Chapter 13
Microglia in Parkinson's Disease

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Abstract Microglia are the most abundant immune cells in the central nervous system (CNS), where they interact with neurons and exhibit a wide array of functions in physiological and pathological conditions. Physiologically, microglia mediate synaptic pruning and remodeling crucial for neural circuits and brain connectivity. In pathological conditions such as neurodegeneration in the Parkinson's disease (PD), microglia are activated, migrated to the injury site, and prone to engulf debris, sense pathology, and secrete possible pro- and anti-inflammatory factors. Microglia mediate responses such as inflammation and phagocytosis associated with neurodegeneration and are pivotal players in exacerbating or relieving disease progression. This chapter provides an overview on microglial function in the neurodegenerative disease—Parkinson's disease (PD). An overview on the pathology of PD will first be given, followed by discussion on receptors and signaling pathways involved in microglia-mediated inflammation and phagocytosis. Mechanism of how microglia contribute to PD by inflammation, phagocytosis of α-Synuclein (α-Syn), and interaction with PD genes will also be discussed.

Keywords Microglia · Neuroinflammation · Parkinson's disease · Phagocytosis · Alpha-synuclein

13.1 Introduction

As the most abundant immune cells residing in the central nervous system (CNS), microglia are small cells intertwining with neurons both physically and functionally, exhibiting a wide array of functions in physiological and pathological conditions. Microglia display differential density in various brain regions, with different combinations of markers underlying their regional identity and distinct functional roles [37]. This distributional difference, dynamic behavior, and unique cellular features

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have made them significant brain cells that receive substantial attention and merit in-depth exploration.

Microglia in physiological conditions mediate a variety of brain functions such as synaptic pruning and remodeling. Neuron-microglia bidirectional signaling is particularly crucial for neural circuits and brain connectivity [98, 114, 142]. Upon pathological trigger, microglia migrate to the injured site and act as a double-edged sword to relieve or exacerbate the injury. Decades of study have indicated that microglia doing these jobs are in two major states, resting and activated, distinguishable by the forms of their morphology. While microglia constantly surf around the environments and sense pathology in their resting state [93], they transit to an activated state once the nervous system is under detrimental attack and becomes pathological. Transition from the resting to activated state requires complex regulation, thus allowing microglial activation to be under tight control [55]. Despite this common bipartite categorization, it is generally believed that different targets and receptors tune microglial responses in a continuous manner and multiple forms of activation state exist [43, 116, 137].

Intriguingly, activation of microglia is often associated with neurodegeneration, a degenerative process underlying the ultimate pathology of neurodegenerative diseases. Distinct from resting microglia, activated microglia are often of amoeboid morphology, short processes, enlarged soma, and de novo expression of cell surface receptors. They are prone to engulf debris, sense pathology, and secrete possible pro- and anti-inflammatory factors that exacerbate or relieve disease progression. Thus, the activation profile of microglia is often an important indicator for and reflects neuronal dysfunction in neurodegenerative diseases. In this chapter, we will discuss microglial function in the neurodegenerative disease Parkinson's disease (PD). An overview of the pathology of PD will first be given, followed by a discussion on receptors and signaling pathways involved in microglia-mediated inflammation and phagocytosis. How microglia contribute to the occurrence of PD pathological hallmarks such as dopaminergic (DA) neuron death and formation of α-Synuclein (α-Syn)-containing Lewy bodies (LB) aggregates and mechanisms pertaining to PD gene function will also be discussed.

13.2 Parkinson's Disease

As the second most common neurodegenerative disorder, PD is clinically characterized by symptoms such as resting tremor, bradykinesia, postural instability, accompanying non-motor symptoms like cognitive impairment and autonomic dysfunction. Inside the brain, a series of neuropathological changes appears throughout the course of PD development, ultimately leading to the diagnostic hallmark: the aggregation of intracellular inclusions named Lewy bodies (LBs) and Lewy Neurites (LNs) and the loss of dopaminergic (DA) neurons in the *substantia nigra pars compacta* (*SNpc*).

This progressive brain pathology can be staged by the LB appearance in different regions of the brain [12, 13], with initial detection of LB in the periphery such as dorsal motor nucleus of the glossopharyngeal and vagal nerves or the olfactory bulb [74], followed by the appearance in the *SNpc* DA neurons in mid-stage, then the rostral propagation to other parts of the brain.

While most of the PD cases are sporadic, studies on rare familial cases offer the strength of identifying possible genetic causes for PD. The central component for LB and LN, α-Synuclein (α-Syn), is the gene product from *SNCA* (*PARK1*)—the first *PARK* gene identified in the studies of rare familial PD cases. Not only that genome-wide association (GWAS) studies have identified *SNCA* SNPs as risk variants for sporadic PD [112, 118], the missense *SNCA* mutation A53T [104], along with many others and duplications in the *SNCA* locus, have all been shown to associate with PD [2, 18, 66, 73, 101, 119, 141]. Interestingly, PD-associated mutations of α-Syn confer differential self-aggregation properties [19, 21, 28, 34, 35, 38], implicating that mutant α-Syn with altered propensities are potentially toxic and more prone for aggregation in disease conditions.

13.3 Microglia in PD

How microglia contribute to PD pathology remains to be an important area of study for researchers centering on the perspective of non-cell-autonomous regulation of neurodegeneration. Although no affirmative connection between DA neuron death and microglial activation has been established yet, microglial activation is thought to be a significant part of the disease process integrated either as a cause or consequence [11, 56]. Some of the earlier studies have provided evidence that microglia are involved in PD. First, the human leukocyte antigen gene (HLA-DRA) expressed specifically in microglia has been identified by a genome-wide association (GWAS) study as a genetic risk factor for late-onset PD [40]. p.R47H variant of microglial triggering receptor expressed on myeloid cells-2 (TREM-2) is also associated with PD [106]. These results suggest that microglia-specific regulation of PD progression exists. In addition, positron emission tomography (PET) studies show that microgliosis is an early and sustained response of PD [6, 33, 122]. Reactive microglia have also been detected in toxin-induced and transgenic mouse models of PD [22, 46, 84, 111]. Brains with an injection of the Gram-negative bacterial endotoxin lipopolysaccharide (LPS), a toxin that specifically induces microgliosis, show signs of DA neuron loss in the substantia nigra (SN). In toto, these findings suggest that microglial activation correlates with PD progression and induces DA neuron toxicity and death. Finally, studies on regional density of microglia revealed that they are prominently distributed in SN and striatum, where microglia exhibit a region- and stage-specific release of cytokines and mediators, thereby affecting DA neuron death [37, 76]. Taken together, these observations indicate a pivotal role for microglia in PD disease progression and raise interests in studying their functional roles during PD pathology (Fig. 13.1).

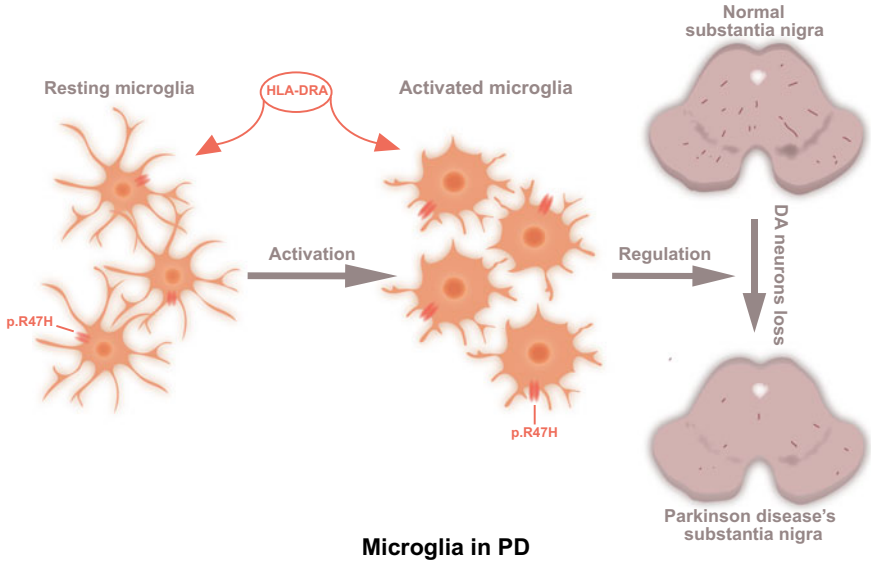

Fig. 13.1 Microglia in PD. Microglia transit from resting state to activating state when the nervous system undergoes pathological attack such as DA neuron loss in PD. A number of observations have dictated a pivotal role for microglia during this process, such as the identification of a microglial specific gene HLA-DRA by GWAS associated with PD, p.R47H variant of TREM-2 associated with PD, and microgliosis as an early and sustained response of PD shown by PET studies

13.4 Microglial Receptors in PD

Similar to other immune cells, CNS microglia express pattern recognition receptors (PRRs) that respond to pathogen-associated molecular patterns (PAMPs) and recognize invading pathogens for host defense immune mechanisms. One type of microglial PRRs, toll-like receptors (TLRs) [132, 136], are single-pass transmembrane proteins with an N-terminal extracellular ligand recognition domain carrying leucine-rich repeats [83] and the C-terminal intracellular Toll-interleukin 1 receptor (TIR) domains transforming extracellular recognition into an intracellular response [15, 48, 140]. TIR domains interact with adaptor molecules such as MyD88, TRIF, and TRAM in response to various stimuli. For instance, α-Syn or Pam3CSK4, a synthetic triacylated lipopeptide, activates TLR2-mediated downstream signaling via the adaptor MyD88 and a co-receptor, either TLR1 or TLR6. Upon α-Syn activation of the TLR1/2 receptor, interaction between MyD88 and TIR domain first activates the kinase activity of the interleukin-1 receptor-associated kinase (IRAK) complex [75], which in turn interacts with and activates the TNF receptor-associated factor 6 (TRAF6) via its K63-linked auto-ubiquitination. These sequential events lead to the activation of the transforming growth factor β-activated kinase-1 (TAK1) complex and the release of IKKs, which mediate IκBα degradation and the ultimate pro-

duction of pro-inflammatory cytokines through MAPK activation and the nuclear translocation of NF-κB, JNK, and p38 (Figs. 13.1 and 13.2) [57, 58, 125].

Microglial TLR1/2 has been shown to be central to the α-Syn pathogenesis: an important therapeutical target for analysis [4]. First, the expression level of microglial TLR2 is elevated in patients of incidental Lewy Body disease (iLBD) which equals to a prodromal Braak stage 1–3, suggesting that elevated TLR2 level correlates early microglial activation response in PD [25]. Next, α-Syn activates microglial TLR1/2 in different experimental systems including BV-2 microglia, primary mouse microglia, or human microglia [7, 23, 60]. Similarly, medium from α-Syn over-expressing SH-SY5Y cells containing oligomeric α-Syn activates microglia in a TLR2-dependent manner [60, 61]. Upon TLR1/2 activation, microglia release pro-inflammatory cytokines tumor necrosis factor-alpha (TNFα) and interleukin (IL)-1β in a MyD88-dependent manner [23, 124, 143]. On the other hand, activated microglia also release anti-inflammatory cytokines, pointing to a diverse functional output upon α-Syn activation of microglial TLR1/2. Taken together, these results suggest that microglial TLR1/2 is a direct α-Syn target and the subsequent TLR1/2-activated signaling pathways participate in PD progression by releasing cytokines that tune the degree of neuroinflammation.

Furthermore, mice lacking the fractalkine receptor CX3CR1 show extensive loss of tyrosine-hydroxylase (TH)-positive neurons in the MPTP-induced PD mouse model [17]. CXCL-CX3CR1 signaling is also involved in a 6-hydroxydopamine (6-OHDA) rat model of PD, where CX3CL1 was found to suppress microglial activation and reduce neuronal loss [96]. It has also been shown that mice lacking CX3CR1 exhibit reduced α-Syn-mediated inflammatory response and microglial phagocytosis, further strengthening the importance of CXCL-CX3CR1 signaling in PD [128].

13.5 Microglia-Mediated Neuroinflammation in PD

The very first evidence that inflammation is involved in PD came from the observation that pro-inflammatory mediators such as TNFα, IL-1β, and IL-6 were detected in elevated levels in the cerebral spinal fluid (CSF) and brains of PD patients, particularly in the striatum [87, 88, 91]. The elevation of cytokine levels is part of the microglial activation and recruitment (microgliosis) process that starts early, accompanies neurodegeneration, and persists throughout the course of PD [50, 51, 65]. When activated microglia induces neuroinflammation, they either exhibit the M1 neurotoxic phenotype or the M2 neuroprotective phenotype [42, 63, 89, 105]. In the scenario of activated M1-like microglia, these cells often adopt an amoeboid morphology, are highly capable to phagocytose and remove apoptotic cell debris, and release massive pro-inflammatory factors such as IL-1β, IL-12, TNFα, and inducible nitric oxide synthase (iNOS). Microglial release of these factors often couples with DA neuron loss in PD. On the contrary, M2-like activated microglia are of thin cellular bodies and ramified processes, and secrete anti-inflammatory cytokines including IL-4, IL-13, IL-10, TGFβ, and neurotrophic insulin-like growth factor 1(IGF-1) to

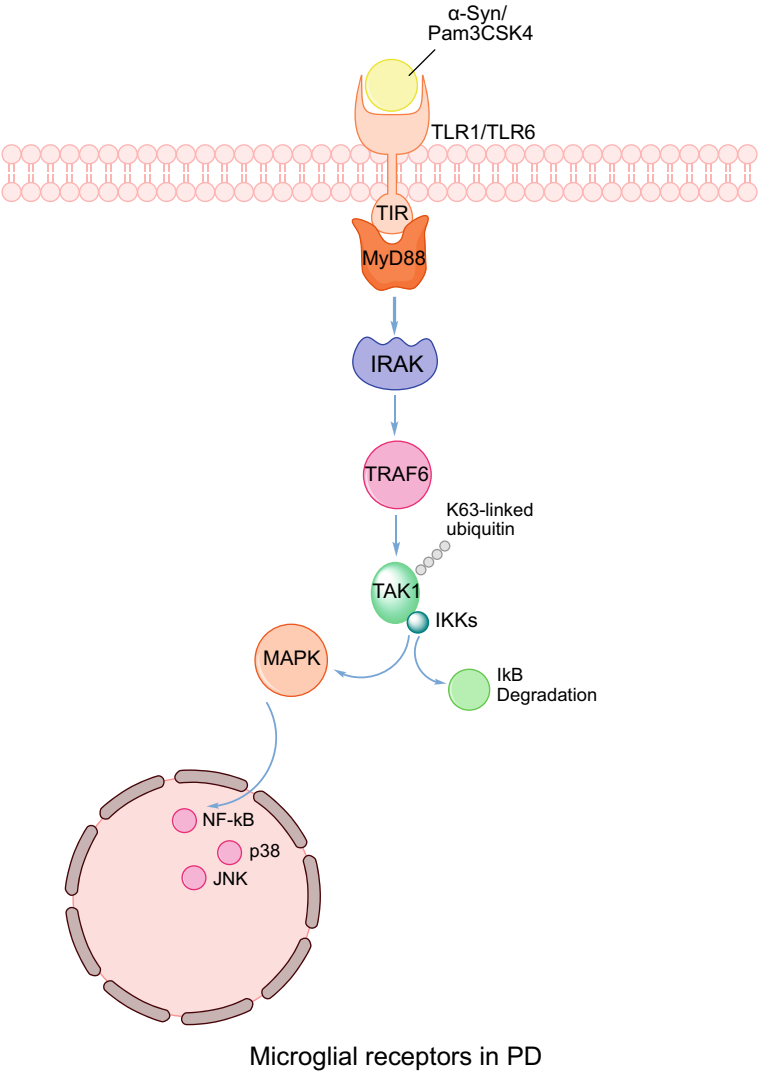

Fig. 13.2 Microglial receptors in PD. An example of microglial receptor TLR1/6 and its downstream pathway was illustrated. TIR domains of TLRs interact with adaptor molecules such as MyD88, TRIF, and TRAM in response to various stimuli. Ligands such as α-Syn or Pam3CSK4 activate TLR2-mediated downstream signaling via the adaptor MyD88 and a co-receptor, either TLR1 or TLR6. Upon α-Syn activation of the TLR1/2 receptor, interaction between MyD88 and TIR domain first activates the kinase activity of the interleukin-1 receptor-associated kinase (IRAK) complex, which in turn interacts with and activates the TNF receptor-associated factor 6 (TRAF6) via its K63-linked auto-ubiquitination. These sequential events lead to the activation of the transforming growth factor β-activated kinase-1 (TAK1) complex and the release of IKKs, which mediate IκBα degradation and the ultimate production of pro-inflammatory cytokines through MAPK activation and the nuclear translocation of NF-κB, JNK, and p38

ease inflammation and accelerate repair. Thus, microglia-mediated inflammation has double-sided effects in terms of relieving and exacerbating disease progression [139]. At one end, the inflammatory response might be beneficial by promoting neuron survival, whereas, on the other hand, the production of neurotoxic factors might also enhance the neurodegeneration. It is noteworthy to mention that microglia-released pro- and anti-inflammatory molecules coexist in the early stage of PD and their expression profiles change over time, suggesting that dynamic regulation of microgliosis correlates with PD progression [102, 113].

Interestingly, prominent microgliosis is detected in various toxin-based models of PD such as 6-OHDA, MPTP, and rotenone [80, 81, 94, 120, 133, 138] as well as transgenic models of PD based on α-Syn. Microgliosis in α-Syn transgenic models occurs early in the stage and precedes DA neuron death, suggesting that cell death is not necessarily a prerequisite for microglial activation [71, 85, 123]. Based on these findings, it has been suggested that signals inducing microgliosis and inflammation might be released from the toxic α-Syn protein aggregates or the degenerated neurons, making an increasing number of microglial cells reactive and migrate to the injury site to defend the progressively degenerating environment.

13.6 Microglial Activation by α-Syn

Microglia-mediated inflammation is regulated by PD risk factors such as DJ-1, LRRK2, and α-Syn. For instance, lacking LRRK2 attenuates inflammation via inhibiting p38 MAPK and NF-κB pathways [59, 86]. α-Syn, as mentioned above, positively regulates microglial inflammatory responses [124, 143]. These findings provide the molecular link between microglia-mediated neuroinflammation and PD pathology. Given that some of these factors might be neuronal specific, bidirectional signaling between neurons and microglia is therefore established as an extremely important theme in PD disease progression.

During PD pathology, α-Syn is secreted to the extracellular space from neurons and detected in the extracellular biological fluids in PD patients [79, 129]. Clear evidence shows that extracellular α-Syn directly activates microglia [124, 143]. This activation has significant consequences. First, it is part of a key event for fully shifting activated microglia to exhibit a pro-inflammatory phenotype [3, 127]. Next, α-Syn-induced microglial activation promotes α-Syn phagocytosis via microglial FcγR receptor and subsequently activates a series of pro-inflammatory events such as nuclear translocation of NFγB p65 and elevated release of cytokines, potentiating the loss of DA neurons and chronic neurodegeneration in PD [16, 64, 69, 72, 124].

Results from studies on the form of α-Syn that activates microglia were contradictory. Different forms of α-Syn exhibit different effects on microglial phagocytosis and inflammatory activation. Pathogenic form of α-Syn, such as $\alpha\text{-Syn}^{A53T}$, triggers pro-inflammatory microglial response and impairs phagocytosis [46, 108]. In a different study, however, $\alpha\text{-Syn}^{A53T}$ is implicated in promoting phagocytosis [109]. Physiological α-Syn, on the other hand, inhibits inflammation yet promotes

phagocytosis [3]. It is generally believed that monomeric α-Syn promotes phagocytosis whereas oligomeric α-Syn acts in an opposite way [100], yet other studies also indicate enhanced microglial phagocytosis by fibrillar and C-terminal truncated α-Syn [29]. Aggregated α-Syn has been shown to inhibit microglial phagocytosis by activating SHP-1 via interaction with FcγRIIB, and is more potent in mediating microglial release of TNFα and IL-1β [20, 47]. Taken together, α-Syn conformation and its pathogenic form play pivotal roles in regulating microglial phagocytosis and subsequent activated inflammatory response, accompanying neurodegeneration in PD.

In addition to the aforementioned TLRs, α-Syn interacts with a number of different microglial receptors for potentiating phagocytosis and inflammatory responses. For instance, in response to α-Syn, the Prostaglandin E receptor subtype 2 (EP2) regulates α-Syn phagocytosis and CD11b-mediated microglial activation [54]. α-Syn also interacts with CD11b to activate NOX2 through Erk1/2 kinase activation and RhoA-dependent pathway to direct microglial migration [49, 134]. Furthermore, α-Syn, in its monomeric or pathogenic mutant form, interacts with the scavenger receptor CD36 to regulate microglial activation and TNFα release [123, 124]. Another receptor associated with α-Syn is the protease-activated receptor (PAR-1), working in a paracrine manner initiated by the secretion of matrix metalloproteinases [69]. The microglial purinergic P2X7 receptor is also implicated in α-Syn-mediated microglial activation via PHOX activation [53]. Taken together, these receptors receive signals from α-Syn and trigger different cascades of signaling pathways within microglia to activate inflammatory responses, creating the diversity in microglial outputs upon pathological trigger as PD progresses.

13.7 Microglial Phagocytosis in PD

Microglia mediate phagocytosis of apoptotic cells, unfolded proteins, or neuronal debris, a process carried out by the resting microglia in the developing brain or the reactive microglia in pathological conditions such as PD [116, 117]. Interestingly, phagocytosis has been considered beneficial associated with the anti-inflammatory function of microglia, raising the interest in studying cellular machinery mediating this process. A list of receptors has been shown to mediate microglial phagocytosis, including TLRs, the scavenger receptors CD14, TAM (Tyro3, Axl, and Mer) receptor, and TREM-2 [31, 41, 121, 131]. First, microglial phagocytosis of α-Syn is impaired in the absence of TLR4, suggesting TLR4 is involved in microglial α-Syn uptake. Alternation of TLR4 signaling modulates pro-inflammatory responses and ROS production, and promotes neurodegeneration [29, 121], whereas treatment of TLR-4 agonist also protects the survival of transgenic α-Syn overexpressing mice [131]. These findings suggest that TLR4 promotes microglial clearance of α-Syn, thus playing a beneficial role in controlling α-Syn spread and PD progression.

TREM-2 is another microglia-specific receptor that mediates phagocytosis of apoptotic neurons [126]. Alternation in TREM-2 expression affects phagocyto-

sis and subsequent microglia-mediated inflammatory responses by regulating pro-inflammatory gene transcription. TREM-2 is considered neuroprotective as increased levels of TREM-2 enhances microglial phagocytosis and decreases pro-inflammatory responses by regulating TLR4-mediated activation of NF-κB signaling [107].

Expression of the scavenger receptor Mannose Receptor C-Type 1 (MRC1) is decreased in an MPTP mice PD model, suggesting MRC1-mediated microglial phagocytosis is crucial for PD progression. Like TREM2, increased MRC1 expression (thus MRC1-mediated phagocytosis) is also beneficial as the increased MRC expression is part of the peroxisome proliferator-activated receptor gamma (PPARγ)-mediated mechanism of neuroprotection [68]. It is noteworthy mentioning that despite the supporting evidence from TREM-2 and MRC1 that microglial phagocytosis is beneficial for PD, other evidence has suggested phagocytosis contributes to neurodegeneration [5]. For instance, loss of TAM phagocytic receptor slightly extended survival of α-Syn^{A53T} overexpressing mice, suggesting TAM-mediated microglial phagocytosis promotes neurodegeneration and accelerates animal death [31] (Fig. 13.3).

Microglial phagocytosis is also regulated by PD risk factors such as DJ-1, α-Syn, and LRRK2 [20, 78, 82, 92, 100]. For instance, DJ-1 regulates microglial phagocy-

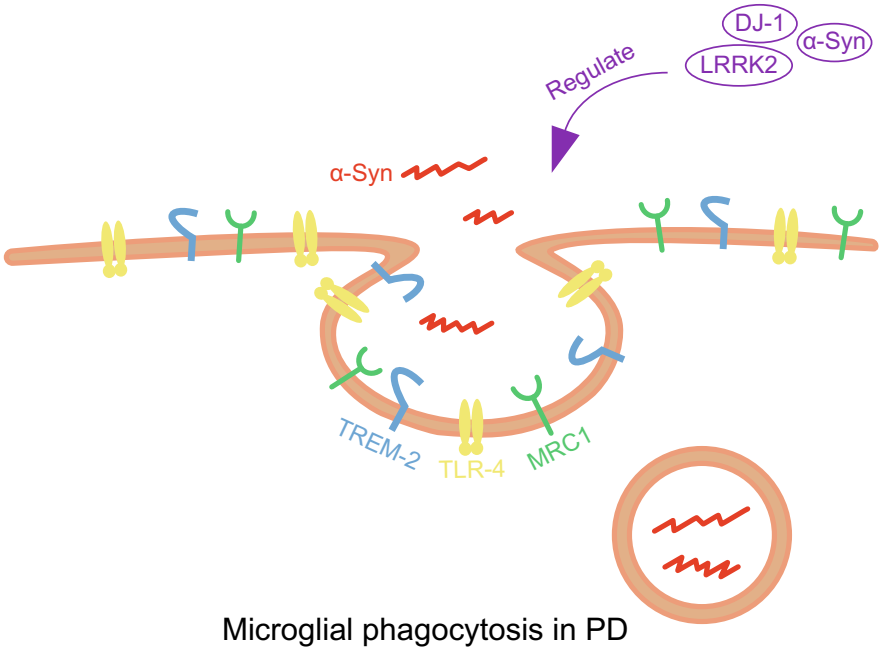

Fig. 13.3 Microglial phagocytosis in PD. Using α-Syn as an example, the receptor-mediated microglial phagocytosis were illustrated. TLR4, TREM-2, and MRC1 are receptors that mediate microglial phagocytosis during PD. This process is under tight regulation by other PD factors such as LRRK2, DJ-1, and α-Syn

tosis of α-Syn via autophagy and in an LC3 (microtubule-associated protein 1A/1B-light chain 3)-dependent (LAP) manner [52, 92], whereas α-Syn is both a regulator and a substrate for microglial phagocytosis. How α-Syn contributes to microglial activation and phagocytosis is discussed above, and microglial phagocytosis of α-Syn is summarized in the next section.

13.8 Microglial Phagocytosis of α-Syn

Previous studies have indicated that microglial phagocytose α-Syn [10, 70]. Some of the receptors functioning in microglial phagocytosis and activation, like TLR2 and TLR4, have been implicated in α-Syn uptake and α-Syn-mediated activation [29, 60, 121, 130]. While TLR4 is required for both microglial activation and phagocytosis of α-Syn [29, 121], TLR2 mainly receives signals from oligomeric α-Syn, but not monomeric or fibrillar α-Syn [60]. TLR2 activation is also crucial in neurons to decrease the uptake and autophagy of α-Syn, promoting neuronal α-Syn accumulation [26, 62]. These findings suggest that signaling cascade initiated by TL2 might be different in neurons and glia, and contribute differently to the disease. Moreover, microglia have been observed in vitro to uptake α-Syn-containing exosomes released by oligodendrocytes via macropinocytosis [30]. In addition to phagocytosis and macropinocytosis, other clathrin-independent routes such as monosialoganglioside (GM1)-dependent lipid rafts have also been shown to mediate microglial uptake of α-Syn [99]. Reduced expression of DJ-1, another PD risk factor, reduces cell surface lipid raft expression in microglia and impairs their ability to uptake soluble α-Syn [92].

13.9 Microglia, LRRK2 and PD

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common cause of familial PD and a risk factor for sporadic PD [44, 67, 97]. In the immune system, LRRK2 expression in monocytes is increased upon inflammation and the release of pro-inflammatory mediators like IL-1β, TNFα, and IFNγ [32]. Upon microglial activation by LPS in the brain, LRRK2 expression is also increased in a TLR4-dependent manner [86]. It is generally believed that LRRK function correlates with its phosphorylation level on Serine residue 935 (Ser935) [27, 115], a site in which phosphorylation level is crucial for microglial activation and induces inflammatory response in PD. It has also been shown that PD-associated mutations of LRRK2 at position R1441 reduce PKA-mediated LRRK2 phosphorylation and prevent its binding with the adaptor protein 14-3-3 binding [90], suggesting that mutations in LRRK2 associated with PD could affect LRRK2 phosphorylation, hence its kinase activity and cellular function.

One of the major LRRK2 funtions is to regulate the autophagy/lysosome degradation pathway. LRRK2 is localized on the autophagosome vesicles as shown by immune-electron microscopy and biochemical approaches [1, 36, 115]. Membrane localization of LRRK2 on autophagic and lysosome-related vesicles indicates that LRRK2 plays a pivotal role in regulating their function [8, 9]. LRRK2 also interacts with membrane proteins on these vesicles such as Rab7 (late endosomes) and Lamp2A [24, 45, 77, 95]. These results suggest that LRRK2 is involved in different steps of autophagy/lysosome pathway and its activity alters the degradative activity, development, or final maturation of these different vesicles.

Interestingly, the PD-associated LRRK2 mutation, G2019S, in its kinase domain results in an upregulation of LRRK2 kinase activity [39, 135] and has been implicated in autophagic dysfunction. Cells expressing $LRRK2^{G2019S}$ consistently exhibit increased autophagic vesicles or marker expression [14, 103, 110], possibly due to an increase in autophagic flux or an arrest in autophagosome/lysosome fusion. It is possible that defects in the autophagy/lysosome pathway caused by increased LRRK2 activity result in insufficient degradation of accumulated protein such as α-Syn, disrupting α-Syn proteostasis and underlying the mechanism of PD.

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