HHS Public Access

Author manuscript

Biochem Soc Trans. Author manuscript; available in PMC 2024 May 22.

Published in final edited form as:

Biochem Soc Trans. 2023 April 26; 51(2): 747–758. doi:10.1042/BST20201091.

The interplay between monocytes, α-synuclein and LRRK2 in Parkinson's disease

Samuel Strader, **Andrew B. West***

Duke Center for Neurodegeneration and Neurotherapeutics, Department of Pharmacology and Cancer Biology, Duke University, 3 Genome Court, Durham, 27710, North Carolina, U.S.A.

Abstract

The accumulation of aggregated α-synuclein in susceptible neurons in the brain, together with robust activation of nearby myeloid cells, are pathological hallmarks of Parkinson's disease (PD). While microglia represent the dominant type of myeloid cell in the brain, recent genetic and whole-transcriptomic studies have implicated another type of myeloid cell, bone-marrow derived monocytes, in disease risk and progression. Monocytes in circulation harbor high concentrations of the PD-linked enzyme leucine-rich repeat kinase 2 (LRRK2) and respond to both intracellular and extracellular aggregated α-synuclein with a variety of strong pro-inflammatory responses. This review highlights recent findings from studies that functionally characterize monocytes in PD patients, monocytes that infiltrate into cerebrospinal fluid, and emerging analyses of whole myeloid cell populations in the PD-affected brain that include monocyte populations. Central controversies discussed include the relative contribution of monocytes acting in the periphery from those that might engraft in the brain to modify disease risk and progression. We conclude that further investigation into monocyte pathways and responses in PD, especially the discovery of additional markers, transcriptomic signatures, and functional classifications, that better distinguish monocyte lineages and responses in the brain from other types of myeloid cells may reveal points for therapeutic intervention, as well as a better understanding of ongoing inflammation associated with PD.

Introduction

Parkinson's disease (PD), a prevalent neurodegenerative movement disorder, is thought to arise from a complexity of genetic risks, aging, and environmental exposures [1]. Pathologically, PD is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta, together with the intracellular accumulation insoluble, proteinaceous aggregates containing α-synuclein in some remaining neurons [2]. Extracellular misfolded α-synuclein is detected in seeding amplification assays [3], as well as increases observed in extracellular vesicles in circulation in the periphery [4]. A substantial loss of dopaminergic neurons precedes clinically apparent motor impairments such as bradykinesia and resting tremors. Though the brain was once thought to be largely privileged from peripheral immune cells, tissue damage and neurodegeneration are both processes well known to elicit both innate and adaptive immunological responses, some thought to arise from the periphery

***Correspondence:** Andrew B. West (andrew.west@duke.edu).

[5]. With respect to innate immune signaling in chronic diseases like PD, deleterious pro-inflammatory signals can be countered by anti-inflammatory responses that could be the difference between resolution of ongoing inflammation or the continuance of damaging responses [6].

Monocytes are an innate immune cell-type originating from the bone marrow and are involved in a multitude of responses, both pro-inflammatory and anti-inflammatory. Their primary activated phenotypes include a robust phagocytic capacity and inflammatory signaling that can control local oxidative responses as well as a potent activation of T-cell subsets. Abundant in peripheral circulation, monocytes respond to infection, injury, and a host of other complex disease responses. In systemic sclerosis, rheumatoid arthritis, irritable bowel syndrome, and other inflammatory diseases, highly motile monocytes efficiently infiltrate diseased tissue and often manifest a pro-inflammatory state, at least initially [7]. As discussed in this mini-review, recent studies in PD suggest the possibility that PD pathogenesis and progression may have more in common with these diseases of inflammation with respect to monocyte function than previously thought. The objective here is to summarize evidence published in the last few years that links monocytes to PD, and how genes linked to PD, *SNCA* encoding α-synuclein protein, and *leucine-rich repeat kinase 2* (*LRRK2*), may alter typical monocyte responses in a manner that promotes disease risk and progression.

Genetic and transcriptomic studies implicate monocytes in PD risk

Genetic studies provide a unique vantage into underlying contributors of disease risk through the nomination of heritable functional modifiers in large and diverse clinical populations. Early genome-wide genetic association studies (GWAS) in late-onset PD identified PD-associated loci near the *human leukocyte antigen* (*HLA*) genes; major-histocompatibility II (MHCII) components typically expressed in innate immune cells like microglia and monocytes [8]. Follow up studies demonstrated that these original associations were primarily driven by idiopathic PD (iPD) cases (e.g., not familial) [9], and variants in other *HLA* genes in newer GWAS studies have since been linked to PD risk or protection. Beyond *HLA* genes, with the caveat that most genes nominated as PD GWAS studies have not yet been validated as an actual gene conferring true PD risk, initial pathway and enrichment strategies demonstrated that PD GWAS loci and associated genes are enriched in monocyte activation genes [10]. Raj et al. noticed that PD-linked genetic variants tended to alter the expression of these associated genes (e.g., *LRRK2* and *Rab29*) in classical monocytes, especially CD14+ cells typically associated with phagocytosis phenotypes, but not in lymphocytes or other cells [11]. In addition, studies identified single nucleotide polymorphisms (SNPs) in or nearby PD GWAS loci and associated nearby genes as particularly active in expression in peripheral monocytes [12,13]. A meta-analysis approach of GWAS loci and their currently associated genes demonstrated multiple sclerosis (MS), Alzheimer's disease, and PD, share some of the same enrichment profiles of genes principally expressed in immune cells, especially monocytes [14]. Employing a conjunction false discovery rate method, PD GWAS loci and their associated genes significantly overlapped with disease-associated genes in several autoimmune diseases including type 1 diabetes, Crohn's disease, and rheumatoid arthritis,

although the directionality of the association for each particular locus (i.e., conferring risk, or protection) was not always the same [15,16]. For example, a GWAS locus nearby a gene expressed in monocytes (e.g., *HLA-DR*) may protect from PD but may predispose to rheumatoid arthritis risk. From the beginning, these studies highlight the intrinsic complexity of different inflammatory responses, with both risk and protection possible, and do not necessarily exclude the function of transcriptionally and mechanistically related innate immune cells (e.g., microglia).

While microglia are difficult to directly study in PD owing to the lack of tissue availability until post-mortem analysis, blood monocytes are readily accessible in all phases of disease, as summarized in Table 1. The application of unbiased transcriptomics and differential gene expression analyses have largely affirmed the presence of dysregulated expression profiles in monocytes from PD patients. In comparison to healthy controls, monocytes isolated and enriched from patients categorized in early stages of PD (i.e. Hoehn and Yahr stages 1 and 2) had some monocyte activation genes differentially expressed early in disease [17]. Additional comparisons between PD patients and healthy controls identified differentially expressed genes that were assigned to several different monocyte inflammatory response pathways [18,19]. Riboldi et al. compared transcriptomic data between PD patients, with and without ß-glucocerebrosidase I (GBAI) variants, to identify dysregulated genes defined to each PD subtype [20]. Genes thought to be involved in α-synuclein degradation, aging, and amyloid processing were especially dysregulated in PD patients with GBAI mutations, compared to non-mutation carriers. Other recent single-cell RNA (scRNA) and proteomic analyses of monocytes from PD patients with intermediate stages of disease (motor symptoms > 3 years, Hoehn and Yahr stage ~4) identified genes enriched in antioxidant, anti-inflammatory, and autophagy responses [21]. As the technology for scRNA and proteomic profiling continues to improve, we can anticipate that the aforementioned observations from both GWAS and bulk transcriptomic studies will be parsed down into individual monocyte subtypes to further understand how PD-isolated monocytes might functionally differ from healthy individuals. As yet, there is no consistent panel of proteins or transcripts that reliably demarcate monocytes in PD versus healthy controls, suggesting heterogeneity of disease between patients, heterogeneity during disease progression, and potentially insufficient resolution to resolve dynamic cell state changes in different monocyte subpopulations.

Increased numbers of peripheral monocytes in PD

While monocyte subtype compositions are undoubtedly important in disease and incredibly complex, the total numbers of monocytes in blood can vary considerably from subject to subject in health and disease, and apparently within PD, as summarized in Table 1. Initial efforts to phenotype monocytes in PD demonstrated increased monocyte precursors in PD, suggesting to the authors' a broader underlying systemic response [22]. Principal component analysis in PD cells revealed differential white-blood cell counts (WBCs) that correlated between monocyte and lymphocyte, eosinophil, or neutrophil ratios. The ratios appeared associated with PD risk but not necessarily disease severity [23]. Other studies suggest ratios of different leukocyte subtypes to total leukocyte counts might better associate with patient-specific characteristics; for example, olfaction and body-mass index (BMI) had

positive associations with lymphocyte-to-monocyte ratio (LMR), where there is a general lower number of monocytes relative to lymphocytes [24]. As the variables that affect monocyte counts and subpopulations are identified in patient populations, their effects might be controlled for in future studies that compare PD cases and controls. Nevertheless, Tian et al. found that activated monocytes were overall increased in PD, while CD8+ T cells and natural killer (NK) cells were decreased [25]. Other leukocyte counts in PD focused on the neutrophil-to-high density lipoprotein ratio (NHR), an indicator of systemic inflammation, to implicate an effect with disease duration. Specifically, Liu et al. found that disease less than 10 years had a mean NHR of 3.3 (2.45 ~ 4.14, 95% CI), whereas patients with greater than 10 years of disease had a ratio of 2.07 (1.96 ~ 2.96, 95% CI). Liu et al. also determined that the monocyte-to-high density lipoprotein ratio (MHR), a marker of peripheral inflammation and oxidative stress, was positively correlated with disease severity (early stage=0.27; advanced stage=0.35 [26]). Like PD, patients with multiple system atrophy (MSA), a rare neurodegenerative disorder with aggregated α- synuclein, had elevated differential WBC ratios including MHR [27]. Overall, these studies suggest an upregulation or expansion of the monocyte compartment in PD, especially in established disease, but it is not clear when this might occur in disease and how different subtypes of monocytes might be associated with disease progression and severity. Indeed, Jensen et al. concluded that lower lymphocyte and monocyte counts prior to PD diagnosis may be associated with PD risk [28]. Future studies that help functionally parse monocyte subtypes with respect to the inherent heterogeneity of disease progression may be revealing to better understand the cell subsets associated with disease risk or protection. One study identified the peripheral immune system is dynamically altered in PD stages and directly related to both symptoms and sex; migratory (CCR2 and CD11b) and phagocytic (CD163) markers were elevated in early PD and associated with cognitive deficits, while TLR2 expression was correlated with motor severity [29,30]. In addition to the TLR-driven monocyte activation, *in vitro* α-synuclein induced transcriptional programs associated with differentiation of monocytes towards macrophages via non-canonical NF-κB signaling, serving as a potential mechanism in which monocytes contribute to peripheral inflammation in PD [31]. Longitudinal studies that follow patient monocyte responses over time will be especially informative in this regard.

If there is a systemic monocyte dysregulation early in PD, what are some of the earliest driving factors? Recent studies have linked different gut microbiome compositions with PD risk, and some comorbidities and risks associated with PD manifest in the form of gastrointestinal (GI) inflammatory complications such as Crohn’s disease, irritable bowel syndrome, and ulcerative colitis [32–34]. A pervasive, emerging hypothesis supposes that circulating monocytes and other immune cells may be primed for function by interactions in the gut, for example with pathogens or toxicants, that may influence blood monocyte subtype compositions and their responses to other inflammatory stimuli in the body. Gut microbiota might signal through the enteric nervous system to the CNS, possibly driving disease progression or initiation [35]. In an assessment of microbiota-associated epitopes, thirteen were indicators of inflammation and associated with increased monocyte counts in the blood [36]. Given the apparent heterogeneity in PD, not only with respect to different risk factors and complications like microbiome and GI disturbances, larger studies that are

powered to stratify PD populations based on clinical subtypes, blood leukocyte counts, and ratios with other immune cells may help clarify these interactions.

Mutations in glucocerebrosidase (GBA1) are linked to an increased risk of PD. These mutations impact the activity of the lysosomal lipid metabolism enzyme (GCase). Interestingly, this GCase activity is reduced in PD monocytes and correlates with plasma ceramide levels, a measure of inflammation [37]. Macrophages of Gaucher disease, caused by the deficiency of lysosomal glucocerebrosidase, have increased IL-1β and IL-6, activated inflammasomes, and impaired autophagy, likely involving elevated levels of p62 that prevents delivery of inflammasomes to autophagosomes [38]. This link between the regulation of lysosomes, autophagy, and inflammation may be relevant to PD. GCase activity has been found reduced in cryopreserved PD patient monocytes and inversely correlates with motor severity [39]. Better understanding the connections between inflammation and function at the lysosome may provide a better mechanistic understanding to interpret some of the aforementioned state and functional changes attributed to monocytes in PD patients.

Brain-infiltrating monocytes in PD

Can circulating monocytes, disrupted in PD, access the deep brain parenchyma, for example the substantia nigra, to affect local glial and adaptive immune responses in the most vulnerable brain nuclei? While the answer is not yet clear to our knowledge, both classical and non-classical monocytes, characterized by either phagocytic or inflammatory functions, have been shown to increase in CSF of PD patients in comparison to controls [40]. Through their robust phagocytic capacity, monocytes are thought to cross the blood-CSF barrier in response to chemokines and other chemical gradients when debris presents from damaged cells, for example from hemorrhage or demyelination [41]. However, despite the presence of monocytes in PD CSF, whether or not they invade the deep brain parenchyma at some point in PD remains a contentious and difficult question to study. In the deep brain parenchyma, monocytes can be expected to readily respond to the microenvironment milieus and differentiate to macrophage phenotypes that may closely resemble other resident myeloid cells, and respond in unique ways to disease.

As in other diseases like Alzheimer’s disease [42], myeloid cell populations in PD brains analyzed by single-cell analysis have not yet been spatially localized down to cellular resolutions to determine positioning in the brain parenchyma or vasculature. In a recent postmortem study, gene expression data demonstrated that prefrontal cortices affected by PD exhibited higher numbers of monocytes in comparison to healthy controls [43]. Of the 21 immune subtypes assigned in that study, monocytes were the only population to show a higher relative abundance. As monocytes are dynamic and demonstrate rapid tissue-specific differentiation to other types of macrophages, homeostatic gene signatures that might demarcate monocytes from other myeloid cells have shown to be lost quickly after exiting from circulation [44]. Transcriptomic signatures, which may be highly dynamic in the individual cells, may also vary considerably depending on the region of the brain where the cells reside. Indeed, the process of monocyte maturation in tissues is further complicated with possible disease-specific changes that would obviate any clear informatic

way to impute data from healthy control brain tissues. However, recent studies have demonstrated that peripheral immune cells, namely adaptive immune cells, do infiltrate in PD brain tissue. As opposed to myeloid cells, T-cells bear distinct immunohistochemical and transcriptional profiles from any abundant brain-resident cell, and the infiltration of T-cells into the brain parenchyma is now well established in both PD and AD [45]. In some PD models, typically involving acute overexpression of α-synuclein or exposure to a toxicant, which may temporarily disrupt brain-CSF barriers, monocytes can abundantly infiltrate into the mouse midbrain [46–50]. Knockout of CCR2, a chemokine receptor for monocyte chemotaxis, was also protective in an adeno-associated viral based α-synuclein model of PD [51]. How well these models and mouse innate immune responses mimic processes in the human brain is difficult to know. While the analysis of myeloid cell populations in PD brain is still in a relatively naïve stage, the application of emerging scRNA profiles in other diseases known for their robust monocyte infiltration to the brain, for example in stroke or MS, may help resolve the lineages and functions of myeloid cells found in future studies in PD brain tissue.

Several studies have identified CD200R, a receptor that regulates the expression of TNFα, IFNγ, and iNOS as a pathway dysregulated in PD. Monocytes of PD patients lack induction of CD200R expression, which reduces serum pro-inflammatory cytokines (TNFα, IL-1β), TLR4 expression on peripheral blood mononuclear cells (PBMs), microglia activation, and inversely correlates with onset age of PD [52–54]. The significance of this signaling pathway was highlighted by the finding that CD200-CD200R protects DA neuronal loss resulting from peripheral LPS administration [55]. However, a recent study found that PD patients have higher CD200 and CD200R mRNA in brain tissue, and higher CD200 in iPSC DA neurons [56]. It should be noted that high mRNA expression does not always translate to higher protein levels. But, further mechanistic studies should be conducted to investigate why this beneficial CD200-CD200R signaling pathway is not occurring in PD patients.

Monocyte responses to pathogenic α-synuclein in the brain.

Through a process not fully understood, α-synuclein protein converts from a typically low-molecular weight soluble form to a high-molecular weight typically insoluble form that collects in many types of neurons and in the extracellular matrix through disease progression in PD. Catecholaminergic neurons in the substantia nigra pars compacta, and locus coeruleus, seem particularly vulnerable to this process, and degenerate in disease. PD and other Lewy body diseases are characterized by the presence of these α-synuclein aggregates in remaining neurons and in the brain parenchyma upon post-mortem examination [2]. In common nomenclature,α-synuclein protein is considered pathogenic in humans when it bears a Mendelian missense variant (e.g., A53T or A30P), over-expressed as through a genomic multiplication, or when it is present in a fibrillated form associated with inclusions and positively measured with diagnostic seeding aggregation assays (e.g., RT-QUIC, or PMCA). Whereas these cellular inclusions may wax and wane in disease as neurons die off and new aggregates form in other neurons, robust myeloid cell activation in these affected areas appears a permanent pathological contribution to pathological staging [57]. Inflammation appears to not resolve for unknown reasons. Though many older studies often presume the whole myeloid cell composition found in the brain as microglia, the markers so

far utilized in the larger histopathological studies (e.g., antibodies to CD68, IbaI, or MHCII) do not typically differentiate microglia from other types of innate immune cells that might include many types of border macrophages and bone-marrow derived monocytes.

Mouse models of PD, that can include selective and robust degeneration of dopaminergic neurons in the substantia nigra, may provide some insights into myeloid populations responding to α-synuclein accumulation. In mouse models, α-synuclein inclusions in neurons induce the expression of MHCII in nearby myeloid cells [58,59]. MHCII induction is important for both antigen presentation and CD4 T-cell activation. *In vitro*, human peripheral monocytes were robustly stimulated through exposures to trace quantities of extracellular aggregated α-synuclein [60]. However, a caveat remains that most recombinant α-synuclein proteins used to stimulate monocytes in experimental settings are purified from gram-negative bacteria, and therefore contains, to some extent, bacterial cell-wall components like lipopolysaccharides (LPS) that also stimulate robust responses in monocytes. Apart from recombinant α-synuclein, blood extracellular vesicles containing pathogenic α-synuclein also activated PD patient-derived monocytes [60,61]. Specifically, classical phagocytic monocytes from PD patients had decreased TNF-α and IL-6 release when stimulated by α-synuclein in comparison to healthy controls [62]. Additional evidence for α-synuclein-stimulated monocytes in PD comes from overexpression transgenic α-synuclein mouse strains [60,63,64]. These studies suggest extracellular aggregated α-synuclein itself may cross the blood brain barrier [65–67], or co-localize with monocytes in the CSF [65,66]. Pericytes that line capillary walls also release strong levels of chemokines known to direct monocyte chemotaxis [65]. Therefore, local resident myeloid cell responses in the brain to α-synuclein accumulation may stimulate potent chemokines like CCL2 and CCL5 that recruit peripheral monocytes. Potentially adding another layer of complexity, one study demonstrated LPS-primed peripheral monocytes internalized and shuttled α-synuclein aggregates from the periphery to the brain parenchyma [68].

Together, these studies suggest an active interaction between aggregated α-synuclein and monocytes. The discovery that ablation of the CCR2 chemokine receptor provided protection in at least one model of PD [58] stands in agreement with other disease models (e.g., in stroke, TBI) where CCR2 knockout was protective [69,70]. Reports in an AD mouse model suggested CCR2 knockout impaired microglial clearance of amyloid-β plaques to exacerbate disease phenotypes [71,72]. The difference between the PD and AD models with respect to the differential role of monocytes in the CCR2 knockout mice may lie in how extracellular debris might drive phenotype, that is, extracellular plaques versus primarily intracellular α-synuclein. Further studies are needed to help understand whether monocytes might principally exert effect in disease risk and progression in the periphery, or whether monocytes might be responding to the secretion of chemokines and other debris from brain resident cells in engrafting in the brain to mediate local inflammatory responses in concert with other myeloid and adaptive immune cell populations. Such experiments might be facilitated with newer conditional genetic approaches that can target microglia (but not monocytes), or with traditional bone-marrow transplantations or adoptive transfer technology to affect mostly bone-marrow derived cells while leaving microglial populations relatively intact.

Role of LRRK2 in PD monocytes

In a broad division of cells in peripheral blood mononuclear cell (PBMC) pellets, Thevenet et al. noticed that LRRK2 protein expression in healthy individuals was confined to mature classical and non-classical monocyte populations [73]. This finding has been replicated in whole proteome and transcriptome studies of human immune cells [74,75]. In PD, flow cytometry approaches of isolated monocytes from PD patients (without pathogenic LRRK2 mutations) demonstrated elevated total LRRK2 protein in two independent studies [76,77]. Pathogenic LRRK2 is linked to PD susceptibility both through rare pathogenic Mendelian missense variants, R1441C and G2019S, as well through common non-coding variants in GWAS [78,79]. LRRK2 expression is upregulated in monocytes following their maturation or through differentiation induced by interferon-gamma (IFNγ) [73,80–82]. Because of the inducible nature of LRRK2 as well as dynamic states associated with monocytes and macrophages, many factors that affect monocyte maturation might be anticipated to affect LRRK2 activity, and potentially vice-versa. The pathogenic G2019S LRRK2 mutation in induced pluripotent stem cell (iPSC) -derived monocytes are pro-inflammatory and have reduced migratory capacity when stimulated with LPS [83]. In another study of pathogenic LRRK2 genetic variants, the R1441C mutation increases LRRK2 kinase activity 3–4 fold [84]. Mice expressing R1441C globally have increased numbers of infiltrating pro-inflammatory monocytes in acute response to α-synuclein fibrils [85]. In monocytes isolated from the mouse brain, exposure to extracellular aggregated α-synuclein induced LRRK2 expression [74]. Following activation of PD patient-derived monocytes in vitro with GM-CSF, scRNA sequencing and proteomics identified LRRK2 protein as a potential biomarker for PD [21]. Peripheral blood monocytes from patients with iPD showed increased LRRK2 levels and IFNγ stimulation-dependent enzymatic activity, measured by Rab10 phosphorylation [86]. Though scRNA databases that include sequencing depths needed to study rare myeloid cell compositions remain in their infancy in PD research, a new study found an upregulation of LRRK2 mRNA in some subsets of microglia in the control (non-PD) brain associated with the main LRRK2 PD genetic variant [87]. In consideration of these studies, LRRK2 is not a homeostatic gene in monocytes, but dynamic and upregulated with inflammation, leading to the question of LRRK2 function in these cells.

Using transgenic mice, Kozina et al. concluded that pathogenic LRRK2 mutations can specifically alter type II interferon responses in peripheral monocytes to exacerbate dopaminergic neuron loss [88]. Earlier work suggested that toll-like receptor four (TLR4) activation induced autophagy driven by membrane-bound LRRK2 [89]. Knock-down of LRRK2 with shRNA impaired autophagy and clearance of extracellular aggregate proteins by myeloid cells [89]. Furthering the link between LRRK2 activity and endolysosomal pathway function, LRRK2 kinase inhibition nominally impaired levels of IL-1β, IL-6, and TNFα mRNA in response to extracellular vesicles harboring pathogenic α-synuclein [90]. In other studies, kinase inhibition of LRRK2 impaired chemotactic responses of macrophages and microglia both in vitro and in vivo [74,91]. The multitude of pathways in monocytes or macrophages currently thought to be affected by LRRK2 expression or activity begs the question of whether or not there can exist a plausible singular mechanism

that links together such diverse responses. As previously mentioned, it is difficult to decouple dynamic monocyte and macrophage activation states from inducible LRRK2 expression and activity, with one probably affecting the other to issue a whole host of functional differences.

Nevertheless, with LRRK2 activity in these cells, perhaps a PD-relevant link resides within the enzymatic capacity of LRRK2 to phosphorylate other proteins. In this regard, recent work to validate authentic LRRK2 kinase substrates in myeloid cells may provide clues how LRRK2 expression and activity modifies other critical pathways in inflammatory signaling. The upregulation of the endolysosomal compartment and phagocytic capacity is a known critical component of monocyte function and response to different stimuli [92–94]. Mechanistic data suggests LRRK2 functions within the endolysosomal compartment to phosphorylate a subset of small GTPase Rab proteins including Rab35 which may be involved in phagocytosis [95], Rab10 which may be involved in bulk-fluid phase endocytosis and recycling of signaling endosomes [96], Rab8a which may be involved in centrosome maintenance and lipid storage [97], Rab12 which may be involved in ciliogenesis [98], and Rab29 which may be involved in endolysosomal and Golgi-vesicle transport and recycling [99]. LRRK2 phosphorylation of any of these GTP-bound Rab substrates is predicted to alter critical interactions based on the modification of critical interacting loops in the GTPase that serve as scaffolds for effector proteins. For example, a recent study suggested that LRRK2 phosphorylation of Rab10 altered the maturation of CCR5-loaded vesicles in AKT-mediated activation pathways, when macrophages were fed CCL5 [96]. Though this is just one example, several experimental paradigms could be contrived that differentially depend on Rab8a, Rab10, Rab12, Rab29, or Rab35, in effecting a monocyte-dependent response. Therefore, depending on the cargo and composition of LRRK2-phosphorylated Rab proteins, a host of monocyte responses could be envisaged depending on the stimulus and experimental constraints. The stimulus used to experimentally elicit a response in monocytes or macrophages, and how relevant this stimulus might be to PD pathogenesis, could be critical factors that help resolve LRRK2 function in pathways.

Concluding Remarks

The role of neuroinflammation has been difficult to understand in PD, ever since the discovery of robust abundant activated immune cells in the brain more than three decades ago. GWAS studies, transcriptomic studies, emerging proteomic studies, and other approaches show that monocytes are disrupted in PD and play some role in disease risk. On a functional level, experiments in both patient populations and PD models indicate monocytes are highly responsive both to PD-associated changes in α-synuclein as well as pathogenic mutations in LRRK2. Emerging data also suggest a role for mutations in GBAI in monocytes. Not surprisingly, monocyte populations are found to be highly dynamic in disease progression, and studies at different stages of disease appear somewhat contradictory at this time. Owing to the dynamic nature of monocytes and plasticity with respect to differential states that can mimic other resident myeloid cells in different tissues, little is yet known whether monocytes might principally exert effects on risk and progression in the periphery or in the brain. While larger longitudinal studies of monocytes in PD and

at-risk populations should be the focus moving forward, the novel discovery of LRRK2 phosphorylation of Rab proteins that are highly expressed in monocytes provides an opportunity to mechanistically explore the interactions between LRRK2 and α-synuclein as they occur in the periphery as well as in the brain. Through a better understanding of these interactions and pathways, new therapeutic interventions that slow or halt disease progression may reveal themselves and help us to better understand neuroinflammation responses in PD.

References

1. Nguyen APT, Tsika E, Kelly K, Levine N, Chen X, West AB, et al. Dopaminergic neurodegeneration induced by Parkinson's disease-linked G2019S LRRK2 is dependent on kinase and GTPase activity. Proc Natl Acad Sci U S A [Internet]. 2020 Jul 21;117(29):17296–307. Available from: 10.1073/pnas.1922184117 [PubMed: 32631998]
2. Spillantini MG, Goedert M. Neurodegeneration and the ordered assembly of α-synuclein. Cell Tissue Res [Internet]. 2018 Jul;373(1):137–48. Available from: 10.1007/s00441-017-2706-9 [PubMed: 29119326]
3. Yoo D, Bang JI, Ahn C, Nyaga VN, Kim YE, Kang MJ, et al. Diagnostic value of α-synuclein seeding amplification assays in α-synucleinopathies: A systematic review and meta-analysis. Parkinsonism Relat Disord [Internet]. 2022 Nov;104:99–109. Available from: 10.1016/j.parkreldis.2022.10.007 [PubMed: 36289019]
4. Magalhães P, Lashuel HA. Opportunities and challenges of alpha-synuclein as a potential biomarker for Parkinson's disease and other synucleinopathies. NPJ Parkinsons Dis [Internet]. 2022 Jul 22;8(1):93. Available from: 10.1038/s41531-022-00357-0 [PubMed: 35869066]
5. Pajares M, I Rojo A, Manda G, Boscá L, Cuadrado A. Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. Cells [Internet]. 2020 Jul 14;9(7). Available from: 10.3390/cells9071687
6. Moehle MS, West AB. M1 and M2 immune activation in Parkinson's Disease: Foe and ally? Neuroscience [Internet]. 2015 Aug 27;302:59–73. Available from: 10.1016/j.neuroscience.2014.11.018 [PubMed: 25463515]
7. Ma WT, Gao F, Gu K, Chen DK. The Role of Monocytes and Macrophages in Autoimmune Diseases: A Comprehensive Review. Front Immunol [Internet]. 2019 May 24;10:1140. Available from: 10.3389/fimmu.2019.01140 [PubMed: 31178867]
8. Hamza TH, Zabetian CP, Tenesa A, Laederach A, Montimurro J, Yearout D, et al. Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. Nat Genet [Internet]. 2010 Sep;42(9):781–5. Available from: 10.1038/ng.642 [PubMed: 20711177]
9. Hill-Burns EM, Wissemann WT, Hamza TH, Factor SA, Zabetian CP, Payami H. Identification of a novel Parkinson's disease locus via stratified genome-wide association study. BMC Genomics [Internet]. 2014 Feb 10;15:118. Available from: 10.1186/1471-2164-15-118 [PubMed: 24511991]
10. Gagliano SA, Pouget JG, Hardy J, Knight J, Barnes MR, Ryten M, et al. Genomics implicates adaptive and innate immunity in Alzheimer's and Parkinson's diseases. Ann Clin Transl Neurol [Internet]. 2016 Dec;3(12):924–33. Available from: 10.1002/acn3.369 [PubMed: 28097204]
11. Raj T, Rothamel K, Mostafavi S, Ye C, Lee MN, Replogle JM, et al. Polarization of the effects of autoimmune and neurodegenerative risk alleles in leukocytes. Science [Internet]. 2014 May 2;344(6183):519–23. Available from: 10.1126/science.1249547 [PubMed: 24786080]
12. Kannarkat GT, Cook DA, Lee JK, Chang J, Chung J, Sandy E, 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 [Internet]. 2015 Apr 22;1:15002 – . Available from: 10.1038/npjparkd.2015.2 [PubMed: 27148593]
13. Chan G, White CC, Winn PA, Cimpean M, Replogle JM, Glick LR, et al. Trans-pQTL study identifies immune crosstalk between Parkinson and Alzheimer loci. Neurol Genet [Internet]. 2016 Aug;2(4):e90. Available from: 10.1212/NXG.0000000000000090 [PubMed: 27504496]

14. Mukherjee S Immune gene network of neurological diseases: Multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). Heliyon [Internet]. 2021 Dec;7(12):e08518. Available from: 10.1016/j.heliyon.2021.e08518 [PubMed: 34926857]
15. Witoelar A, Jansen IE, Wang Y, Desikan RS, Gibbs JR, Blauwendraat C, et al. Genome-wide Pleiotropy Between Parkinson Disease and Autoimmune Diseases. JAMA Neurol [Internet]. 2017 Jul 1;74(7):780–92. Available from: 10.1001/jamaneurol.2017.0469 [PubMed: 28586827]
16. Heng H, Liu J, Hu M, Li D, Su W, Li J. WDR43 is a potential diagnostic biomarker and therapeutic target for osteoarthritis complicated with Parkinson's disease. Front Cell Neurosci [Internet]. 2022 Nov 7;16:1013745. Available from: 10.3389/fncel.2022.1013745 [PubMed: 36419937]
17. Schlachetzki JCM, Prots I, Tao J, Chun HB, Saijo K, Gosselin D, et al. A monocyte gene expression signature in the early clinical course of Parkinson's disease. Sci Rep [Internet]. 2018 Jul 17;8(1):10757. Available from: 10.1038/s41598-018-28986-7 [PubMed: 30018301]
18. Fan Y, Li J, Yang Q, Gong C, Gao H, Mao Z, et al. Dysregulated Long Non-coding RNAs in Parkinson's Disease Contribute to the Apoptosis of Human Neuroblastoma Cells. Front Neurosci [Internet]. 2019 Dec 13;13:1320. Available from: 10.3389/fnins.2019.01320 [PubMed: 31920490]
19. Navarro E, Udine E, de Paiva Lopes K, Parks M, Riboldi G, Schilder BM, et al. Dysregulation of mitochondrial and proteolysosomal genes in Parkinson's disease myeloid cells. Nat Aging [Internet]. 2021 Sep;1(9):850–63. Available from: 10.1038/s43587-021-00110-x [PubMed: 35005630]
20. Riboldi GM, Vialle RA, Navarro E, Udine E, de Paiva Lopes K, Humphrey J, et al. Transcriptome deregulation of peripheral monocytes and whole blood in GBA-related Parkinson's disease. Mol Neurodegener [Internet]. 2022 Aug 17;17(1):52. Available from: 10.1186/s13024-022-00554-8 [PubMed: 35978378]
21. Abdelmoaty MM, Machhi J, Yeapuri P, Shahjin F, Kumar V, Olson KE, et al. Monocyte biomarkers define sargramostim treatment outcomes for Parkinson's disease. Clin Transl Med [Internet]. 2022 Jul;12(7):e958. Available from: 10.1002/ctm2.958 [PubMed: 35802825]
22. Funk N, Wieghofer P, Grimm S, Schaefer R, Bühring HJ, Gasser T, et al. Characterization of peripheral hematopoietic stem cells and monocytes in Parkinson's disease. Mov Disord [Internet]. 2013 Mar;28(3):392–5. Available from: 10.1002/mds.25300 [PubMed: 23401086]
23. Wang Y, Gao H, Jiang S, Luo Q, Han X, Xiong Y, et al. Principal component analysis of routine blood test results with Parkinson's disease: A case-control study. Exp Gerontol [Internet]. 2021 Feb;144:111188. Available from: 10.1016/j.exger.2020.111188 [PubMed: 33279667]
24. Umehara T, Oka H, Nakahara A, Matsuno H, Murakami H. Differential leukocyte count is associated with clinical phenotype in Parkinson's disease. J Neurol Sci [Internet]. 2020 Feb 15;409:116638. Available from: 10.1016/j.jns.2019.116638 [PubMed: 31865186]
25. Tian J, Dai SB, Jiang SS, Yang WY, Yan YQ, Lin ZH, et al. Specific immune status in Parkinson's disease at different ages of onset. NPJ Parkinsons Dis [Internet]. 2022 Jan 10;8(1):5. Available from: 10.1038/s41531-021-00271-x [PubMed: 35013369]
26. Liu Z, Fan Q, Wu S, Wan Y, Lei Y. Compared with the monocyte to high-density lipoprotein ratio (MHR) and the neutrophil to lymphocyte ratio (NLR), the neutrophil to high-density lipoprotein ratio (NHR) is more valuable for assessing the inflammatory process in Parkinson's disease. Lipids Health Dis [Internet]. 2021 Apr 19;20(1):35. Available from: 10.1186/s12944-021-01462-4 [PubMed: 33874966]
27. Jiang L, Zhong Z, Huang J, Bian H, Huang W. Monocytohigh-density lipoprotein ratio has a high predictive value for the diagnosis of multiple system atrophy and the differentiation from Parkinson's disease. Front Aging Neurosci [Internet]. 2022 Oct 13;14:1035437. Available from: 10.3389/fnagi.2022.1035437 [PubMed: 36313023]
28. Jensen MP, Jacobs BM, Dobson R, Bandres-Ciga S, Blauwendraat C, Schrag A, et al. Lower Lymphocyte Count is Associated With Increased Risk of Parkinson's Disease. Ann Neurol [Internet]. 2021 Apr;89(4):803–12. Available from: 10.1002/ana.26034 [PubMed: 33527442]
29. Nissen SK, Ferreira SA, Nielsen MC, Schulte C, Shrivastava K, Hennig D, et al. Soluble CD163 Changes Indicate Monocyte Association With Cognitive Deficits in Parkinson's Disease. Mov Disord [Internet]. 2021 Apr;36(4):963–76. Available from: 10.1002/mds.28424 [PubMed: 33332647]

30. Konstantin Nissen S, Farmen K, Carstensen M, Schulte C, Goldeck D, Brockmann K, et al. Changes in CD163+, CD11b+, and CCR2+ peripheral monocytes relate to Parkinson's disease and cognition. Brain Behav Immun [Internet]. 2022 Mar;101:182–93. Available from: 10.1016/j.bbi.2022.01.005 [PubMed: 35026420]

31. Bearoff F, Dhavale D, Kotzbauer P, Kortagere S. Aggregated alpha-synuclein transcriptionally activates pro-inflammatory canonical and non-canonical NF-κB signaling pathways in peripheral monocytic cells. Mol Immunol [Internet]. 2023 Feb;154:1–10. Available from: 10.1016/j.molimm.2022.12.006 [PubMed: 36571978]

32. Mulak A, Bonaz B. Brain-gut-microbiota axis in Parkinson's disease. World J Gastroenterol [Internet]. 2015 Oct 7;21(37):10609–20. Available from: 10.3748/wjg.v21.i37.10609 [PubMed: 26457021]

33. Chen QQ, Haikal C, Li W, Li JY. Gut Inflammation in Association With Pathogenesis of Parkinson's Disease. Front Mol Neurosci [Internet]. 2019 Sep 13;12:218. Available from: 10.3389/fnmol.2019.00218 [PubMed: 31572126]

34. Shannon KM. Gut-Derived Sterile Inflammation and Parkinson's Disease. Front Neurol [Internet]. 2022 Mar 29;13:831090. Available from: 10.3389/fneur.2022.831090 [PubMed: 35422756]

35. Wang Q, Luo Y, Ray Chaudhuri K, Reynolds R, Tan EK, Pettersson S. The role of gut dysbiosis in Parkinson's disease: mechanistic insights and therapeutic options. Brain [Internet]. 2021 Oct 22;144(9):2571–93. Available from: 10.1093/brain/awab156 [PubMed: 33856024]

36. Li Z, Lu G, Li Z, Wu B, Luo E, Qiu X, et al. Altered Actinobacteria and Firmicutes Phylum Associated Epitopes in Patients With Parkinson's Disease. Front Immunol [Internet]. 2021 Jul 2;12:632482. Available from: 10.3389/fimmu.2021.632482 [PubMed: 34276644]

37. Atashrazm F, Hammond D, Perera G, Dobson-Stone C, Mueller N, Pickford R, et al. Reduced glucocerebrosidase activity in monocytes from patients with Parkinson's disease. Sci Rep [Internet]. 2018 Oct 18;8(1):15446. Available from: 10.1038/s41598-018-33921-x [PubMed: 30337601]

38. Aflaki E, Moaven N, Borger DK, Lopez G, Westbroek W, Chae JJ, et al. Lysosomal storage and impaired autophagy lead to inflammasome activation in Gaucher macrophages. Aging Cell [Internet]. 2016 Feb;15(1):77–88. Available from: 10.1111/acel.12409 [PubMed: 26486234]

39. Hughes LP, Pereira MMM, Hammond DA, Kwok JB, Halliday GM, Lewis SJG, et al. Glucocerebrosidase Activity is Reduced in Cryopreserved Parkinson's Disease Patient Monocytes and Inversely Correlates with Motor Severity. J Parkinsons Dis [Internet]. 2021;11(3):1157–65. Available from: 10.3233/JPD-202508 [PubMed: 33935104]

40. Pillny C, Nitsch L, Proske-Schmitz S, Sharma A, Wüllner U. Abnormal subpopulations of monocytes in the cerebrospinal fluid of patients with Parkinson's disease. Parkinsonism Relat Disord [Internet]. 2021 Mar;84:144–5. Available from: 10.1016/j.parkreldis.2021.02.017 [PubMed: 33631553]

41. Rahimi J, Woehrer A. Overview of cerebrospinal fluid cytology. Handb Clin Neurol [Internet]. 2017;145:563–71. Available from: 10.1016/B978-0-12-802395-2.00035-3 [PubMed: 28987194]

42. Olah M, Menon V, Habib N, Taga MF, Ma Y, Yung CJ, et al. Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. Nat Commun [Internet]. 2020 Nov 30;11(1):6129. Available from: 10.1038/s41467-020-19737-2 [PubMed: 33257666]

43. Batchu S Prefrontal Cortex Transcriptomic Deconvolution Implicates Monocyte Infiltration in Parkinson's Disease. Neurodegener Dis [Internet]. 2020 Sep 25;20(2–3):110–2. Available from: 10.1159/000510218 [PubMed: 32980850]

44. Baufeld C, O'Loughlin E, Calcagno N, Madore C, Butovsky O. Differential contribution of microglia and monocytes in neurodegenerative diseases. J Neural Transm [Internet]. 2018 May;125(5):809–26. Available from: 10.1007/s00702-017-1795-7 [PubMed: 29063348]

45. Gate D, Saligrama N, Leventhal O, Yang AC, Unger MS, Middeldorp J, et al. Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. Nature [Internet]. 2020 Jan;577(7790):399–404. Available from: 10.1038/s41586-019-1895-7

46. Williams GP, Marmion DJ, Schonhoff AM, Jurkuvenaite A, Won WJ, Standaert DG, et al. T cell infiltration in both human multiple system atrophy and a novel mouse model of the disease. Acta

Neuropathol [Internet]. 2020 May;139(5):855–74. Available from: 10.1007/s00401-020-02126-w [PubMed: 31993745]

47. Parillaud VR, Lornet G, Monnet Y, Privat AL, Haddad AT, Brochard V, et al. Analysis of monocyte infiltration in MPTP mice reveals that microglial CX3CR1 protects against neurotoxic over-induction of monocyte-attracting CCL2 by astrocytes. J Neuroinflammation [Internet]. 2017 Mar 21;14(1):60. Available from: 10.1186/s12974-017-0830-9 [PubMed: 28320442]
48. Williams GP, Schonhoff AM, Jurkuvenaite A, Thome AD, Standaert DG, Harms AS. Targeting of the class II transactivator attenuates inflammation and neurodegeneration in an alpha-synuclein model of Parkinson's disease. J Neuroinflammation [Internet]. 2018 Aug 30;15(1):244. Available from: 10.1186/s12974-018-1286-2 [PubMed: 30165873]
49. Choi DJ, Yang H, Gaire S, Lee KA, An J, Kim BG, et al. Critical roles of astrocytic-CCL2-dependent monocyte infiltration in a DJ-1 knockout mouse model of delayed brain repair. Glia [Internet]. 2020 Oct;68(10):2086–101. Available from: 10.1002/glia.23828 [PubMed: 32176388]
50. Espinosa-Oliva AM, de Pablos RM, Sarmiento M, Villarán RF, Carrillo-Jiménez A, Santiago M, et al. Role of dopamine in the recruitment of immune cells to the nigro-striatal dopaminergic structures. Neurotoxicology [Internet]. 2014 Mar;41:89–101. Available from: 10.1016/j.neuro.2014.01.006 [PubMed: 24486959]
51. Harms AS, Thome AD, Yan Z, Schonhoff AM, Williams GP, Li X, et al. Peripheral monocyte entry is required for alpha-Synuclein induced inflammation and Neurodegeneration in a model of Parkinson disease. Exp Neurol [Internet]. 2018 Feb;300:179–87. Available from: 10.1016/j.expneurol.2017.11.010 [PubMed: 29155051]
52. Luo XG, Zhang JJ, Zhang CD, Liu R, Zheng L, Wang XJ, et al. Altered regulation of CD200 receptor in monocyte-derived macrophages from individuals with Parkinson's disease. Neurochem Res [Internet]. 2010 Apr;35(4):540–7. Available from: 10.1007/s11064-009-0094-6 [PubMed: 19924532]
53. Zhang S, Wang XJ, Tian LP, Pan J, Lu GQ, Zhang YJ, et al. CD200-CD200R dysfunction exacerbates microglial activation and dopaminergic neurodegeneration in a rat model of Parkinson's disease. J Neuroinflammation [Internet]. 2011 Nov 6;8:154. Available from: 10.1186/1742-2094-8-154 [PubMed: 22053982]
54. Xia L, Xie X, Liu Y, Luo X. Peripheral Blood Monocyte Tolerance Alleviates Intraperitoneal Lipopolysaccharides-Induced Neuroinflammation in Rats Via Upregulating the CD200R Expression. Neurochem Res [Internet]. 2017 Nov;42(11):3019–32. Available from: 10.1007/s11064-017-2334-5 [PubMed: 28664397]
55. Xie X, Luo X, Liu N, Li X, Lou F, Zheng Y, et al. Monocytes, microglia, and CD200-CD200R1 signaling are essential in the transmission of inflammation from the periphery to the central nervous system. J Neurochem [Internet]. 2017 Apr;141(2):222–35. Available from: 10.1111/jnc.13972 [PubMed: 28164283]
56. Rabaneda-Lombarte N, Vidal-Taboada JM, Valente T, Ezquerra M, Fernández-Santiago R, Martí MJ, et al. Altered expression of the immunoregulatory ligand-receptor pair CD200-CD200R1 in the brain of Parkinson's disease patients. NPJ Parkinsons Dis [Internet]. 2022 Mar 16;8(1):27. Available from: 10.1038/s41531-022-00290-2 [PubMed: 35296683]
57. Imamura K, Hishikawa N, Sawada M, Nagatsu T, Yoshida M, Hashizume Y. Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. Acta Neuropathol [Internet]. 2003 Dec;106(6):518–26. Available from: 10.1007/s00401-003-0766-2 [PubMed: 14513261]
58. Harms AS, Delic V, Thome AD, Bryant N, Liu Z, Chandra S, et al. α-Synuclein fibrils recruit peripheral immune cells in the rat brain prior to neurodegeneration. Acta Neuropathol Commun [Internet]. 2017 Nov 21;5(1):85. Available from: 10.1186/s40478-017-0494-9 [PubMed: 29162163]
59. Juul-Madsen K, Qvist P, Bendtsen KL, Langkilde AE, Vestergaard B, Howard KA, et al. Size-Selective Phagocytic Clearance of Fibrillar α-Synuclein through Conformational Activation of Complement Receptor 4. J Immunol [Internet]. 2020 Mar 1;204(5):1345–61. Available from: 10.4049/jimmunol.1900494 [PubMed: 31969389]

60. Grozdanov V, Bousset L, Hoffmeister M, Bliederhaeuser C, Meier C, Madiona K, et al. Increased Immune Activation by Pathologic α-Synuclein in Parkinson's Disease. Ann Neurol [Internet]. 2019 Oct;86(4):593–606. Available from: 10.1002/ana.25557 [PubMed: 31343083]
61. Gardai SJ, Mao W, Schüle B, Babcock M, Schoebel S, Lorenzana C, et al. Elevated alpha-synuclein impairs innate immune cell function and provides a potential peripheral biomarker for Parkinson's disease. PLoS One [Internet]. 2013 Aug 23;8(8):e71634. Available from: 10.1371/journal.pone.0071634 [PubMed: 24058406]
62. Su Y, Shi C, Wang T, Liu C, Yang J, Zhang S, et al. Dysregulation of peripheral monocytes and pro-inflammation of alpha-synuclein in Parkinson's disease. J Neurol [Internet]. 2022 Dec;269(12):6386–94. Available from: 10.1007/s00415-022-11258-w [PubMed: 35895134]
63. Drouin-Ouellet J, St-Amour I, Saint-Pierre M, Lamontagne-Proulx J, Kriz J, Barker RA, et al. Toll-like receptor expression in the blood and brain of patients and a mouse model of Parkinson's disease. Int J Neuropsychopharmacol [Internet]. 2014 Dec 7;18(6). Available from: 10.1093/ijnp/pyu103
64. Taguchi T, Ikuno M, Hondo M, Parajuli LK, Taguchi K, Ueda J, et al. α-Synuclein BAC transgenic mice exhibit RBD-like behaviour and hyposmia: a prodromal Parkinson's disease model. Brain [Internet]. 2020 Jan 1;143(1):249–65. Available from: 10.1093/brain/awz380 [PubMed: 31816026]
65. Dohgu S, Takata F, Matsumoto J, Kimura I, Yamauchi A, Kataoka Y. Monomeric α-synuclein induces blood-brain barrier dysfunction through activated brain pericytes releasing inflammatory mediators in vitro. Microvasc Res [Internet]. 2019 Jul;124:61–6. Available from: 10.1016/j.mvr.2019.03.005 [PubMed: 30885616]
66. Shahnawaz M, Tokuda T, Waragai M, Mendez N, Ishii R, Trenkwalder C, et al. Development of a Biochemical Diagnosis of Parkinson Disease by Detection of α-Synuclein Misfolded Aggregates in Cerebrospinal Fluid. JAMA Neurol [Internet]. 2017 Feb 1;74(2):163–72. Available from: 10.1001/jamaneurol.2016.4547 [PubMed: 27918765]
67. Peelaerts W, Bousset L, Van der Perren A, Moskalyuk A, Pulizzi R, Giugliano M, et al. α-Synuclein strains cause distinct synucleinopathies after local and systemic administration. Nature [Internet]. 2015 Jun 18;522(7556):340–4. Available from: 10.1038/nature14547
68. Peralta Ramos JM, Iribarren P, Bousset L, Melki R, Baekelandt V, Van der Perren A. Peripheral Inflammation Regulates CNS Immune Surveillance Through the Recruitment of Inflammatory Monocytes Upon Systemic α-Synuclein Administration. Front Immunol [Internet]. 2019 Jan 29;10:80. Available from: 10.3389/fimmu.2019.00080 [PubMed: 30761145]
69. Hsieh CL, Niemi EC, Wang SH, Lee CC, Bingham D, Zhang J, et al. CCR2 deficiency impairs macrophage infiltration and improves cognitive function after traumatic brain injury. J Neurotrauma [Internet]. 2014 Oct 15;31(20):1677–88. Available from: 10.1089/neu.2013.3252 [PubMed: 24806994]
70. Somebang K, Rudolph J, Imhof I, Li L, Niemi EC, Shigenaga J, et al. CCR2 deficiency alters activation of microglia subsets in traumatic brain injury. Cell Rep [Internet]. 2021 Sep 21;36(12):109727. Available from: 10.1016/j.celrep.2021.109727 [PubMed: 34551293]
71. El Khoury J, Toft M, Hickman SE, Means TK, Terada K, Geula C, et al. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. Nat Med [Internet]. 2007 Apr;13(4):432–8. Available from: 10.1038/nm1555 [PubMed: 17351623]
72. Ben-Yehuda H, Arad M, Peralta Ramos JM, Sharon E, Castellani G, Ferrera S, et al. Key role of the CCR2-CCL2 axis in disease modification in a mouse model of tauopathy. Mol Neurodegener [Internet]. 2021 Jun 25;16(1):39. Available from: 10.1186/s13024-021-00458-z [PubMed: 34172073]
73. Thévenet J, Pescini Gobert R, Hooft van Huijsduijnen R, Wiessner C, Sagot YJ. Regulation of LRRK2 expression points to a functional role in human monocyte maturation. PLoS One [Internet]. 2011 Jun 27;6(6):e21519. Available from: 10.1371/journal.pone.0021519 [PubMed: 21738687]
74. Xu E, Boddu R, Abdelmotilib HA, Sokratian A, Kelly K, Liu Z, et al. Pathological α-synuclein recruits LRRK2 expressing pro-inflammatory monocytes to the brain. Mol Neurodegener [Internet]. 2022 Jan 10;17(1):7. Available from: 10.1186/s13024-021-00509-5 [PubMed: 35012605]

75. Fan Y, Nirujogi RS, Garrido A, Ruiz-Martínez J, Bergareche-Yarza A, Mondragón-Rezola E, et al. R1441G but not G2019S mutation enhances LRRK2 mediated Rab10 phosphorylation in human peripheral blood neutrophils. Acta Neuropathol [Internet]. 2021 Sep;142(3):475–94. Available from: 10.1007/s00401-021-02325-z [PubMed: 34125248]
76. Cook DA, Kannarkat GT, Cintron AF, Butkovich LM, Fraser KB, Chang J, et al. LRRK2 levels in immune cells are increased in Parkinson's disease. NPJ Parkinsons Dis [Internet]. 2017 Mar 28;3:11. Available from: 10.1038/s41531-017-0010-8 [PubMed: 28649611]
77. Bliederhaeuser C, Zondler L, Grozdanov V, Ruf WP, Brenner D, Melrose HL, et al. LRRK2 contributes to monocyte dysregulation in Parkinson's disease. Acta Neuropathol Commun [Internet]. 2016 Nov 24;4(1):123. Available from: 10.1186/s40478-016-0396-2 [PubMed: 27884177]
78. Lake J, Reed X, Langston RG, Nalls MA, Gan-Or Z, Cookson MR, et al. Coding and noncoding variation in LRRK2 and Parkinson's disease risk. Mov Disord [Internet]. 2022 Jan;37(1):95–105. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mds.28787 [PubMed: 34542912]
79. Bryant N, Malpeli N, Ziaee J, Blauwendraat C, Liu Z, AMP PD Consortium, et al. Identification of LRRK2 missense variants in the accelerating medicines partnership Parkinson's disease cohort. Hum Mol Genet [Internet]. 2021 Apr 30;30(6):454–66. Available from: 10.1093/hmg/ddab058 [PubMed: 33640967]
80. Hakimi M, Selvanantham T, Swinton E, Padmore RF, Tong Y, Kabbach G, et al. Parkinson's disease-linked LRRK2 is expressed in circulating and tissue immune cells and upregulated following recognition of microbial structures. J Neural Transm [Internet]. 2011 May;118(5):795–808. Available from: 10.1007/s00702-011-0653-2 [PubMed: 21552986]
81. Kuss M, Adamopoulou E, Kahle PJ. Interferon-γ induces leucine-rich repeat kinase LRRK2 via extracellular signal-regulated kinase ERK5 in macrophages. J Neurochem [Internet]. 2014 Jun;129(6):980–7. Available from: 10.1111/jnc.12668 [PubMed: 24479685]
82. Ikezu T, Koro L, Wolozin B, Farraye FA, Strongosky AJ, Wszolek ZK. Crohn's and Parkinson's Disease-Associated LRRK2 Mutations Alter Type II Interferon Responses in Human CD14 Blood Monocytes Ex Vivo. J Neuroimmune Pharmacol [Internet]. 2020 Dec;15(4):794–800. Available from: 10.1007/s11481-020-09909-8 [PubMed: 32180132]
83. Speidel A, Felk S, Reinhardt P, Sterneckert J, Gillardon F. Leucine-Rich Repeat Kinase 2 Influences Fate Decision of Human Monocytes Differentiated from Induced Pluripotent Stem Cells. PLoS One [Internet]. 2016 Nov 3;11(11):e0165949. Available from: 10.1371/journal.pone.0165949 [PubMed: 27812199]
84. Fan Y, Nirujogi RS, Garrido A, Ruiz-Martínez J, Bergareche-Yarza A, Mondragón-Rezola E, et al. R1441G but not G2019S mutation enhances LRRK2 mediated Rab10 phosphorylation in human peripheral blood neutrophils. Acta Neuropathol [Internet]. 2021 Sep;142(3):475–94. Available from: 10.1007/s00401-021-02325-z [PubMed: 34125248]
85. Xu E, Boddu R, Abdelmotilib HA, Sokratian A, Kelly K, Liu Z, et al. Pathological α-synuclein recruits LRRK2 expressing pro-inflammatory monocytes to the brain. Mol Neurodegener [Internet]. 2022 Jan 10;17(1):7. Available from: 10.1186/s13024-021-00509-5 [PubMed: 35012605]
86. Wallings RL, Hughes LP, Staley HA, Simon ZD, McFarland NR, Alcalay RN, et al. WHOPPA Enables Parallel Assessment of Leucine-Rich Repeat Kinase 2 and Glucocerebrosidase Enzymatic Activity in Parkinson's Disease Monocytes. Front Cell Neurosci [Internet]. 2022 Jun 9;16:892899. Available from: 10.3389/fncel.2022.892899 [PubMed: 35755775]
87. Langston RG, Beilina A, Reed X, Singleton AB, Blauwendraat C, Gibbs JR, et al. Association of a Common Genetic Variant with Parkinson's Disease is Propagated through Microglia [Internet]. bioRxiv. 2021 [cited 2023 Jan 19]. p. 2021.01.15.426824. Available from: https://www.biorxiv.org/content/10.1101/2021.01.15.426824v1.abstract
88. Kozina E, Sadasivan S, Jiao Y, Dou Y, Ma Z, Tan H, et al. Mutant LRRK2 mediates peripheral and central immune responses leading to neurodegeneration in vivo. Brain [Internet]. 2018 Jun 1;141(6):1753–69. Available from: 10.1093/brain/awy077 [PubMed: 29800472]
89. Schapansky J, Nardozzi JD, Felizia F, LaVoie MJ. Membrane recruitment of endogenous LRRK2 precedes its potent regulation of autophagy. Hum Mol Genet [Internet]. 2014 Aug 15;23(16):4201–14. Available from: 10.1093/hmg/ddu138 [PubMed: 24682598]

90. Liu Z, Chan RB, Cai Z, Liu X, Wu Y, Yu Z, et al. α-Synuclein-containing erythrocytic extracellular vesicles: essential contributors to hyperactivation of monocytes in Parkinson's disease. J Neuroinflammation [Internet]. 2022 Feb 22;19(1):53. Available from: 10.1186/s12974-022-02413-1 [PubMed: 35193594]
91. Moehle MS, Daher JPL, Hull TD, Boddu R, Abdelmotilib HA, Mobley J, et al. The G2019S LRRK2 mutation increases myeloid cell chemotactic responses and enhances LRRK2 binding to actin-regulatory proteins. Hum Mol Genet [Internet]. 2015 Aug 1;24(15):4250–67. Available from: 10.1093/hmg/ddv157 [PubMed: 25926623]
92. Chen CC, Krogsaeter E, Kuo CY, Huang MC, Chang SY, Biel M. Endolysosomal cation channels point the way towards precision medicine of cancer and infectious diseases. Biomed Pharmacother [Internet]. 2022 Apr;148:112751. Available from: 10.1016/j.biopha.2022.112751 [PubMed: 35240524]
93. Sitia R, Rubartelli A. The unconventional secretion of IL-1β: Handling a dangerous weapon to optimize inflammatory responses. Semin Cell Dev Biol [Internet]. 2018 Nov;83:12–21. Available from: 10.1016/j.semcdb.2018.03.011 [PubMed: 29571971]
94. Kugeratski FG, Kalluri R. Exosomes as mediators of immune regulation and immunotherapy in cancer. FEBS J [Internet]. 2021 Jan;288(1):10–35. Available from: 10.1111/febs.15558 [PubMed: 32910536]
95. Bae EJ, Kim DK, Kim C, Mante M, Adame A, Rockenstein E, et al. LRRK2 kinase regulates α-synuclein propagation via RAB35 phosphorylation. Nat Commun [Internet]. 2018 Aug 27;9(1):3465. Available from: 10.1038/s41467-018-05958-z [PubMed: 30150626]
96. Liu Z, Xu E, Zhao HT, Cole T, West AB. LRRK2 and Rab10 coordinate macropinocytosis to mediate immunological responses in phagocytes. EMBO J [Internet]. 2020 Oct 15;39(20):e104862. Available from: 10.15252/embj.2020104862 [PubMed: 32853409]
97. Madero-Pérez J, Fdez E, Fernández B, Lara Ordóñez AJ, Blanca Ramírez M, Gómez-Suaga P, et al. Parkinson disease-associated mutations in LRRK2 cause centrosomal defects via Rab8a phosphorylation. Mol Neurodegener [Internet]. 2018 Jan 23;13(1):3. Available from: 10.1186/s13024-018-0235-y [PubMed: 29357897]
98. Steger M, Diez F, Dhekne HS, Lis P, Nirujogi RS, Karayel O, et al. Systematic proteomic analysis of LRRK2-mediated Rab GTPase phosphorylation establishes a connection to ciliogenesis. Elife [Internet]. 2017 Nov 10;6. Available from: 10.7554/eLife.31012
99. Purlyte E, Dhekne HS, Sarhan AR, Gomez R, Lis P, Wightman M, et al. Rab29 activation of the Parkinson's disease-associated LRRK2 kinase. EMBO J [Internet]. 2018 Jan 4;37(1):1–18. Available from: 10.15252/embj.201798099 [PubMed: 29212815]

Perspectives

- PD is the second most common neurodegenerative disease. Monocytes are dysregulated early in disease, remain altered throughout disease progression, and harbor known genetic risks for PD.
- Model systems in PD suggest that monocytes that are recruited to the brain parenchyma in response to PD-associated stimuli, especially abnormal α-synuclein, may be deleterious and pro-inflammatory in nature, through the possible release of damaging cytokines and other oxidative responses.
- Future efforts might focus on understanding how genetic variants contribute to monocyte dysregulation, how changes correlate with disease progression, and the relative contribution of peripheral and infiltrating cells throughout the disease process

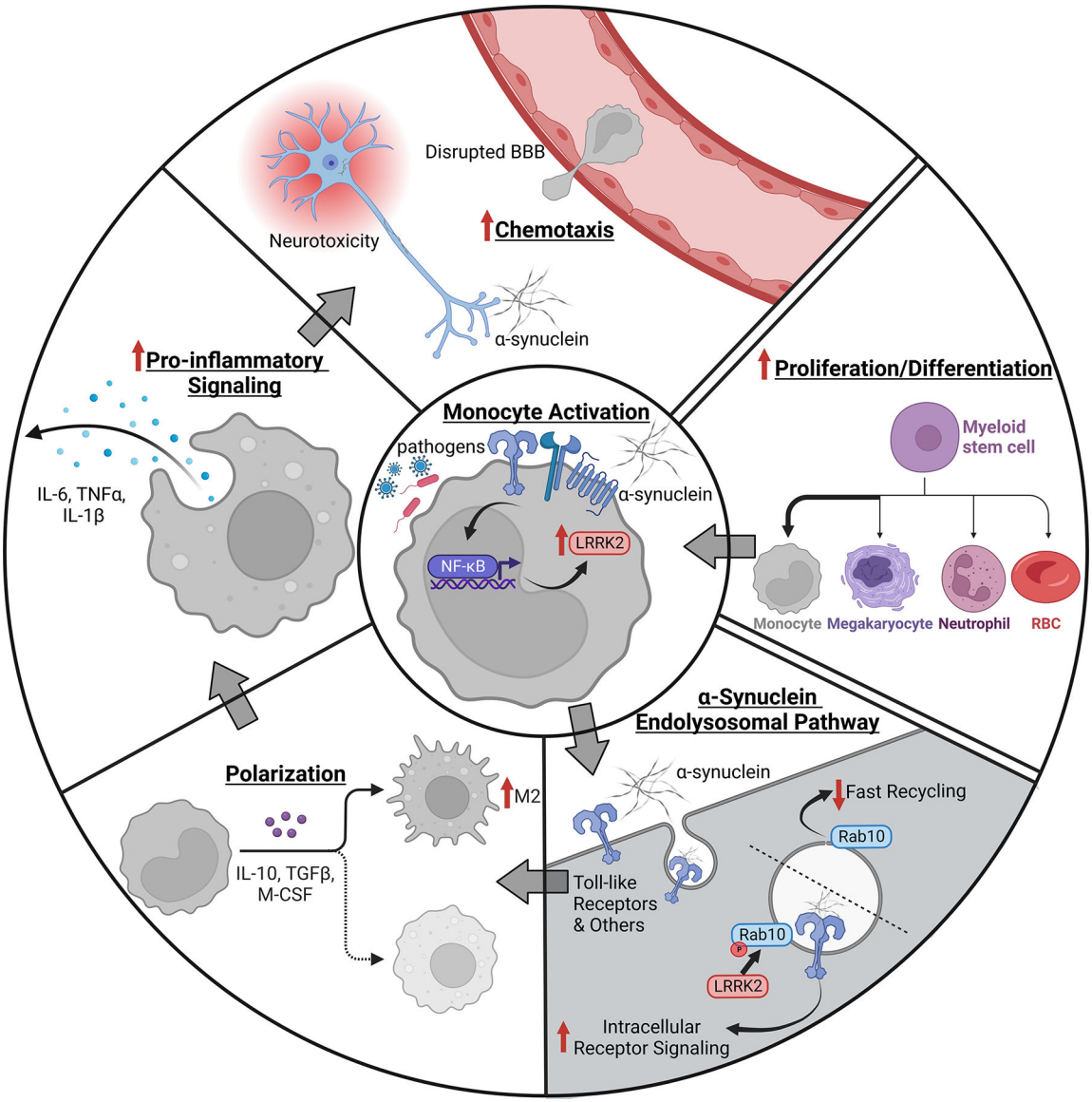

Figure 1.

An overview of the cellular processes intrinsic to monocytes associated with PD. Intra- and extracellular α-synuclein aggregates serve principally as a stimulus of monocyte activation, whereas LRRK2 expression and Rab phosphorylation may modify signaling pathways and other monocyte responses.

Table 1.

Characteristics of selected monocyte-focused studies in PD patients and controls.

PD Cases	Controls	Conclusion	Reference
Early PD (n=8) Intermediate PD (n=2)	HC (n=10)	Monocyte activation genes correlate with disease severity and early PD	Schlachetzki 2018 [17]
PD (n=72)	HC (n=22)	Distinct mRNA and lncRNAs in circulating leukocytes in PD vs. controls.	Fan 2019 [18]
iPD (n=135)	HC (n=95)	Transcriptomes of monocytes are distinct from microglia in PD: Mitochondria and proteasome	Navarro 2021 [19]
PD (n=56) PD/GBA (n=23)	HC (n=23) CTRL/GBA (n=13)	Genes in □-synuclein degradation, aging, and amyloid processing were dysregulated in PD/GBA patients compared to PD patients.	Riboldi 2022 [20]
PD (n=5)	N/A	Monocytes in PD patients are enriched in antioxidant, inflammatory, and autophagy responses.	Abdelmoaty 2022 [21]
iPD (n=25) LRRK2 PD (n=10)	HC (n=54)	LRRK2+ and - PD have higher production of monocyte and early granulocyte precursors.	Funk 2013 [22]
PD (n=453)	HC (n=436)	Decreased lymphocyte ratio, lymphocyte count, mean platelet volume, and plateletcrit values. Increased neutrophil-lymphocyte ratio values which correlated with PD severity.	*Wang 2021 [23]
“mild” PD (n=123)	N/A	Differential leukocyte count associated with clinical PD phenotypes.	Umehara 2020 [24]
Early-onset PD (n=10) Late-onset PD (n=12)	Young HC (n=10) Elder HC (n=8)	Low effector CD8+ T-cells, cytotoxic natural killer cells, and high activated monocytes in PD. Ratio of inactivated monocytes is lower in early PD.	Tian 2022 [25]
Early-stage PD (n=44) Advanced PD (n=54)	HC (n=98)	Neutrophil and monocyte high-density lipoprotein ratio correlates with PD duration and severity, respectively.	Liu 2021 [26]
PD (n=465)	HC (n=312125)	Lower lymphocyte and monocyte counts prior to diagnosis associated with PD risk.	*Jensen 2021 [28]
Serum: Early iPD (n=63) Late iPD (n=46) CSF: Early iPD (n=57) Late iPD (n=49)	Serum: HC (n=44) CSF: HC (n=16)	Soluble CD163 is elevated in blood serum of female patients. Soluble CD163 is increased in the CSF of late-stage iPD patients and is inversely correlated with cognitive scores.	Nissen 2021 [29]
Early iPD (n=39) Late iPD (n=39)	HC (n=28)	Migratory and phagocytic monocyte markers were elevated in early iPD and associated with cognitive deficits. TLR2 expression was correlated with motor severity.	Konstantin 2022 [30]

* indicates a meta-analysis of patient records.