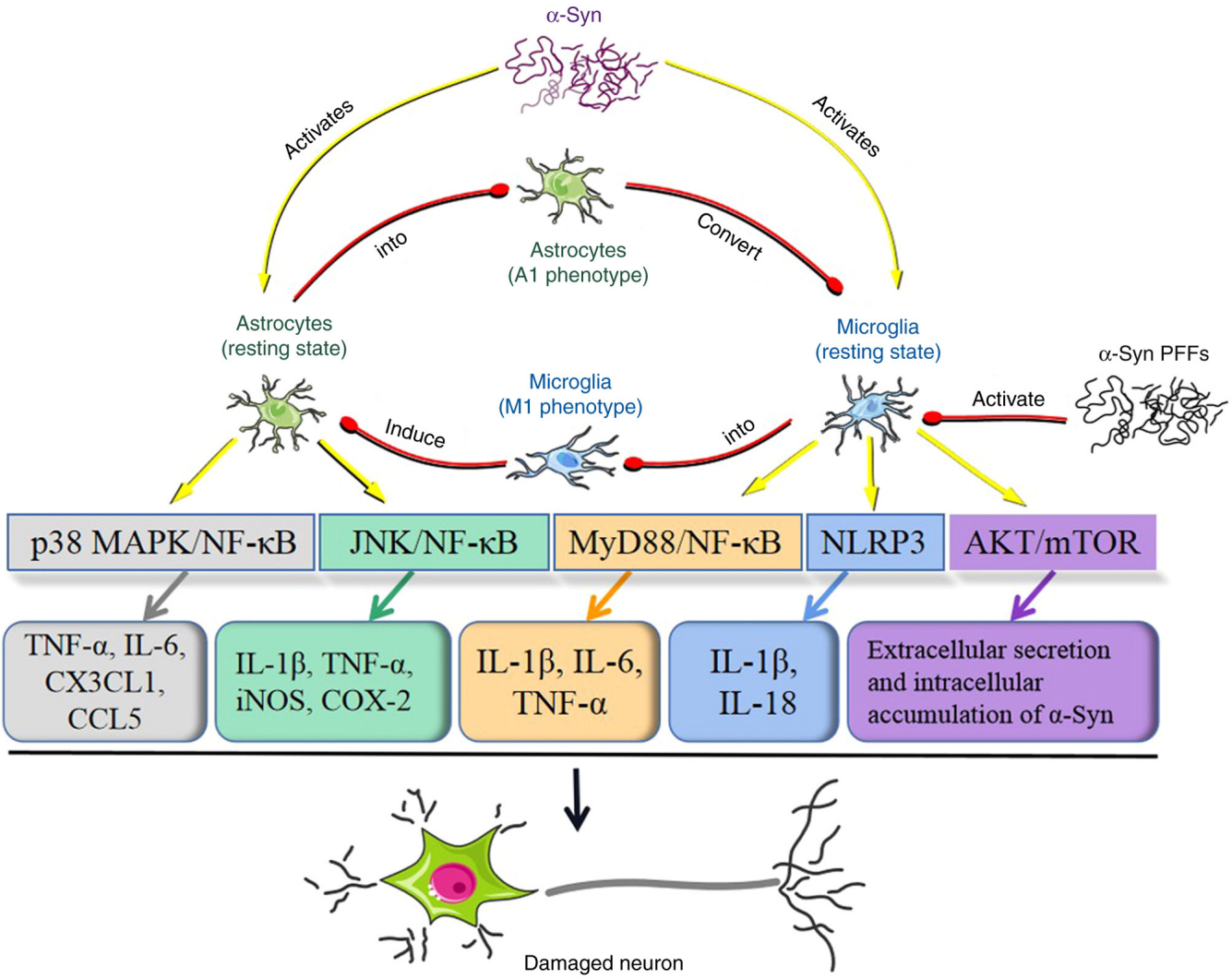

Figure 4. Inflammatory activation of astrocytes and microglia by α-Syn and phenotypic switching between astrocytes and microglia. α-Syn induces the expression of CX3CL1, CCL5, IL-6 and TNF-α in astrocytes through the p38 MAPK and NF-κB signaling pathways. α-Syn aggregates also activate astrocytes and trigger neuroinflammation through the JNK and NF-κB signaling pathways. This leads astrocytes to express COX-2, iNOS, TNF-α and IL-1β. In microglia, α-Syn activates the MyD88-NF-κB signaling pathway, leading microglia to generate proinflammatory factors, including IL-6, IL-1β and TNF-α. α-Syn can prime and activate the microglial NLRP3 inflammasome, leading to the generation of IL-18 and IL-1β by microglia. Exosomal α-Syn suppresses autophagy in microglia through activation of the AKT/mTOR signaling pathway, which leads to accelerated extracellular α-Syn secretion and increased intracellular α-Syn accumulation. These inflammatory responses induced by α-Syn are conducive to DA neuronal death. α-Syn PFFs activate microglia into the M1 phenotype, which in turn induces astrocytes to develop into a neurotoxic A1 phenotype. The inflammatory responses in astrocytes are also capable of converting microglia into an M1-like phenotype. α-Syn, α-synuclein; PFFs, preformed fibrils; CX3CL1, C-X3-C motif chemokine ligand 1; CCL5, chemokine (C-C motif) ligand 5; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; NLRP3, nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing 3; MyD88, myeloid differentiation factor 88; DA, dopaminergic.

microglia lose their M2 anti-inflammatory phenotypic characteristics and preferentially differentiate into the proinflammatory M1 state (92).

Interactions between α-Syn and microglia may serve a pivotal role in PD pathogenesis (85). Similar to astrocytes, microglia are able to take up α-Syn released by neurons (30,57,78). It has been previously reported that the phagocytosis of α-Syn by microglia is dependent on TLR2 and TLR4 (Fig. 2) (36,78). TLR2 accounts for the microglial uptake of soluble α-Syn oligomers; however, the specific α-Syn forms internalized by microglia via TLR4 remain to be further investigated (78). TLR4 promotes extracellular α-Syn clearance and DA neuronal survival in the SN, while elimination of TLR4 impairs the ability of microglia to phagocytose α-Syn, enhancing dyskinesia and death of nigral DA neurons (93). It been reported that TLR2-deficient microglia can also endocytose α-Syn monomers and low concentrations of α-Syn fibrils and oligomers. A previous study indicated that the phagocytosis of cellular α-Syn by microglia depends not only on TLR2 receptors but also on numerous other types of receptors (30). For instance, the uptake of extracellular α-Syn fibrils by microglia is also reliant on receptors including lymphocyte-activation gene 3 and Fc gamma receptor IIB (Fig. 2) (78). It is possible that each type of receptor only recognizes one specific α-Syn conformation (30). EVs, including exosomes and microvesicles, have been reported as possible routes of α-Syn transmission in the CNS. The α-Syn oligomers in EVs are more easily endocytosed and cause more damage to recipient cells than non-EV-encapsulated α-Syn oligomers (87). Another study has confirmed that microglia may

achieve efficient uptake of exosomes containing monomeric and oligomeric α-Syn and that microglia can be activated by these exosomes. Exosomal α-Syn suppresses autophagy in microglia through activation of the AKT/mTOR signaling pathway, which leads to accelerated extracellular α-Syn secretion and increased intracellular α-Syn accumulation (Fig. 4) (94). Additionally, microglia may promote the transfer of α-Syn to neurons by releasing exosomal α-Syn (Fig. 2) (94).

TLRs, as receptors for extracellular α-Syn, account for not only the binding and internalization of α-Syn but also signal conduction and the inflammatory response (36,57,78,85). TLR1, TLR2, TLR4 and TLR5 are responsible for α-Syn-induced inflammatory activation of microglia (57,85,95,96). Previous studies have reported that TLR7 and TLR8 may also account for microglial activation (96,97). A previous study also reported that α-Syn oligomers convert microglia into the M1 phenotype via the TLR1 and TLR7 signaling pathways (98). In addition, α-Syn can activate microglia through other receptors, such as purinergic receptor P2X ligand-gated ion channel 7 (P2X7 receptor), CD36 and Fcγ receptors expressed in microglia (57,99). Notably, each α-Syn receptor may only interact with a specific conformation of α-Syn for the uptake of α-Syn by microglia, as previously described (30). α-Syn receptors involved in the activation of microglia may also be conformationally sensitive. A previous study reported that the TLR2 ligand activity of α-Syn possesses conformational sensitivity and that TLR2 is activated only by particular forms of oligomers (100). Adenoviral vector-treated differentiated SY5Y neuroblastoma cells (AVT-dSY5Y) overexpress human α-Syn and the α-Syn in the cytoplasm of these cells is predominantly monomeric. The extracellular protein outside the cytosol contains many stable α-Syn oligomers. The α-Syn released by AVT-dSY5Y, not the intracytoplasmic α-Syn fraction, activates microglia through a TLR2-dependent mechanism (100). Moreover, misfolded α-Syn increases the expression levels of TLR2 and TLR3 in microglial culture (80). It has also been reported that treatment of microglia with α-Syn leads to elevated expression of TLR1 and TLR7 (101). TLR1, TLR2 and TLR4 on the surface of microglia are able to respond to monomeric, oligomeric and fibrillar forms of α-Syn and activate the myeloid differentiation factor 88 (MyD88)-NF-κB signaling pathway, which leads to α-Syn-induced neuroinflammation (57). Activation of NF-κB in the MyD88-dependent pathway produces various proinflammatory factors, including IL-6, IL-1β and TNF-α (Fig. 4) (85). Monomeric and oligomeric α-Syn are able to prime and activate the microglial nucleotide-binding oligomerization domain leucine-rich repeat and pyrin domain-containing 3 (NLRP3) inflammasome, a multiunit protein complex, through TLR2 and TLR5 ligation (95). The NLRP3 inflammasome recruits the small adaptor molecule apoptosis-associated speck-like protein, which subsequently triggers cysteine-aspartate protease-1 (caspase-1) activation (74,86). Caspase-1 is capable of producing the mature proinflammatory factors IL-18 and IL-1β by cleaving their precursor forms (Fig. 4) (16,57,86). In addition, activated caspase-1 results in C-terminal truncation of α-Syn, which leads to the formation of more aggregates and an increased inflammatory response (16,17). Microglia in patients with PD may be overactivated and inflammatory factors generated by microglia are one of the causes of DA neuronal death (27).

Interactions between microglia and astrocytes may also take place. α-Syn PFFs can activate microglia into the M1 phenotype, which in turn induces astrocytes to acquire a neurotoxic A1 phenotype. This microglia-mediated induction of astrocytes to an A1 subtype is directly blocked by glucagon-like peptide-1 receptor agonists (102). Notably, it has previously been reported that the inflammatory response in astrocytes is also capable of converting microglia into an M1-like phenotype through paracrine action (Fig. 4) (18).

Membrane receptors expressed by glial cells, including astrocytes and microglia, are structurally sensitive and recognize only specific forms of α-Syn. Notably, certain membrane receptors on the surfaces of glial cells are involved in α-Syn endocytosis, while others are implicated in α-Syn-mediated inflammatory responses. Although several α-Syn-related receptors and their corresponding α-Syn forms have been identified, the specific α-Syn form binding to TLR4 remains unclear. Moreover, potential receptors for α-Syn, which have not yet been discovered, may exist. Further research is needed to develop therapeutic interventions to selectively inhibit glial receptors from binding to α-Syn, thereby preventing glial inflammatory responses.

7. α-synuclein and oligodendrocytes

Oligodendrocytes are glial cells of the CNS that possess numerous functions, including myelin generation, metabolic support, immunomodulation and production of neurotrophins, such as glial cell line-derived neurotrophic factor, BDNF and IGF-1 (73,103).

The expression of α-Syn in oligodendroglial cells is low under normal physiological conditions (73). The amount of endogenous α-Syn protein expressed by rat oligodendrocyte lineage cells is ~20% of that expressed by neurons (104). In multiple system atrophy (MSA), a rare neurodegenerative disorder, pathological α-Syn accumulates in oligodendrocytes, forming glial cytoplasmic inclusions (GCIs), which is a unique hallmark of this disease (31,103). In PD, by contrast, misfolded α-Syn mainly appears in neurons (105), forming LNs and LBs. A previous study reported that α-Syn inclusions are present in oligodendrocytes in the midbrains of patients with PD but that they differ in topography and antigenicity from GCIs in MSA oligodendrocytes (106). Oligodendrocytes in certain parts of the brain in patients with PD appear to be unaffected by α-Syn. Several years before the onset of PD motor dysfunction, α-Syn is already present in the anterior olfactory nucleus (AON) of the olfactory bulb (5). In AON regions of post-mortem patients with PD, α-Syn is present in some neurons, astrocytes, microglia and pericytes, whereas no α-Syn is present in oligodendrocytes (5). In MSA, oligodendrocytes are affected by α-Syn and α-Syn aggregates to form GCIs, while in PD, α-Syn mainly affects neurons and aggregates to form LNs and LBs (2,3,31,103,105). This is a future research direction which requires further study, as related studies may be of significance for revealing the toxicity of α-Syn and the pathogenesis of synucleinopathies, including MSA and PD.

Oligodendrocytes are able to take up monomeric and oligomeric forms of α-Syn and small amounts of α-Syn fibrils in a dynamin-dependent manner both *in vivo* and *in vitro* (107). Exogenous α-Syn PFFs can also be phagocytosed by

oligodendrocyte precursor cells (OPCs), which increases the expression of endogenous α-Syn and triggers impairment of autophagy in OPCs, which can result in endogenous α-Syn accumulation (104). In addition, it has been reported that α-Syn can be transferred from neurons to oligodendrocytes (Fig. 2) (107). α-Syn uptake by oligodendrocytes is dependent on clathrin and is inhibited when clathrin expression is silenced (108). In addition, the phagocytosis of α-Syn by oligodendrocytes is both time- and dose-dependent (108). Finally, it has been previously identified that heparan sulfate and exosomes are involved in oligodendroglial phagocytosis of extracellular α-Syn fibrils (Fig. 2) (31,109).

A previous study reported that TLR4 expression is upregulated in α-Syn-transgenic MSA mice, an effect that is related to oligodendroglial overexpression of α-Syn (110). However, it remains unclear whether there is an interaction between TLR4 and α-Syn in oligodendrocytes in PD. In OPCs treated with α-Syn PFFs, the mRNA expression levels of myelinization-inhibiting cytokines, such as IL-1β and Sirtuin2, are increased, while the mRNA expression levels of myelinization-promoting cytokines, such as Contactin 1 and chemokine C-X-C-motif receptor 7, are decreased (104). Overexpression of α-Syn by oligodendrocytes may lead to neuroinflammation associated with nitrogen stress in a transgenic MSA mouse model (110). Certain studies have indicated that oligodendrocytes are able to produce a range of chemokines and cytokines, including CCL2/5, chemokine (CXC motif) ligand 9/10 and IL1-β (104,111). Oligodendrocytes also express receptors capable of transducing immune-related signals (111). However, whether α-Syn triggers an inflammatory response in oligodendrocytes in PD remains largely unknown.

8. α-synuclein and acquired immunity

The brain was previously thought to be an immune-privileged organ that was not easily infiltrated by peripheral immune cells because of the blood-cerebrospinal fluid barrier and blood-brain barrier (BBB) (16,112). However, it has been reported that there exists bidirectional communication between the CNS and the immune system (113,114).

Further evidence indicates that acquired immunity, also known as adaptive immunity, serves a role in the pathogenesis of PD (25,27). In animal models of PD, T cells have been reported to infiltrate the SN (115). In α-Syn PFF-inoculated mouse brains, the relative percentages of natural killer cells, $CD8^+$ T cells, $CD19^+$ B cells, $CD4^+$ T cells and activated myeloid cells ($CD11b^+CD45^{high}$) are increased (116). In patients with PD, peripheral T cells can access the brain and invade the SN (37). For instance, $CD3^+$, $CD4^+$ and $CD8^+$ T cells have been reported in the brains of patients with PD (25). Furthermore, α-Syn proteins from dead cells are reported to be capable of activating microglia (37). The activated microglia secrete a series of inflammatory factors, including IL-1β and TNF-α (73,85), which act on microvascular endothelial cells, leading to increased BBB permeability that facilitates T cell entry into the brain (Fig. 5) (37). Likewise, astrocytes around blood vessels produce inflammatory factors under pathological conditions, such as IL-6, IL-1β and TNF-α, also resulting in an increase in BBB permeability (Fig. 5) (33). Additionally, microglia take up α-Syn proteins and process them in endosomes (117). Then, the microglia express MHC-II proteins that present α-Syn antigenic peptides to $CD4^+$ T cells, therefore initiating acquired immunity (Fig. 5) (117-119). $CD4^+$ T cells can be activated into proinflammatory T helper (Th)-type cells, such as Th17 and Th1 cells and anti-inflammatory T cells, such as regulatory T (Treg) cells, which have different functions (Fig. 5) (28). Th17 and Th1 cells are involved in enhancing the inflammatory response, mediating PD pathology and inducing DA neuronal death (Fig. 5) (28). On the other hand, Treg cells are involved in the maintenance of immune homeostasis, reduction of inflammation and secretion of protective factors, such as IL-10 and TGF-β (37). Notably, nitrated α-Syn is able to induce harmful Th cell maturation, which can cause severe neural damage (32). Degradation of α-Syn may produce potential antigenic peptides, which can be loaded onto MHC-I proteins and ultimately presented to $CD8^+$ T cells (Fig. 5) (90,117). $CD8^+$ T cells are involved in neuronal death and α-Syn aggregation in PD (120). Astrocytes with accumulated α-Syn also generate large amounts of MHC-II molecules in the brains of patients with PD (Fig. 5). These astrocytes are present near $CD4^+$ T cells in the brain, implying that there may exist a cross-interaction between $CD4^+$ T cells and astrocytes (18). A previous study reported that astrocytes containing accumulated α-Syn are more likely to activate $CD4^+$ T cells via the MHC-II signaling pathway *in vitro* compared with microglia containing accumulated α-Syn (18,121). Furthermore, it has been reported that DA neurons also express MHC in PD, which suggests that α-Syn may be an antigenic substance capable of facilitating T cell activation (27). A number of antigenic regions have been identified in α-Syn. Of these regions, one consists of aa 31-45 and 32-46 is located near the N-terminus, while the other antigenic region, comprising aa 116-140, is close to the C-terminus (122). The researchers examined the response of T cells to the α-Syn antigenic peptides in 9 patients with PD. For the majority of patients, it is mainly $CD4^+$ T cells secreting IL-4 or IFN-γ that respond to α-Syn antigenic peptides, while for only 1 patient, the response to α-Syn antigenic peptides is mediated by IFNγ-producing $CD8^+$ T cells (122). A previous study also suggested that the reactivity of $CD4^+$ T cells against α-Syn could be detected ~10 years before the onset of motor disorders associated with PD and is positively correlated with age (123).

Overall, through studies on animal PD models and PD patients, it has been established that peripheral immune cell infiltration in the brain exists in PD, suggesting an imbalance of immune homeostasis in the pathological state. This imbalanced immune homeostasis may be, at least in part, caused by a complex interaction among α-Syn, DA neurons, microglia, astrocytes and peripheral immune cells.

9. α-synuclein and glial cell senescence

Senescence may occur in certain types of brain cells, such as endothelial cells, astrocytes, microglia, neurons and oligodendroglial progenitor cells (27). Senescent cells exhibit a senescence-associated secretory phenotype (SASP), the main feature of which is the generation of multiple factors, including IL-1β and IL-6 (124,125). During aging, cells such

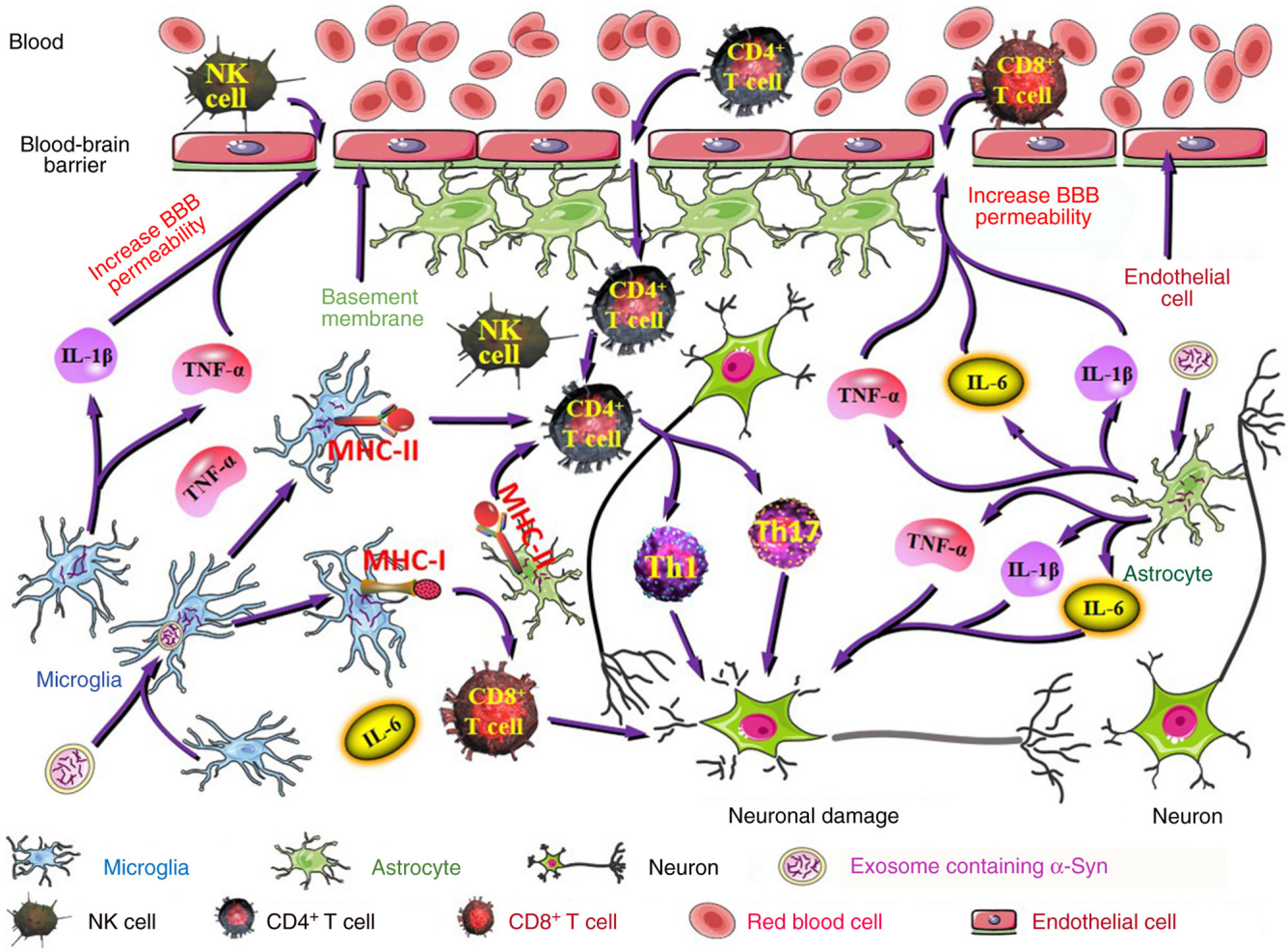

Figure 5. Adaptive immunity is implicated in PD pathogenesis. The inflammatory factors (IL-1β and TNF-α) produced by activated microglia act on microvascular endothelial cells, resulting in increased BBB permeability that facilitates NK cell, $CD8^+$ T cell and $CD4^+$ T cell entry into the brain. Likewise, astrocytes around the blood vessels produce inflammatory factors under pathological conditions, such as IL-6, IL-1β and TNF-α, which results in an increase in BBB permeability. Degradation of α-Syn may produce potentially antigenic peptides. Microglia and astrocytes express MHC-II proteins that present α-Syn antigenic peptides to $CD4^+$ T cells, which are subsequently activated into proinflammatory Th17 and Th1 cells. α-Syn antigenic peptides can also be loaded onto MHC-I proteins and ultimately presented to $CD8^+$ T cells by microglia. Th17 and Th1 cells are involved in enhancing inflammatory reactions, mediating PD pathology and inducing DA neuronal death. $CD8^+$ T cells are involved in neuronal death and α-Syn aggregation in PD. PD, Parkinson's disease; BBB, blood-brain barrier; NK cells, natural killer cells; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; MHC-I, major histocompatibility complex class I; MHC-II, major histocompatibility complex class II; Th1 cells, type 1 T helper cells; Th17 cells, type 17 T helper cells; DA, dopaminergic.

as astrocytes, express the SASP phenotype, exhibiting changes in nuclear ultrastructure and increased expression of vimentin filaments, GFAP, HMGB1 (a nuclear protein), IL-1β, IL-6 and TNF-α (33). IL-1β, IL-6 and TNF-α may also be biological markers of PD (126), which suggests a possible relationship between aging and PD. The SASP contributes to immune monitoring and clearance of senescent cells, which may be responsible for leukocyte infiltration and death of DA neurons in the SN (27). Previous research indicated that aging and the SASP may be important promoters of PD pathology (40). However, not all SASPs of senescent cells cause apoptosis, inflammation and fibrosis. The SASP may entail regenerative and growth cytokines in certain senescent cells (127). When senescent cells cannot be cleared in time, after a certain threshold is exceeded, the number of proinflammatory or proapoptotic senescent cells continues to increase, which leads to tissue damage and the progression of age-related diseases (127).

Both cellular aging and α-Syn are involved in PD pathology. Microglial senescence is an important factor in the development of PD (28). Microglia can engulf and degrade α-Syn in normal physiological states; however, the phagocytic ability of microglia decreases under aging conditions, leading to α-Syn accumulation and neurotoxicity (36). The α-Syn ingested by microglia is then degraded in autophagosomes (128). There is a reduction in the expression of autophagic protein during aging, which directly influences α-Syn clearance (57). Previous research has reported that decreased autophagy is associated with aggregation of α-Syn (31). Compared with microglia isolated from young mice, microglia isolated from adult mice exhibit a lower capacity to phagocytose α-Syn and secrete more inflammatory factors (57). Senescent microglia generate TNF-α, which promotes α-Syn deposition (28). A previous study reported that selective clearance of senescent microglia from the brain can relieve dyskinesia in animal PD models and significantly reduce the level of α-Syn in cerebrospinal

fluid (125). In addition to senescent microglia, activated microglia can also produce TNF-α, which enhances neuronal α-Syn secretion and thus promotes intercellular α-Syn propagation. Moreover, microglia-derived TNF-α promotes the SASP of neurons and causes neuronal aging (60).

α-Syn PFFs induce senescence in microglia and astrocytes, which results in altered expression of cellular senescence markers (40). Specifically, in microglia and astrocytes of α-Syn PFF-injected mice, α-Syn PFF-induced toxicity downregulates the expression of cellular senescence markers, such as HMGB1 and Lamin B1, whilst upregulating the expression of the p21 aging marker (40). These results are consistent with the observations in substantia nigra pars compacta tissues of postmortem patients with PD (40). In general, the expression levels of HMGB1 and Lamin B1 are decreased in senescent cells, while the expression level of p21 is increased (129-131). However, other animal experiments have reported that HMGB1 expression increases in astrocytes and decreases in neurons with advancing age (33,132). Therefore, the mechanism of α-Syn regulation of senescence markers and the phenotypes of distinct senescent cells should be further elucidated. HMGB1, which is located mainly in the nucleus, is involved in various physiological processes associated with DNA (including DNA repair, replication and transcription) (133). In senescent cells, HMGB1 is secreted into the extracellular space from the nucleus (129), resulting in DNA double-strand breaks (132). In certain cases, senescent astrocytes can release HMGB1 and this extracellular HMGB1 induces healthy astrocytes to develop a senescent-like phenotype (134). In addition, HMGB1 actively released into the extracellular space by aging cells, may stimulate target cells to secrete TNF-α, IL-6 and IL-1β by activating relevant receptors of target cells, such as TLR4 (134). Therefore, it can be suggested that α-Syn-induced glial cell senescence may affect the surrounding cells and tissue microenvironment by secreting related proteins, which may explain the toxic effects of α-Syn.

α-Syn may induce senescence in microglia and astrocytes; however, whether it can induce senescence in other types of cells requires further research. Senescent cells lose their normal physiological functions and produce harmful substances, which can affect the function of tissues. It is generally difficult to reverse the process of cellular aging, although progress has been made (135-137). Transplantation of exogenous stem cells may be a future treatment for PD. Stem cells have previously been reported to have anti-inflammatory effects and regenerative abilities, which may benefit patients with PD (92).

10. Conclusion

Various risk factors are implicated in the onset of PD, including the expression of pathological α-Syn. Pathological α-Syn can induce a variety of toxic effects that result in DA neuronal death and pathogenesis associated with PD. Drugs that suppress α-Syn aggregation or target α-Syn for degradation may have potential in the future for the treatment of patients with PD. PD is also an age-related neurodegenerative disorder and several characteristics of PD are similar to certain manifestations of aging. Previous research has shown that α-Syn spreads more easily, for example from the intestine to the brain, in aged animals. Under aging conditions, the ability of cells to take up and degrade α-Syn decreases, which leads to α-Syn accumulation and neuroinflammation. Additionally, α-Syn has the potential to induce senescence in glial cells, which is associated with changes in the expression of cellular senescence markers. Given that the toxic effects of α-Syn are associated with aging, the possibility of treating PD with antiaging drugs should be explored. In addition, as α-Syn expression may originate in the intestines, further research should focus on the intestinal function, intestinal symptoms and the intestinal microbiota of patients with PD. Research on such topics may be helpful to understand the pathogenesis of PD and provide a basis for the development of new therapeutic drugs. Drugs that prolong life and reduce age-related decline in intestinal function, such as rapamycin, also warrant further research. Both cellular aging and inflammation are implicated in PD pathology. Transplantation of exogenous stem cells with anti-inflammatory and regenerative properties may be a worthwhile therapeutic approach. Moreover, PD is caused by the selective death of DA neurons; hence, transplantation of DA neurons may replace these dead DA neurons. However, cell transplantation is associated with a number of issues, such as problems associated with the source of transplanted cells, ethical issues, survival of transplanted cells and the ability of transplanted cells to establish functional synaptic connections with other neurons. The excessive inflammatory response of glial cells triggered by α-Syn mediates the death of DA neurons. In addition, activated glial cells secrete inflammatory factors, which lead to an increase in BBB permeability, which causes T cell infiltration into the brain. Certain T cell subtypes enhance the inflammatory response and induce DA neuronal death. Therefore, blocking the binding of α-Syn to the relevant receptors of glial cells or regulating the inflammatory response of glial cells could be a promising strategy for PD treatment.

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Authors' contributions

NZ wrote the original draft of the manuscript. ZY and HX reviewed and edited the manuscript. RC reviewed and improved the language of this manuscript. SS and SX created the figures. SW reviewed and edited the manuscript, supervised the project and obtained funding. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhu B, Yin D, Zhao H and Zhang L: The immunology of Parkinson's disease. Semin Immunopathol 44: 659-672, 2022.
2. Jang JH, Yeom MJ, Ahn S, Oh JY, Ji S, Kim TH and Park HJ: Acupuncture inhibits neuroinflammation and gut microbial dysbiosis in a mouse model of Parkinson's disease. Brain Behav Immun 89: 641-655, 2020.
3. Fields CR, Bengoa-Vergniory N and Wade-Martins R: Targeting alpha-synuclein as a therapy for Parkinson's disease. Front Mol Neurosci 12: 299, 2019.
4. Zhao Y, Zhang Z, Qin S, Fan W, Li W, Liu J, Wang S, Xu Z and Zhao M: Acupuncture for Parkinson's disease: Efficacy evaluation and mechanisms in the dopaminergic neural circuit. Neural Plast 2021: 9926445, 2021.
5. Stevenson TJ, Murray HC, Turner C, Faull RLM, Dieriks BV and Curtis MA: α-synuclein inclusions are abundant in non-neuronal cells in the anterior olfactory nucleus of the Parkinson's disease olfactory bulb. Sci Rep 10: 6682, 2020.
6. Campo F, Carletti R, Fusconi M, Pellicano C, Pontieri FE, Di Gioia CR and de Vincentiis M: Alpha-synuclein in salivary gland as biomarker for Parkinson's disease. Rev Neurosci 30: 455-462, 2019.
7. Jansen van Rensburg Z, Abrahams S, Bardien S and Kenyon C: Toxic feedback loop involving iron, reactive oxygen species, α-synuclein and neuromelanin in Parkinson's disease and intervention with turmeric. Mol Neurobiol 58: 5920-5936, 2021.
8. Guerrero-Ferreira R, Taylor NM, Mona D, Ringler P, Lauer ME, Riek R, Britschgi M and Stahlberg H: Cryo-EM structure of alpha-synuclein fibrils. Elife 7: e36402, 2018.
9. Vasquez V, Mitra J, Wang H, Hegde PM, Rao KS and Hegde ML: A multi-faceted genotoxic network of alpha-synuclein in the nucleus and mitochondria of dopaminergic neurons in Parkinson's disease: Emerging concepts and challenges. Prog Neurobiol 185: 101729, 2020.
10. Burré J, Sharma M and Südhof TC: Cell biology and pathophysiology of α-synuclein. Cold Spring Harb Perspect Med 8: a024091, 2018.
11. Fujioka S, Ogaki K, Tacik PM, Uitti RJ, Ross OA and Wszolek ZK: Update on novel familial forms of Parkinson's disease and multiple system atrophy. Parkinsonism Relat Disord 20 (Suppl 1): S29-S34, 2014.
12. Koo HJ, Lee HJ and Im H: Sequence determinants regulating fibrillation of human alpha-synuclein. Biochem Biophys Res Commun 368: 772-778, 2008.
13. Liu W, Lim KL and Tan EK: Intestine-derived α-synuclein initiates and aggravates pathogenesis of Parkinson's disease in Drosophila. Transl Neurodegener 11: 44, 2022.
14. Choi ML, Chappard A, Singh BP, Maclachlan C, Rodrigues M, Fedotova EI, Berezhnov AV, De S, Peddie CJ, Athauda D, *et al*: Pathological structural conversion of α-synuclein at the mitochondria induces neuronal toxicity. Nat Neurosci 25: 1134-1148, 2022.
15. Pacheco CR, Morales CN, Ramírez AE, Muñoz FJ, Gallegos SS, Caviedes PA, Aguayo LG and Opazo CM: Extracellular α-synuclein alters synaptic transmission in brain neurons by perforating the neuronal plasma membrane. J Neurochem 132: 731-741, 2015.
16. Cardinale A, Calabrese V, de Iure A and Picconi B: Alpha-synuclein as a prominent actor in the inflammatory synaptopathy of Parkinson's disease. Int J Mol Sci 22: 6517, 2021.
17. Chakroun T, Evsyukov V, Nykänen NP, Höllerhage M, Schmidt A, Kamp F, Ruf VC, Wurst W, Rösler TW and Höglinger GU: Alpha-synuclein fragments trigger distinct aggregation pathways. Cell Death Dis 11: 84, 2020.
18. Wang C, Yang T, Liang M, Xie J and Song N: Astrocyte dysfunction in Parkinson's disease: From the perspectives of transmitted α-synuclein and genetic modulation. Transl Neurodegener 10: 39, 2021.
19. Yu WW, Cao SN, Zang CX, Wang L, Yang HY, Bao XQ and Zhang D: Heat shock protein 70 suppresses neuroinflammation induced by α-synuclein in astrocytes. Mol Cell Neurosci 86: 58-64, 2018.
20. Kim C, Spencer B, Rockenstein E, Yamakado H, Mante M, Adame A, Fields JA, Masliah D, Iba M, Lee HJ, *et al*: Immunotherapy targeting toll-like receptor 2 alleviates neurodegeneration in models of synucleinopathy by modulating α-synuclein transmission and neuroinflammation. Mol Neurodegener 13: 43, 2018.
21. Sian-Hulsmann J and Riederer P: The role of alpha-synuclein as ferrireductase in neurodegeneration associated with Parkinson's disease. J Neural Transm (Vienna) 127: 749-754, 2020.
22. Riederer P, Monoranu C, Strobel S, Iordache T and Sian-Hülsmann J: Iron as the concert master in the pathogenic orchestra playing in sporadic Parkinson's disease. J Neural Transm (Vienna) 128: 1577-1598, 2021.
23. Melo TQ, Copray SJCVM and Ferrari MFR: Alpha-synuclein toxicity on protein quality control, mitochondria and endoplasmic reticulum. Neurochem Res 43: 2212-2223, 2018.
24. Ninkina N, Tarasova TV, Chaprov KD, Roman AY, Kukharsky MS, Kolik LG, Ovchinnikov R, Ustyugov AA, Durnev AD and Buchman VL: Alterations in the nigrostriatal system following conditional inactivation of α-synuclein in neurons of adult and aging mice. Neurobiol Aging 91: 76-87, 2020.
25. Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE and Joers V: Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol 22: 657-673, 2022.
26. Zhao YF, Qiong-Zhang, Zhang JF, Lou ZY, Zu HB, Wang ZG, Zeng WC, Kai-Yao and Xiao BG: The synergy of aging and LPS exposure in a mouse model of Parkinson's disease. Aging Dis 9: 785-797, 2018.
27. Russo T and Riessland M: Age-related midbrain inflammation and senescence in Parkinson's disease. Front Aging Neurosci 14: 917797, 2022.
28. Su R and Zhou T: Alpha-synuclein induced immune cells activation and associated therapy in Parkinson's disease. Front Aging Neurosci 13: 769506, 2021.
29. Tremblay ME, Cookson MR and Civiero L: Glial phagocytic clearance in Parkinson's disease. Mol Neurodegener 14: 16, 2019.
30. Kim C, Kwon S, Iba M, Spencer B, Rockenstein E, Mante M, Adame A, Shin SJ, Fields JA, Rissman RA, *et al*: Effects of innate immune receptor stimulation on extracellular α-synuclein uptake and degradation by brain resident cells. Exp Mol Med 53: 281-290, 2021.
31. Fellner L, Gabassi E, Haybaeck J and Edenhofer F: Autophagy in α-synucleinopathies-an overstrained system. Cells 10: 3143, 2021.
32. Caggiu E, Arru G, Hosseini S, Niegowska M, Sechi G, Zarbo IR and Sechi LA: Inflammation, infectious triggers, and Parkinson's disease. Front Neurol 10: 122, 2019.
33. Salminen A, Ojala J, Kaarniranta K, Haapasalo A, Hiltunen M and Soininen H: Astrocytes in the aging brain express characteristics of senescence-associated secretory phenotype. Eur J Neurosci 34: 3-11, 2011.
34. Coleman C and Martin I: Unraveling Parkinson's disease neurodegeneration: Does aging hold the clues? J Parkinsons Dis 12: 2321-2338, 2022.
35. Pang SY, Ho PW, Liu HF, Leung CT, Li L, Chang EES, Ramsden DB and Ho SL: The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. Transl Neurodegener 8: 23, 2019.
36. Wendimu MY and Hooks SB: Microglia phenotypes in aging and neurodegenerative diseases. Cells 11: 2091, 2022.
37. Nasrolahi A, Safari F, Farhoudi M, Khosravi A, Farajdokht F, Bastaminejad S, Sandoghchian Shotorbani S and Mahmoudi J: Immune system and new avenues in Parkinson's disease research and treatment. Rev Neurosci 30: 709-727, 2019.
38. Van Den Berge N, Ferreira N, Mikkelsen TW, Alstrup AKO, Tamgüney G, Karlsson P, Terkelsen AJ, Nyengaard JR, Jensen PH and Borghammer P: Ageing promotes pathological alpha-synuclein propagation and autonomic dysfunction in wild-type rats. Brain 144: 1853-1868, 2021.

39. Challis C, Hori A, Sampson TR, Yoo BB, Challis RC, Hamilton AM, Mazmanian SK, Volpicelli-Daley LA and Gradinaru V: Gut-seeded α-synuclein fibrils promote gut dysfunction and brain pathology specifically in aged mice. Nat Neurosci 23: 327-336, 2020.
40. Verma DK, Seo BA, Ghosh A, Ma SX, Hernandez-Quijada K, Andersen JK, Ko HS and Kim YH: Alpha-synuclein preformed fibrils induce cellular senescence in Parkinson's disease models. Cells 10: 1694, 2021.
41. Rotter A, Lenz B, Pitsch R, Richter-Schmidinger T, Kornhuber J and Rhein C: Alpha-synuclein RNA expression is increased in major depression. Int J Mol Sci 20: 2029, 2019.
42. Phan HTM, Bartz JC, Ayers J, Giasson BI, Schubert M, Rodenhausen KB, Kananizadeh N, Li Y and Bartelt-Hunt SL: Adsorption and decontamination of α-synuclein from medically and environmentally-relevant surfaces. Colloids Surf B Biointerfaces 166: 98-107, 2018.
43. D'Onofrio M, Munari F and Assfalg M: Alpha-synuclein-nanoparticle interactions: Understanding, controlling and exploiting conformational plasticity. Molecules 25: 5625, 2020.
44. Makasewicz K, Wennmalm S, Stenqvist B, Fornasier M, Andersson A, Jönsson P, Linse S and Sparr E: Cooperativity of α-synuclein binding to lipid membranes. ACS Chem Neurosci 12: 2099-2109, 2021.
45. Davidson WS, Jonas A, Clayton DF and George JM: Stabilization of alpha-synuclein secondary structure upon binding to synthetic membranes. J Biol Chem 273: 9443-9449, 1998.
46. George JM, Jin H, Woods WS and Clayton DF: Characterization of a novel protein regulated during the critical period for song learning in the zebra finch. Neuron 15: 361-372, 1995.
47. Uéda K, Fukushima H, Masliah E, Xia Y, Iwai A, Yoshimoto M, Otero DA, Kondo J, Ihara Y and Saitoh T: Molecular cloning of cDNA encoding an unrecognized component of amyloid in Alzheimer disease. Proc Natl Acad Sci USA 90: 11282-11286, 1993.
48. Weinreb PH, Zhen W, Poon AW, Conway KA and Lansbury PT Jr: NACP, a protein implicated in Alzheimer's disease and learning, is natively unfolded. Biochemistry 35: 13709-13715, 1996.
49. Acquasaliente L, Pontarollo G, Radu CM, Peterle D, Artusi I, Pagotto A, Uliana F, Negro A, Simioni P and De Filippis V: Exogenous human α-synuclein acts in vitro as a mild platelet antiaggregant inhibiting α-thrombin-induced platelet activation. Sci Rep 12: 9880, 2022.
50. Dedmon MM, Lindorff-Larsen K, Christodoulou J, Vendruscolo M and Dobson CM: Mapping long-range interactions in alpha-synuclein using spin-label NMR and ensemble molecular dynamics simulations. J Am Chem Soc 127: 476-477, 2005.
51. Bogale TA, Faustini G, Longhena F, Mitola S, Pizzi M and Bellucci A: Alpha-synuclein in the regulation of brain endothelial and perivascular cells: Gaps and future perspectives. Front Immunol 12: 611761, 2021.
52. Bozelli JC Jr, Kamski-Hennekam E, Melacini G and Epand RM: α-Synuclein and neuronal membranes: Conformational flexibilities in health and disease. Chem Phys Lipids 235: 105034, 2021.
53. Chakraborty R and Chattopadhyay K: Cryo-electron microscopy uncovers key residues within the core of alpha-synuclein fibrils. ACS Chem Neurosci 10: 1135-1136, 2019.
54. Walsh DM and Selkoe DJ: A critical appraisal of the pathogenic protein spread hypothesis of neurodegeneration. Nat Rev Neurosci 17: 251-260, 2016.
55. Choi ML and Gandhi S: Crucial role of protein oligomerization in the pathogenesis of Alzheimer's and Parkinson's diseases. FEBS J 285: 3631-3644, 2018.
56. Liu G, Aliaga L and Cai H: α-Synuclein, LRRK2 and their interplay in Parkinson's disease. Future Neurol 7: 145-153, 2012.
57. Wang R, Ren H, Kaznacheyeva E, Lu X and Wang G: Association of glial activation and α-synuclein pathology in Parkinson's disease. Neurosci Bull 39: 479-490, 2022.
58. Imbriani P, Schirinzi T, Meringolo M, Mercuri NB and Pisani A: Centrality of early synaptopathy in Parkinson's disease. Front Neurol 9: 103, 2018.
59. Kam TI, Mao X, Park H, Chou SC, Karuppagounder SS, Umanah GE, Yun SP, Brahmachari S, Panicker N, Chen R, *et al*: Poly(ADP-ribose) drives pathologic α-synuclein neurodegeneration in Parkinson's disease. Science 362: eaat8407, 2018.
60. Bae EJ, Choi M, Kim JT, Kim DK, Jung MK, Kim C, Kim TK, Lee JS, Jung BC, Shin SJ, *et al*: TNF-α promotes α-synuclein propagation through stimulation of senescence-associated lysosomal exocytosis. Exp Mol Med 54: 788-800, 2022.
61. Gelpi E, Navarro-Otano J, Tolosa E, Gaig C, Compta Y, Rey MJ, Martí MJ, Hernández I, Valldeoriola F, Reñé R and Ribalta T: Multiple organ involvement by alpha-synuclein pathology in Lewy body disorders. Mov Disord 29: 1010-1018, 2014.
62. Donadio V, Incensi A, Piccinini C, Cortelli P, Giannoccaro MP, Baruzzi A and Liguori R: Skin nerve misfolded α-synuclein in pure autonomic failure and Parkinson disease. Ann Neurol 79: 306-316, 2016.
63. Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White Iii CL, Akiyama H, Caviness JN, Shill HA, Sabbagh MN, *et al*: Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol 119: 689-702, 2010.
64. Braak H, Rüb U, Gai WP and Del Tredici K: Idiopathic Parkinson's disease: Possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm (Vienna) 110: 517-536, 2003.
65. Braak H, Ghebremedhin E, Rüb U, Bratzke H and Del Tredici K: Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 318: 121-134, 2004.
66. Liu B, Fang F, Pedersen NL, Tillander A, Ludvigsson JF, Ekbom A, Svenningsson P, Chen H and Wirdefeldt K: Vagotomy and Parkinson disease: A Swedish register-based matched-cohort study. Neurology 88: 1996-2002, 2017.
67. Ho PW, Leung CT, Liu H, Pang SY, Lam CS, Xian J, Li L, Kung MH, Ramsden DB and Ho SL: Age-dependent accumulation of oligomeric SNCA/α-synuclein from impaired degradation in mutant LRRK2 knockin mouse model of Parkinson disease: Role for therapeutic activation of chaperone-mediated autophagy (CMA). Autophagy 16: 347-370, 2020.
68. Henderson MX, Trojanowski JQ and Lee VMY: α-Synuclein pathology in Parkinson's disease and related α-synucleinopathies. Neurosci Lett 709: 134316, 2019.
69. Iba M, McDevitt RA, Kim C, Roy R, Sarantopoulou D, Tommer E, Siegars B, Sallin M, Kwon S, Sen JM, *et al*: Aging exacerbates the brain inflammatory micro-environment contributing to α-synuclein pathology and functional deficits in a mouse model of DLB/PD. Mol Neurodegener 17: 60, 2022.
70. Rauschenberger L, Behnke J, Grotemeyer A, Knorr S, Volkmann J and Ip CW: Age-dependent neurodegeneration and neuroinflammation in a genetic A30P/A53T double-mutated α-synuclein mouse model of Parkinson's disease. Neurobiol Dis 171: 105798, 2022.
71. Yang W, Li X, Li X and Yu S: Hemoglobin-α-synuclein complex exhibited age-dependent alterations in the human striatum and peripheral RBCs. Neurosci Lett 736: 135274, 2020.
72. Ma M, Li H, Wu J, Zhang Y, Shen H, Li X, Wang Z and Chen G: Roles of prokineticin 2 in subarachnoid hemorrhage-induced early brain injury via regulation of phenotype polarization in astrocytes. Mol Neurobiol 57: 3744-3758, 2020.
73. Jeon YM, Kwon Y, Jo M, Lee S, Kim S and Kim HJ: The role of glial mitochondria in alpha-synuclein toxicity. Front Cell Dev Biol 8: 548283, 2020.
74. Li Q and Haney MS: The role of glia in protein aggregation. Neurobiol Dis 143: 105015, 2020.
75. Wang P and Ye Y: Astrocytes in neurodegenerative diseases: A perspective from tauopathy and α-synucleinopathy. Life (Basel) 11: 938, 2021.
76. Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, *et al*: Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541: 481-487, 2017.
77. Diniz LP, Araujo APB, Matias I, Garcia MN, Barros-Aragão FGQ, de Melo Reis RA, Foguel D, Braga C, Figueiredo CP, Romão L and Gomes FCA: Astrocyte glutamate transporters are increased in an early sporadic model of synucleinopathy. Neurochem Int 138: 104758, 2020.
78. Chavarria C, Ivagnes R and Souza JM: Extracellular alpha-synuclein: Mechanisms for glial cell internalization and activation. Biomolecules 12: 655, 2022.
79. Vargas JY, Grudina C and Zurzolo C: The prion-like spreading of α-synuclein: From in vitro to in vivo models of Parkinson's disease. Ageing Res Rev 50: 89-101, 2019.

80. Wang J, Chen Z, Walston JD, Gao P, Gao M and Leng SX: α-Synuclein activates innate immunity but suppresses interferon-γ expression in murine astrocytes. Eur J Neurosci: 10.1111/ejn.13956, 2018 (Epub ahead of print).
81. Hua J, Yin N, Xu S, Chen Q, Tao T, Zhang J, Ding J, Fan Y and Hu G: Enhancing the astrocytic clearance of extracellular α-synuclein aggregates by ginkgolides attenuates neural cell injury. Cell Mol Neurobiol 39: 1017-1028, 2019.
82. Chavarría C, Rodríguez-Bottero S, Quijano C, Cassina P and Souza JM: Impact of monomeric, oligomeric and fibrillar alpha-synuclein on astrocyte reactivity and toxicity to neurons. Biochem J 475: 3153-3169, 2018.
83. Liscovitch N and French L: Differential co-expression between α-synuclein and IFN-γ signaling genes across development and in Parkinson's disease. PLoS One 9: e115029, 2014.
84. Wang J, Chen Z, Walston JD, Gao P, Gao M and Leng SX: Interferon-γ potentiates α-synuclein-induced neurotoxicity linked to toll-like receptors 2 and 3 and tumor necrosis factor-α in murine astrocytes. Mol Neurobiol 56: 7664-7679, 2019.
85. Liu CY, Wang X, Liu C and Zhang HL: Pharmacological targeting of microglial activation: New therapeutic approach. Front Cell Neurosci 13: 514, 2019.
86. Li Y, Xia Y, Yin S, Wan F, Hu J, Kou L, Sun Y, Wu J, Zhou Q, Huang J, *et al*: Targeting microglial α-synuclein/TLRs/NF-kappaB/NLRP3 inflammasome axis in Parkinson's disease. Front Immunol 12: 719807, 2021.
87. Zhao Y and Yang G: Potential of extracellular vesicles in the Parkinson's disease-pathological mediators and biomarkers. Neurochem Int 144: 104974, 2021.
88. Sarlus H and Heneka MT: Microglia in Alzheimer's disease. J Clin Invest 127: 3240-3249, 2017.
89. Neefjes J, Jongsma ML, Paul P and Bakke O: Towards a systems understanding of MHC class I and MHC class II antigen presentation. Nat Rev Immunol 11: 823-836, 2011.
90. Chhatbar C and Prinz M: The roles of microglia in viral encephalitis: From sensome to therapeutic targeting. Cell Mol Immunol 18: 250-258, 2021.
91. Kong W, Wang X, Yang X, Huang W, Han S, Yin J, Liu W, He X and Peng B: Activation of TRPV1 contributes to recurrent febrile seizures via inhibiting the microglial M2 phenotype in the immature brain. Front Cell Neurosci 13: 442, 2019.
92. Gordon J, Lockard G, Monsour M, Alayli A, Choudhary H and Borlongan CV: Sequestration of inflammation in Parkinson's Disease via stem cell therapy. Int J Mol Sci 23: 10138, 2022.
93. Stefanova N, Fellner L, Reindl M, Masliah E, Poewe W and Wenning GK: Toll-like receptor 4 promotes α-synuclein clearance and survival of nigral dopaminergic neurons. Am J Pathol 179: 954-963, 2011.
94. Xia Y, Zhang G, Han C, Ma K, Guo X, Wan F, Kou L, Yin S, Liu L, Huang J, *et al*: Microglia as modulators of exosomal alpha-synuclein transmission. Cell Death Dis 10: 174, 2019.
95. Scheiblich H, Bousset L, Schwartz S, Griep A, Latz E, Melki R and Heneka MT: Microglial NLRP3 inflammasome activation upon TLR2 and TLR5 ligation by distinct α-synuclein assemblies. J Immunol 207: 2143-2154, 2021.
96. Watson MB, Richter F, Lee SK, Gabby L, Wu J, Masliah E, Effros RB and Chesselet MF: Regionally-specific microglial activation in young mice over-expressing human wildtype alpha-synuclein. Exp Neurol 237: 318-334, 2012.
97. Wallach T, Raden M, Hinkelmann L, Brehm M, Rabsch D, Weidling H, Krüger C, Kettenmann H, Backofen R and Lehnardt S: Distinct SARS-CoV-2 RNA fragments activate Toll-like receptors 7 and 8 and induce cytokine release from human macrophages and microglia. Front Immunol 13: 1066456, 2023.
98. Du XY, Xie XX and Liu RT: The role of α-synuclein oligomers in Parkinson's disease. Int J Mol Sci 21: 8645, 2020.
99. Zhang YN, Fan JK, Gu L, Yang HM, Zhan SQ and Zhang H: Metabotropic glutamate receptor 5 inhibits α-synuclein-induced microglia inflammation to protect from neurotoxicity in Parkinson's disease. J Neuroinflammation 18: 23, 2021.
100. Kim C, Ho DH, Suk JE, You S, Michael S, Kang J, Joong Lee S, Masliah E, Hwang D, Lee HJ and Lee SJ: Neuron-released oligomeric α-synuclein is an endogenous agonist of TLR2 for paracrine activation of microglia. Nat Commun 4: 1562, 2013.
101. Heidari A, Yazdanpanah N and Rezaei N: The role of Toll-like receptors and neuroinflammation in Parkinson's disease. J Neuroinflammation 19: 135, 2022.
102. Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, Kwon SH, Park YJ, Karuppagounder SS, Park H, *et al*: Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat Med 24: 931-938, 2018.
103. Kermorgant M, Fernagut PO, Meissner WG, Arvanitis DN, N'Guyen D, Senard JM and Pavy-Le Traon A: Age and Gender differences in cardiovascular autonomic failure in the transgenic PLP-syn mouse, a model of multiple system atrophy. Front Neurol 13: 874155, 2022.
104. Kaji S, Maki T, Kinoshita H, Uemura N, Ayaki T, Kawamoto Y, Furuta T, Urushitani M, Hasegawa M, Kinoshita Y, *et al*: Pathological endogenous α-synuclein accumulation in oligodendrocyte precursor cells potentially induces inclusions in multiple system atrophy. Stem Cell Reports 10: 356-365, 2018.
105. Dutta S, Hornung S, Kruayatidee A, Maina KN, Del Rosario I, Paul KC, Wong DY, Duarte Folle A, Markovic D, Palma JA, *et al*: α-Synuclein in blood exosomes immunoprecipitated using neuronal and oligodendroglial markers distinguishes Parkinson's disease from multiple system atrophy. Acta Neuropathol 142: 495-511, 2021.
106. Wakabayashi K, Hayashi S, Yoshimoto M, Kudo H and Takahashi H: NACP/alpha-synuclein-positive filamentous inclusions in astrocytes and oligodendrocytes of Parkinson's disease brains. Acta Neuropathol 99: 14-20, 2000.
107. Reyes JF, Rey NL, Bousset L, Melki R, Brundin P and Angot E: Alpha-synuclein transfers from neurons to oligodendrocytes. Glia 62: 387-398, 2014.
108. Kisos H, Pukaß K, Ben-Hur T, Richter-Landsberg C and Sharon R: Increased neuronal α-synuclein pathology associates with its accumulation in oligodendrocytes in mice modeling α-synucleinopathies. PLoS One 7: e46817, 2012.
109. Ihse E, Yamakado H, van Wijk XM, Lawrence R, Esko JD and Masliah E: Cellular internalization of alpha-synuclein aggregates by cell surface heparan sulfate depends on aggregate conformation and cell type. Sci Rep 7: 9008, 2017.
110. Stefanova N, Reindl M, Neumann M, Kahle PJ, Poewe W and Wenning GK: Microglial activation mediates neurodegeneration related to oligodendroglial alpha-synucleinopathy: Implications for multiple system atrophy. Mov Disord 22: 2196-2203, 2007.
111. Raffaele S, Boccazzi M and Fumagalli M: Oligodendrocyte dysfunction in amyotrophic lateral sclerosis: Mechanisms and therapeutic perspectives. Cells 10: 565, 2021.
112. Ratnam NM, Sonnemann HM, Frederico SC, Chen H, Hutchinson MND, Dowdy T, Reid CM, Jung J, Zhang W, Song H, *et al*: Reversing epigenetic gene silencing to overcome immune evasion in CNS malignancies. Front Oncol 11: 719091, 2021.
113. Tait AS, Butts CL and Sternberg EM: The role of glucocorticoids and progestins in inflammatory, autoimmune, and infectious disease. J Leukoc Biol 84: 924-931, 2008.
114. Enzmann G, Kargaran S and Engelhardt B: Ischemia-reperfusion injury in stroke: Impact of the brain barriers and brain immune privilege on neutrophil function. Ther Adv Neurol Disord 11: 1756286418794184, 2018.
115. Chandra G, Roy A, Rangasamy SB and Pahan K: Induction of adaptive immunity leads to nigrostriatal disease progression in MPTP mouse model of Parkinson's disease. J Immunol 198: 4312-4326, 2017.
116. Earls RH, Menees KB, Chung J, Barber J, Gutekunst CA, Hazim MG and Lee JK: Intrastriatal injection of preformed alpha-synuclein fibrils alters central and peripheral immune cell profiles in non-transgenic mice. J Neuroinflammation 16: 250, 2019.
117. Sun C, Jia G, Wang X, Wang Y and Liu Y: Immunoproteasome is up-regulated in rotenone-induced Parkinson's disease rat model. Neurosci Lett 738: 135360, 2020.
118. Ferreira SA and Romero-Ramos M: Microglia response during Parkinson's Disease: Alpha-synuclein intervention. Front Cell Neurosci 12: 247, 2018.
119. Kannarkat GT, Cook DA, Lee JK, Chang J, Chung J, Sandy E, Paul KC, Ritz B, Bronstein J, Factor SA, *et al*: Common genetic variant association with altered HLA expression, synergy with pyrethroid exposure, and risk for Parkinson's disease: An observational and case-control study. NPJ Parkinsons Dis 1: 15002, 2015.
120. Galiano-Landeira J, Torra A, Vila M and Bové J: CD8 T cell nigral infiltration precedes synucleinopathy in early stages of Parkinson's disease. Brain 143: 3717-3733, 2020.

121. Rostami J, Fotaki G, Sirois J, Mzezewa R, Bergström J, Essand M, Healy L and Erlandsson A: Astrocytes have the capacity to act as antigen-presenting cells in the Parkinson's disease brain. J Neuroinflammation 17: 119, 2020.
122. Sulzer D, Alcalay RN, Garretti F, Cote L, Kanter E, Agin-Liebes J, Liong C, McMurtrey C, Hildebrand WH, Mao X, *et al*: T cells from patients with Parkinson's disease recognize α-synuclein peptides. Nature 546: 656-661, 2017.
123. Lindestam Arlehamn CS, Dhanwani R, Pham J, Kuan R, Frazier A, Rezende Dutra J, Phillips E, Mallal S, Roederer M, Marder KS, *et al*: α-Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease. Nat Commun 11: 1875, 2020.
124. Kwon JH, Kim M, Um S, Lee HJ, Bae YK, Choi SJ, Hwang HH, Oh W and Jin HJ: Senescence-associated secretory phenotype suppression mediated by small-sized mesenchymal stem cells delays cellular senescence through TLR2 and TLR5 signaling. Cells 10: 63, 2021.
125. Xu Z, Qu A, Zhang H, Wang W, Hao C, Lu M, Shi B, Xu L, Sun M, Xu C and Kuang H: Photoinduced elimination of senescent microglia cells in vivo by chiral gold nanoparticles. Chem Sci 13: 6642-6654, 2022.
126. Badanjak K, Fixemer S, Smajić S, Skupin A and Grünewald A: The contribution of microglia to neuroinflammation in Parkinson's disease. Int J Mol Sci 22: 4676, 2021.
127. Chaib S, Tchkonia T and Kirkland JL: Cellular senescence and senolytics: The path to the clinic. Nat Med 28: 1556-1568, 2022.
128. Choi I, Zhang Y, Seegobin SP, Pruvost M, Wang Q, Purtell K, Zhang B and Yue Z: Microglia clear neuron-released α-synuclein via selective autophagy and prevent neurodegeneration. Nat Commun 11: 1386, 2020.
129. Menon R, Behnia F, Polettini J, Saade GR, Campisi J and Velarde M: Placental membrane aging and HMGB1 signaling associated with human parturition. Aging (Albany NY) 8: 216-230, 2016.
130. Wang AS, Nakamizo S, Ishida Y, Klassen G, Chong P, Wada A, Lim JSY, Wright GD, Kabashima K and Dreesen O: Identification and quantification of senescent cell types by lamin B1 and HMGB1 in Actinic keratosis lesions. J Dermatol Sci 105: 61-64, 2022.
131. Johmura Y, Yamanaka T, Omori S, Wang TW, Sugiura Y, Matsumoto M, Suzuki N, Kumamoto S, Yamaguchi K, Hatakeyama S, *et al*: Senolysis by glutaminolysis inhibition ameliorates various age-associated disorders. Science 371: 265-270, 2021.
132. Enokido Y, Yoshitake A, Ito H and Okazawa H: Age-dependent change of HMGB1 and DNA double-strand break accumulation in mouse brain. Biochem Biophys Res Commun 376: 128-133, 2008.
133. Mandke P and Vasquez KM: Interactions of high mobility group box protein 1 (HMGB1) with nucleic acids: Implications in DNA repair and immune responses. DNA Repair (Amst) 83: 102701, 2019.
134. Gaikwad S, Puangmalai N, Bittar A, Montalbano M, Garcia S, McAllen S, Bhatt N, Sonawane M, Sengupta U and Kayed R: Tau oligomer induced HMGB1 release contributes to cellular senescence and neuropathology linked to Alzheimer's disease and frontotemporal dementia. Cell Rep 36: 109419, 2021.
135. Yang JH, Petty CA, Dixon-McDougall T, Lopez MV, Tyshkovskiy A, Maybury-Lewis S, Tian X, Ibrahim N, Chen Z, Griffin PT, *et al*: Chemically induced reprogramming to reverse cellular aging. Aging (Albany NY) 15: 5966-5989, 2023.
136. Sarkar TJ, Quarta M, Mukherjee S, Colville A, Paine P, Doan L, Tran CM, Chu CR, Horvath S, Qi LS, *et al*: Transient non-integrative expression of nuclear reprogramming factors promotes multifaceted amelioration of aging in human cells. Nat Commun 11: 1545, 2020.
137. Browder KC, Reddy P, Yamamoto M, Haghani A, Guillen IG, Sahu S, Wang C, Luque Y, Prieto J, Shi L, *et al*: In vivo partial reprogramming alters age-associated molecular changes during physiological aging in mice. Nat Aging 2: 243-253, 2022.