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Reviews and Theoretical Articles

Neuroinflammation and Immune Dysfunction in the Mechanisms of Development of Parkinson's Disease

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Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by the death of dopamine neurons, aggregation of α-synuclein, and severe motor impairment. This review examines current evidence on the key roles of neuroinflammation and immune dysfunction in neurodegeneration and development of the disease. Clinical and experimental evidence of microglial activation and the participation of Toll-like receptors, a wide range of chemokines, and pro- and anti-inflammatory cytokines in the dynamics of this disease is presented. Particular attention is paid to the roles of the innate and adaptive immune responses in the mechanisms of systemic inflammation in the brain and periphery. Brain-infiltrating immune cells and their subpopulations have been shown to be involved in neuroinflammation and neurodegeneration; changes in the composition and phenotype of peripheral immune cells and their functional characteristics have been demonstrated. Analysis of immune cell subsets and their ratios identifies fine PD-specific changes in cell populations which provide reliable biomarkers for diagnosis and prognosis of the course of the disease and for development of new approaches to anti-inflammatory and targeted therapy for PD.

Keywords: Parkinson's disease, dopamine, α-synuclein, neuroinflammation, microglia, Toll-like receptors, chemokines, pro- and anti-inflammatory cytokines, monocytes, T- and B-cell subpopulations.

Introduction. Parkinson's disease (PD) ranks second among the most common neurodegenerative diseases, affecting millions of patients [Dauer and Przedborski, 2003; Kalia and Lang, 2015; Balestrino and Schapira, 2020]. PD most often occurs in older people and is generally sporadic (70–90% of the total number of cases). The incidence of the rarer, familial form of PD, caused by mutations in genes encoding proteins such as α-synuclein (α-syn), PARK2, DJ1, LRKK2, PINK1, and ND5, is approximately 10–15% of PD patients [Blauwendraat et al., 2020; Tansey et al., 2022].

PD is characterized by progressive degeneration of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc) and resultant loss of their axon terminals in the nigrostriatal system of the brain [Kalia and Lang, 2015; Abdurasulova et al., 2019; Balestrino and Schapira, 2020]. Regardless of the form of PD, the death of DA neurons is accompanied by the formation of intraneuronal cytoplasmic inclusions of aggregated α-syn (Lewy bodies and neurites), whose presence is regarded as the main pathomorphological sign not only of PD, but also of other synucleinopathies [Sulzer and Edwards, 2019].

Dysfunction of the basal ganglia resulting from DA depletion leads to the expression of motor symptoms such as bradykinesia, rigidity, resting tremor, and postural instability. Pathological changes, particularly α-syn accumulation and aggregation, spread to other parts of the brain (the locus coeruleus, hippocampus, cortical structures) and can cause emotional and cognitive disorders which often precede the onset of the classical signs [Braak et al., 2003; Ugrumov, 2020; Harms et al., 2021; Hirsch and Standaert, 2021; Williams et al., 2021; Lai et al., 2022; Tian et al., 2022]. Although the development of PD is known to be influenced by various factors (aging, gender, genetic predisposition, environmental influences) (Fig. 1), the exact etiology of the disease remains unclear; effective treatments are lacking and are symptomatic in nature.

Evidence accumulated to date suggests that inflammation and immune system dysregulation play important roles in the pathophysiology of PD, and these have been the

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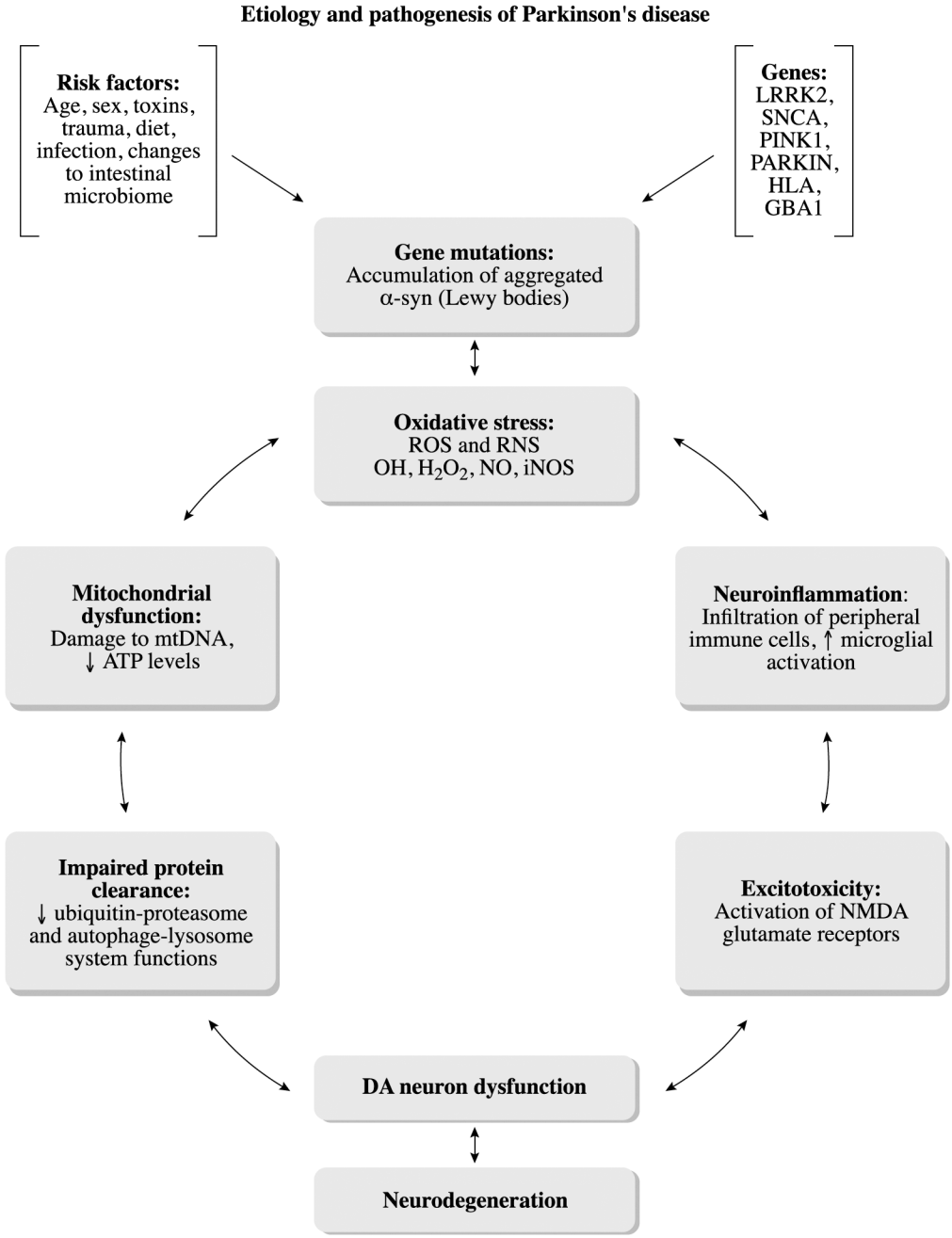

Fig. 1. Etiology of Parkinson's disease (PD) involves the complex actions of environmental and genetic factors. The pathogenetic mechanisms of PD include aggregation of α-synuclein (α-syn), mitochondrial dysfunction with DNA (mtDNA) damage and impaired adenosine triphosphate (ATP) synthesis, accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), disruption of the ubiquitin-proteasome and autophagolysosomal systems, neuroinflammation, and excitotoxicity.

subject of a significant number of reports [McGeer et al., 1988; Nagatsu et al., 2000; Gao et al., 2011; Grozdanov et al., 2014; Kustrimovic et al., 2018; Idova et al., 2021] and reviews [Ugrumov, 2020; Harms et al., 2021; Hirsch and Standaert, 2021; Williams et al., 2021; Lai et al., 2022; Tian et al., 2022].

Extensive evidence supporting the contribution of chronic inflammation to the mechanisms of PD has been obtained from studies of patients' brains, cerebrospinal fluid (CSF), serum, and plasma, as well as in a variety of experimental models [McGeer et al., 1988; Nagatsu et al., 2000; Gao et al., 2011; Gerhard, 2016; Tan et al., 2020; Harms et al., 2021; Hirsch and Standaert, 2021; Tansey et al., 2022; Tian et al., 2022].

Epidemiological studies have demonstrated the existence of common genetic variants characteristic of PD and a number of autoimmune diseases such as type 1 diabetes, rheumatism, Crohn's disease, and ulcerative colitis [Hirsch

and Standaert, 2021; Lai et al., 2022; Tansey et al., 2022]. In addition, long-term use of non-steroidal anti-inflammatory drugs or corticosteroids may delay or prevent the onset of PD [Chen et al., 2003]. Genetic analysis has identified more than 90 human leukocyte antigen (HLA) gene loci encoded by the class II major histocompatibility complex (MHC-II). These genes are involved in antigen presentation during the immune response, mainly in sporadic PD [Tan et al., 2020; Hirsch and Standaert, 2021; Lai et al., 2022].

Concepts which have emerged in recent years indicate that immune disorders in PD occur at an early stage of the disease and change dynamically as it progresses, contributing to neuronal degeneration and the manifestation of new clinical symptoms [Harms et al., 2021; Hirsch and Standaert, 2021; Idova et al., 2022; Lai et al., 2022; Tian et al., 2022]. Signs of systemic inflammation involving innate and adaptive immune factors are found both in the brain and in the peripheral immune system [McGeer et al., 1988; Nagatsu et al., 2000; Brochard et al., 2009; Gerhard, 2016; Terada et al., 2016; Boyko et al., 2017; Chen et al., 2018; Hickman et al., 2018; Harms et al., 2021; Hirsch and Standaert, 2021; Lai et al., 2022; Tian et al., 2022].

Contribution of Neuroinflammation to the Pathogenesis of PD. Neuroinflammation is seen as a key mechanism in the development of PD, though whether it triggers the pathological process or contributes to its progression remains a matter of debate [McGeer et al., 1988; Nagatsu et al., 2000; Brochard et al., 2000; Gerhard, 2016; Terada et al., 2016; Boyko et al., 2017; Hickman et al., 2018; Harms et al., 2021; Hirsch and Standaert, 2021; Tian et al., 2022].

The association between inflammation and neurodegeneration in PD was demonstrated in early studies of post-mortem brain specimens, which revealed the presence of reactive microgliosis and free neuromelanin in areas of accumulation of damaged neurons containing Lewy bodies, along with infiltration of CD4+ and CD8+ T lymphocytes into the basal ganglia and deposits of immunoglobulin G (IgG) on neuromelanin-positive neurons and increases in proinflammatory cytokine/chemokine contents in the cerebral parenchyma [McGeer et al., 1988; Nagatsu et al., 2000; Orr et al., 2005; Brochard et al., 2009; Reale et al., 2009; Dzamko et al., 2017; Bhatia et al., 2021; Harms et al., 2021; Hirsch and Standaert, 2021; Williams et al., 2021].

Microglia make up approximately 5–12% of central nervous system (CNS) cells, forming the brain's own immune system and providing immune defense for structures of the brain [Hickman et al., 2018; Kam et al., 2020; Harms et al., 2021]. In physiological conditions, microglial cells, together with perivascular macrophages, control inflammation in brain tissue, though excessive activation of microglia in the setting of primary neurodegeneration, axonal degeneration, and/or peripheral inflammatory processes can provoke chronic inflammation, leading to accelerated neuronal damage [Hickman et al., 2018; Harms et al., 2021]. Initially neuroprotective microglia become toxic to DA neurons as a result of the accumulation of reactive oxygen species (ROS) associated with neuroinflammatory enzymes such as cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS), as well as the cytokines widely used as markers of inflammation [Nagatsu et al. al., 2000; Fellner et al., 2013; Hirsch and Standaert, 2021].

Activated microglia exist primarily in two polarized states known as the M1 and M2 phenotypes. The M1 phenotype is characterized by increased quantities of MHC-I and MHC-II molecules and is associated with the release of proinflammatory chemokines and cytokines with toxic effects on neurons [Theodore et al., 2008; Chen et al., 2018; Kam et al., 2020; Tan et al., 2020; Harms et al., 2021; Lai et al., 2022]. Moreover, M1 microglial cells influence the homeostasis of the blood–brain barrier (BBB), causing infiltration of peripheral immune cells and exacerbating the pathological process [Iba et al., 2020; Cardinale et al., 2021; Lai et al., 2022].

The M2 phenotype, conversely, is accompanied by the production of anti-inflammatory cytokines and other endogenous mediators (resolvins, protectins, maresins), the actions of which are aimed at suppressing the inflammatory response [Kam et al., 2020; Cardinale et al., 2021; Lai et al., 2022]. These changes may also occur in other neurodegenerative diseases, though microglia exhibit a mixed phenotype in most cases, with features consistent both with harmful inflammation and with its resolution [Harms et al., 2021; Tan et al., 2021] (Fig. 2).

An important role in these processes is played by endogenous α-syn, which is a pathological marker for PD and is widely expressed in the nuclei and synapses of neurons [Burré, 2015; Wang et al., 2016; Sulzer and Edwards, 2019; Cardinale et al., 2021; La Vitola et al., 2021].

The physiological function of α-syn is not yet fully understood, though it is known to be involved in processes such as the release and recycling of synaptic vesicles [Burré, 2015; Sulzer and Edwards, 2019; Harms et al., 2021], to act as a molecular chaperone for the formation of the SNARE protein complex [Burré, 2015], and have roles in the binding of DA and serotonin transporters [Burré, 2015] and the regulation of some forms of synaptic plasticity [Sulzer and Edwards, 2019].

There is evidence for the involvement of α-syn in the normal/homeostatic activation of microglia, where the rate of degradation of α-syn aggregates in the brain parenchyma is maximal [Stefanis et al., 2019; Cardinale et al., 2021]. On the other hand, microglial activation may be accompanied by the release of toxic factors, such as caspase-1 and calpains, and can lead to increased pathological aggregation of native α-syn and widening of its distribution in brain structures [Kim et al., 2013; Wang et al., 2019; Cardinale et al., 2021]. Microglia in mice with knockout of the gene encoding α-syn (*SNCA*) have been shown to have a proinflammatory profile and reduced phagocytic activity, while administration of synthetic α-syn preformed fibrils (PFF)

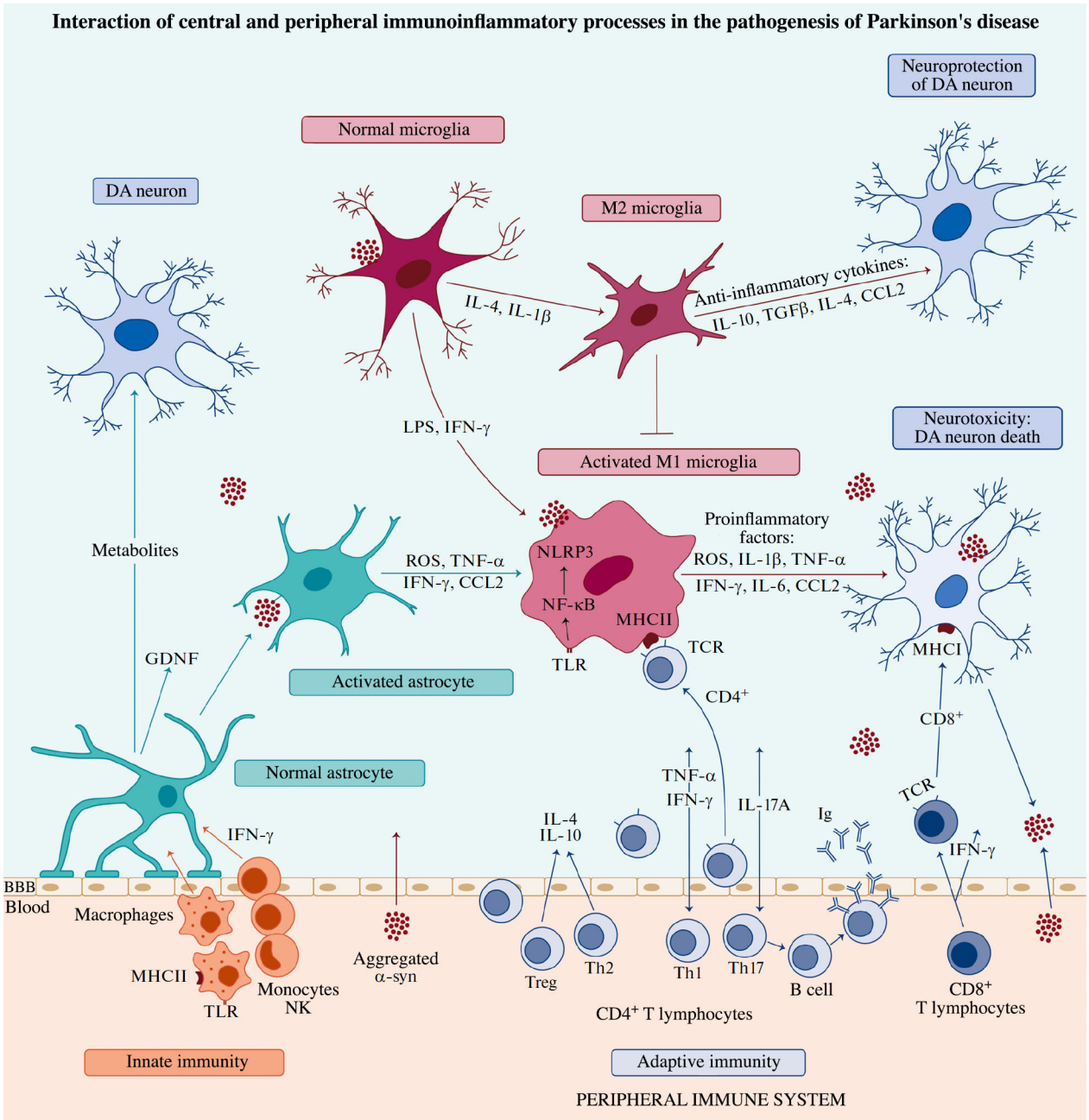

Fig. 2. Damage to the blood–brain barrier (BBB) in Parkinson's disease (PD) allows proinflammatory molecules from the periphery to enter the brain and cause long-term activation of glial cells (microglia, astrocytes). Depending on the effector signal (pathologically folded α-syn or bacterial infections), microglia polarize into a proinflammatory (M1) or an anti-inflammatory (M2) phenotype. Activated M1 microglia release free radicals (ROS, NO) and proinflammatory cytokines – interleukin (IL-1β), interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α), which lead to neurodegeneration. Damaged neurons release α-syn, adenosine triphosphate (ATP), and other molecules which support the toxic sequence of the inflammatory response. Neuroprotective M2 microglia secrete anti-inflammatory cytokines, such as IL-10 or transforming growth factor β (TGFβ), which, in contrast, suppress the functions of M1 microglia. Infiltration of peripheral $CD4^+$ T helper (Th) cells (Th1 and Th17) into the brain, these cells producing proinflammatory cytokines, increases inflammation and promotes neuron loss, while Th2 and regulatory T cells (Treg) have anti-inflammatory actions. Th stimulate B cells to produce immunoglobulins (Ig) involved in neuroinflammation. $CD8^+$ T lymphocytes recognize major histocompatibility complex class I (MHC-I) molecules expressed on neuron surfaces and induce their death by releasing cytolytic substances or IFN-γ.

leads to increased release of proinflammatory factors from microglia and infiltration of peripheral immune cells into the CNS [Kim et al, 2013; Cardinale et al., 2021]. The accumulation of toxic α-syn affects synapses, blocking long-term expression of synaptic plasticity with a subsequent increase in glutamate receptor phosphorylation and a decrease in the GluN2A/GluN2B receptor subunit ratio, which contributes to neuron degeneration [Cardinale et al., 2021].

Particular attention is currently being paid to studies of the role of α-syn in initiating or maintaining neuroinflammatory responses through receptors on innate immune cells, i.e., Toll-like receptors (TLR), which are present on neurons, astrocytes, and microglia, as well as on peripheral immune cells [Fellner et al., 2013; Dzamko et al., 2017; Heidari et al., 2022]. PD patients show increases in the expression of TLR2 and ionized calcium-binding adapter molecule 1 (IBA1), a microglial marker ($IBA1^+$ cells) over levels in controls [Dzamko et al., 2017]. Multiprotein complexes (NLRP1, NLRP3, and NLRP4) have been shown to form inflammasomes, leading to further neurological damage [Yan et al., 2015; Pirozhkov et al., 2018; Kam et al., 2020; Tan et al., 2020 ; Cardinale et al., 2021; Harms et al., 2021; Williams et al., 2021; Lai et al., 2022] (Fig. 2).

DA negatively regulates NLRP3 activation in primary microglial astrocytes [Yan et al., 2015]. NLRP3 knockout mice do not show signs of parkinsonism when given 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is converted into the neurotoxin MTP^+, which can lead to the death of DA neurons [Yan et al., 2015]. Mice deficient in the DA D1 receptor gene have been shown to be more susceptible to MPTP-induced neuroinflammation, which is accompanied by activation of NLRP3 inflammasomes, than control animals [Yan et al., 2015; Pirozhkov et al., 2018]. Binding of α-syn to TLR on microglia induces the release of proinflammatory cytokines able to cause misfolding and aggregation of endogenous α-syn [Gruden et al., 2012; Kim et al., 2013; King and Thomas, 2017]. Aggregated α-syn, in turn, enhances the infiltration of peripheral immune cells (mononuclear phagocytes, T cells), which actively produce proinflammatory cytokines, maintaining neuroinflammation in a chronic state and leading to accelerated cell apoptosis and degeneration of DA neurons [Brochard et al., 2009; Liu et al., 2017; Sulzer and Edwards, 2017; Iba et al., 2020; Lai et al., 2022] (Fig. 2).

Morphological data have been confirmed by contemporary neuroimaging methods based on assessment of brain tissue binding of highly sensitive radiopharmaceuticals, primarily translocator protein (TSPO), which is a peripheral benzodiazepine receptor widely expressed by activated myeloid cells and astrocytes and is used for positron emission tomography (PET). The use of various ligands for PET imaging, such as ^{11}C-PK11195, ^{11}C-DPA713, ^{18}F-FEPPA, and ^{18}F-DPA714, has led to detection of signs of microglial activation not only in the SNpc, but also in other areas of the brain (the pons, basal ganglia, putamen, and the occipital, temporal, parietal, and frontal areas of the cortex) [Gerhard, 2016; Terada et al., 2016; Belova et al., 2020; Kouli et al., 2020; Harms et al., 2021; Lavisse et al., 2021; Williams et al., 2021; Lai et al., 2022; Tian et al., 2022].

Signs of neuroinflammation were found in patients with PD regardless of the timing of disease onset [Gerhard, 2016], suggesting high microglial activity at the early stages of disease, i.e., before the death of DA neurons in the SNpc, and occurring in parallel with increasing neuronal dysfunction and loss of DA terminals. This state primes microglia for a more robust response to subsequent stimuli (including neuron death), which can increase inflammation-induced oxidative stress in vulnerable areas of the brain [Gerhard, 2016].

Apart from α-syn pathology, other mechanisms may contribute to the pattern of motor and non-motor symptoms in patients with PD, as studies have shown that Lewy body accumulation does not necessarily correlate with symptom severity [Bengoa-Vergniory et al., 2017; Harms et al, 2021]. In addition, high Lewy body loads have been described in healthy people who do not exhibit symptoms typical of PD [Bengoa-Vergniory et al., 2017]. Post-mortem histological studies of the brain have shown that microglial activation in PD is accompanied by increased expression of specific proteins, such as $HLA\text{-}DR^+$ (a component of MHC-II), which is regarded as an early pathological sign of the disease [McGeer et al., 1988; Orr et al., 2005 ; Dzamko et al., 2017; Harms et al., 2021]. Another marker of the proinflammatory phenotype of microglia in PD is activation of the phagocyte receptor CD68 (also known as macrosialin, widely used in experimental models of PD). However, there is a strong possibility that some of these cells may be macrophages of peripheral origin [Orr et al., 2005; Doorn et al., 2014; Dzamko et al., 2017; Harms et al., 2021].

PET results have demonstrated that patients with early-stage PD have increased astrocyte activation in the cortex and brainstem, these cells being involved in a variety of physiological functions such as the maintenance of neurons and regulation of synapse and BBB functions [Khakh and Sofroniew, 2015; Cardinale et al., 2021].

The BBB is a highly specialized functional structure which is needed to protect the brain from toxic compounds and pathogens present in the circulating blood [Daneman and Prat, 2015; Sweeney et al., 2019; Yang et al., 2022]. The main anatomical substrate of the BBB consists of endothelial cells of capillaries, which, interacting with auxiliary cells (astrocytes, pericytes, microglia, neurons) form "neurovascular units" which play a key role in maintaining CNS homeostasis [Daneman and Prat, 2015; Sweeney et al., 2019; Yang et al., 2022]. Disruption of BBB permeability underlies the pathogenesis of many diseases associated with neuroinflammation and neurodegeneration, including PD [Cardinale et al., 2021; Yang et al., 2022]. Chronic inflammation in PD can cause weakening or destruction of tight junctions between endothelial cells, which allows inflammatory mediators such as chemokines and cytokines, as well as peripheral immune cells (monocytes, T cells) to cross the BBB and enhance neuroinflammation and neurodegeneration [Cardinale et al., 2021; Lai et al., 2022; Yang et al., 2022]. This results in a vicious circle between the innate and adaptive immune systems and chronic neuroinflammation, resulting in progression of neurodegeneration.

The Roles of Chemokines and Cytokines in Neuroinflammation and Neurodegeneration in PD. Chemokines are chemoattractant cytokines which regulate the targeted

migration of immune cells in the blood and tissues; depending on the positions of the first two cysteine residues in the molecule, they are divided into separate families – C, CC, CXC, and CXXXC. Along with other inflammatory markers such as cytokines or C-reactive protein (CRP), chemokines are regarded as important signal molecules for immune activation, exerting effects both in the CNS and in the periphery [Luo et al., 2019; Pawelec et al., 2020; Tan et al., 2020; Camacho-Hernández and Penga, 2023]. Chemokine receptors are widely expressed on neurons, astrocytes, and microglial cells, and are important regulators of intercellular interactions in health and various brain diseases [Luo et al., 2019; Pawelec et al., 2020; Tan et al., 2020; Camacho-Hernández and Penga, 2023]. Chemokines are known to modulate the production and release of proinflammatory cytokines (tumor necrosis factor α – TNF-α, IL-1β, IL-6) by microglia and can increase BBB permeability, facilitating the penetration of immune cells and proteins into the CNS, which makes an important contribution to the development of neuroinflammation in many neurological disorders, including PD [Luo et al., 2019; Pawelec et al., 2020; Tan et al., 2020; Camacho-Hernández and Penga, 2023].

CC-group chemokines – monocyte chemotactic protein 1 (MCP1) (or CCL2) and macrophage inflammatory protein 1α (MIP1α) – have been found in the striatum and midbrain of mice with parkinsonism induced by the neurotoxin MPTP [Tan et al., 2020]. Animals lacking microglial CX3CR1 receptors, which bind chemokine CX3CL1 (also known as fractalkine), the most highly expressed chemokine in the CNS, showed more marked loss of DA neurons after administration of the neurotoxins MPTP or 6-OHDA [Luo et al., 2019]. In addition, CX3CR1 activation prevented microglial neurotoxicity and neuron necrosis in the SNpc in mice both after administration of neurotoxins and during neurodegeneration due to α-syn overexpression [Nash et al., 2015; Thome et al., 2015; Camacho-Hernández and Penga, 2023].

Results from clinical studies point to the occurrence of a peripheral inflammatory response [Pawelec et al., 2020; Tan et al., 2020; Harms et al., 2021; Qu et al., 2023]. Despite frequent discrepancies in estimates of circulating chemokine contents in PD patients, data from meta-analyses in recent years have shown increases in levels of chemokines such as CCL5 (RANTES), MCP-1, MIP1α, IL-8, CXCL12 and its receptor CXCR4, CX3CL1, and soluble tumor necrosis factor receptor (CTNFR) [Qu et al., 2023]. An increase in MCP-1 had a stronger association with non-motor symptoms and was detected not only in the blood, but also in the CSF [Qu et al., 2023].

Most studies indicate that PD involves increases in proinflammatory cytokine levels in the brain [Harms et al., 2021; Hirsch and Standaert, 2021]. Fluctuations in the levels of cytokines such as TNF-α, interferon γ (IFNγ), IL-1β, IL-2, IL-4, and IL-6 [King and Thomas, 2017; Galiano-Landeira et al., 2020; Kouli et al., 2020; Voronina et al., 2021] may depend on the brain structure under investigation. Thus, as compared with heathy controls, PD patients show elevated expression of the proinflammatory cytokine IL-1β in the SNpc and frontal cortex, but not in other areas of the brain [Kouli et al., 2020].

The progression of neurodegradation in PD is associated not only with accumulation of pathological α-syn in brain structures, but also with significant increases in its serum and CSF levels, indicating the development of a systemic inflammatory response and a close relationship between regional neuroinflammation and peripheral immunological processes [Theodore et al ., 2008; Sergeyeva and Sergeyev, 2011; Gruden et al., 2012; Boyko et al., 2017; Eidson et al., 2017; King and Thomas, 2017]. There is evidence that increased titers of circulating anti-α-syn antibodies are accompanied by the accumulation of endogenous α-syn in DA neurons [Sergeyeva and Sergeyev, 2011], as well as increases in the serum levels of proinflammatory cytokines enhancing the aggregation of endogenous α-syn [Gruden et al., 2012; Kim et al., 2013; King and Thomas, 2017]. Other authors have established a direct relationship between CSF and serum IFNγ and C-reactive protein levels on the one hand and fluctuations in the CSF α-syn content on the other [Eidson et al., 2017].

Changes in the contents of pro- and anti-inflammatory cytokines and other immune-associated molecules in the CSF, serum, or plasma in patients with PD have been confirmed by a significant number of studies [Brodacki et al., 2008; Reale et al., 2009; Milyukhina et al., 2015; Boyko et al., 2017; King and Thomas, 2017; Karpenko et al., 2018; Lai et al., 2022; Tian et al., 2022; Qu et al., 2023].

Increased levels of TNF-α, IL-1β, IL-2, IL-6, and IL-4 have been demonstrated in the CSF of PD patients [Reale et al., 2009; Milyukhina et al., 2015; King and Thomas, 2017; Karpenko et al., 2018; Lai et al., 2022; Qu et al., 2023], while fluctuations in the levels of some cytokines depended on the nature of the course of the disease, the severity of some symptoms, and, in some cases, complications associated with the treatments provided [Yu et al., 2014; Milyukhina et al., 2015; Eidson et al., 2017; King and Thomas, 2017; Karpenko et al., 2018; Qu et al., 2023]. In particular, CSF IL-6 levels in PD patients correlated with the severity of cognitive impairment [Yu et al., 2014], while the CSF TNF-α level was significantly higher in moderate and slow progression of PD than in rapid progression [Milyukhina et al., 2015].

The combination of IL-1β, IL-2, and IL-6 suggests a proinflammatory response, as all three cytokines have deleterious effects on neurons and other cell types involved in the pathogenesis of inflammatory diseases [Filiano et al., 2017]. However, IL-4 is involved in neuroprotective and neuroregenerative processes in the central nervous system [Filiano et al., 2017] and the development of allergic and autoimmune diseases [Gadani et al., 2012]. More recent studies have found increased TNF-α and IFN-γ production

in the CSF of PD patients, these substances having marked immunoactivatory and neurotoxic effects; there were also increases in the anti-inflammatory cytokine IL-10, which is primarily involved in modulating innate immunity with the participation of T-regulatory cells (Treg) [Brodacki et al., 2008; Filiano et al., 2017].

Most studies point to increases in key inflammatory factors (TNF-α, IFNγ, IL-1β, IL-2, IL-6, RANTES, C-reactive protein) and anti-inflammatory factors (IL-10, IL-4) in the serum or plasma of PD patients [Brodacki et al., 2008; Reale et al., 2009; Gruden et al., 2012; Williams-Gray et al., 2016; Eidson et al., 2017; King and Thomas, 2017; Karpenko et al., 2018; Usenko et al., 2020; Lai et al., 2022; Qu et al., 2023]. However, results showing the direction of changes in some peripheral markers of inflammation in PD do not always coincide. Serum IFNγ may be increased [Brodacki et al., 2008], decreased, or remain unaltered [Gruden et al., 2012; Eidson et al., 2017] in patients at different stages of PD as compared with healthy individuals of the same age. Similarly, there is evidence of both increases [Brodacki et al., 2008; Gruden et al., 2012; Williams-Gray et al., 2016] and decreases [Gupta et al, 2016; Eidson et al., 2017] in serum TNF-α levels in PD patients. Evidence supporting an association between serum IL-6 and IL-1β levels with the duration of PD and the rate of its progression has been reported from studies in patients [Milyukhina et al., 2015; Karpenko et al., 2018] and in models of parkinsonism in experimental animals [Harms et al., 2021]. Serum TNFα and IL-10 levels in PD patients have been shown to correlate with disturbances in motor functions, sleep, and the severity of cognitive deficits [Milyukhina et al., 2015; Williams-Gray et al., 2016; Karpenko et al., 2018; Qu et al., 2023]. High IL-10 levels also correlated with feelings of fatigue and elevated anxiety and depression [Milyukhina et al., 2015; Karpenko et al., 2018]. Relationships have been demonstrated between serum and CSF levels of cytokines IL-1β, IL-6, IL-10, and C-reactive protein [Eidson et al., 2017; Karpenko et al., 2018].

Interestingly, chronic overexpression of a single proinflammatory cytokine in the SNpc, such as IL-1β, can cause most of the features of PD, including progressive DA cell death, akinesia, and glial activation [Ferrari et al., 2011].

The presence of high CSF and peripheral blood concentrations of certain cytokines, indicating the presence of systemic inflammation, does not appear to be specific to PD [Grigoryan et al., 2000; Boyko et al., 2017]. For example, increased CSF IL-1β levels are seen not only in patients with PD, but also in those with Alzheimer's disease and Lewy body dementia, in combination with increased IL-1β expression by microglia close to neurons with high immunoreactivity for β-amyloid precursor protein [Grigoryan et al., 2000]. Elevated peripheral blood IL-6, IL-1β, and TNF-α levels are often found in both PD and many other neurodegenerative diseases [Boyko et al., 2017].

It can be suggested that soluble circulating cytokine molecules support a close interaction between processes occurring in the central nervous system and the peripheral immune system in neurodegenerative diseases, including PD [Kortekaas et al., 2005; Reale et al., 2009; Dzamko et al., 2017; Sweeney et al., 2019; Bhatia et al., 2021; Hirsch and Standaert, 2021; Williams et al., 2021].

Fluctuations in the production of chemokines and cytokines in the brain and periphery are accompanied by changes in the content and activity of various cell populations (monocytes, natural killer cells, T and B cells) and their subpopulations.

Involvement of Different Subpopulations of Immune Cells in the Pathogenesis of PD. Changes in the composition and migratory properties of peripheral immune cells in PD include dysregulation of innate immune cells such as monocytes/macrophages and neutrophils, which, like microglia, are cells of myeloid origin and can infiltrate the CNS in the pathological conditions associated with neuroinflammation and neurodegeneration [Harms et al., 2021; Nissen et al., 2021; Su et al., 2022; Tian et al., 2022; Williams et al., 2022].

Monocytes are generally divided into three functionally distinct subclasses: classical, i.e., with the $CD14^{++}CD16^{-}$ marker phenotype, intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$) monocytes [Harms et al., 2021]. Classical monocytes make up 90% of the overall population and are the precursors of tissue macrophages and dendritic cells, which have high levels of phagocytic and antigen-presenting activities and participate in the innate immune response. These cells are characterized by increased expression of chemokine receptors and, when activated, release IL-10, CCL2, IL-6, and RANTES [Harms et al., 2021; Tian et al., 2022; Williams et al., 2022]. Intermediate monocytes express the highest levels of antigen presentation-related molecules (MHCII) and, like non-classical monocytes, secrete TNF, IL-1β, IL-6, and IL-8 [Harms et al., 2021; Tian et al., 2022; Williams et al., 2022].

Elevated contents of CCL2-expressing classical monocytes were found in the peripheral blood and CSF of patients with PD [Grozdanov et al., 2014]. $CD14^{+}$ monocytes isolated from PD patients displayed hypersensitivity to LPS stimulation and an altered response to pathological α-syn [Grozdanov et al., 2014; Harms et al., 2018, 2021]. Other data indicate that peripheral blood monocytes from PD patients have reduced sensitivity to LPS and fibrillar α-syn, cannot modulate the expression of proteins such as CD163, and produce cytokines efficiently [Harms et al., 2021; Nissen et al., 2021]. Moreover, the number of monocytes with the CD163 phenotype correlated positively with neurodegenerative and neuronal markers, such as α-syn and total and phosphorylated h-TAU protein, but not with cognitive indicators [Nissen et al., 2021].

The directions of changes in the proliferative and phagocytic activities of peripheral blood mononuclear cells in PD can be different and depend on many factors, such as disease severity and duration, the immune stimuli used,

and markers of innate immunity [Wijeyekoon et al., 2018; Harms et al., 2021; Nissen et al., 2021; Su et al., 2022]. Thus, monocyte phagocytic capacity was greater in PD patients only in the early stages after diagnosis. However, despite the increased expression of TLR4 on these cells, serum α-syn clearance did not change, indicating a selective deficiency or suppression of α-syn uptake [Wijeyekoon et al., 2018; Harms et al., 2021].

Even at the initial stages of disease, circulating monocytes show changes in the expression of genes involved in immune activation, such as HLADQB1 (the MHCII system), MYD88, which is associated with TLR2 and TLR4 receptors, transcription factors of the NFκB/Rel family, and neurotrophic factor-α (NFα) [Harms et al., 2021; Nissen et al., 2021; Tian et al., 2022], indicating early immune dysfunction in PD.

Monocytes constitute a highly dynamic population and participate in the integrated immune response in PD [Pey et al., 2014; Harms et al., 2018, 2021]. Infiltration of peripheral monocytes/macrophages in PD is supported by data showing increased expression in the brain of proteins such as CD163 and CCR2, which are associated with non-microglial myeloid cells [Pey et al., 2014; Harms et al., 2018, 2021]. Increases in the number of CD163-expressing cells are also seen in experimental rodent models of PD [Tentillier et al, 2016; Harms et al., 2021]. Overexpression of human α-syn in mice causes significant infiltration of proinflammatory peripheral $CCR2^+$ receptor-bearing monocytes into the substantia nigra (SN); genetic deletion of these receptors prevents monocyte infiltration into the brain, attenuates MHCII expression, and blocks subsequent degeneration of DA neurons [Harms et al., 2018, 2021]. $CCR2^+$ is activated in classical monocytes from PD patients, even despite a decrease in the total number of $CCR2^+$ monocytes [Funk et al., 2013], though other authors have demonstrated activation of the CCR2-CCL2 axis and enrichment of CCL2 in patients' blood [Reale et al., 2009; Grozdanov et al., 2014].

Despite some discrepancies in the results obtained, there is convincing evidence that the innate immune response plays an important role in the immune mechanisms of the development of PD and its manifestations, both in the periphery and in brain structures.

T cells, which are a major component of the adaptive immune system, are among the first candidates for potential involvement in the pathogenesis of PD [González et al., 2013, 2015; Jiang et al., 2017; Kustrimovic et al., 2018; Sun et al., 2019; MacMahon Copas et al., 2021; Contaldi et al., 2022; Garetti et al., 2022; Weiss et al., 2022]. These cells have a heterogeneous composition, which includes $CD4^+$Th types 1 and 2, $CD4^+$Th17, cytotoxic $CD4^+$ and $CD8^+$ cells, and $CD4^+CD25^+$ and $CD8^+CD25^+$ Treg cells; each of these subpopulations plays its own specific role in the mechanisms of neuroinflammation and neurodegeneration in PD, which will be discussed below.

$CD4^+$ T lymphocytes ($CD4^+$Th) make up the largest subpopulation of T cells, and, providing an effective immune response, play a decisive role in the pathogenesis of immune and inflammatory diseases. Naïve $CD4^+$Th, when stimulated, can display pro- (Th1 and Th17) or anti-inflammatory (Th2 and Treg) phenotypes both in the periphery and in brain structures [O'Shea and Paul, 2010; Zhu et al., 2010; González et al., 2015; Kustrimovic et al., 2018; Filliano et al., 2017; Baird et al., 2019]. $CD4^+$ T cells are currently divided into eight subtypes: naïve $CD4^+$ T cells, central memory $CD4^+$ T cells, cytotoxic $CD4^+$ T cells, Th1, Th2, Th17, and follicular Th – Tfh – cells, and Treg cells [Wang et al., 2021]; each subtype produces its own set of cytokines, expresses different transcription factors [DuPage and Bluestone, 2016], and has different roles in the pathogenesis of PD [Chen et al., 2015; Kustrimovich et al., 2018; Wang et al., 2021; Liu et al., 2021; Yan et al., 2021]. Significant increases were found in PD in the number of Th1 cells with high levels of expression of the CD4 marker and the genes for granzymes A and B and perforin, which perform a cytotoxic function [Wang et al., 2021]. Notably, the of cytotoxic $CD4^+$ T cell (CD4 CTL) population in PD patients is clonally expanded and may be the source of centrally infiltrating cytotoxic $CD4^+$ T cells [Wang et al., 2021], which penetrate into the SN from the periphery and promote microglial activation and DA neuron death [Brochard et al., 2009; González et al., 2015; Iba et al., 2020; Rostami et al., 2020; Wang et al., 2021; Li et al., 2021b; MacMahon Copas et al., 2021; Yan et al., 2021]. This was detected in post mortem brain sections, mainly in the perivascular space and the walls of vessels in direct contact with astrocytes expressing MHC-II and, probably, factors required for T cell activation during the progression of PD [Rostami et al., 2020]. In addition, $CD4^+$ T cell deficiency has been shown to result in significant attenuation of neurodegeneration in an MPTP-induced mouse model of PD, suggesting a fundamental role for inflammatory $CD4^+$ T cells in neuron death [Benner et al., 2008; Brochard et al., 2009; Sommer et al., 2016; MacMahon Copas et al., 2021].

Studies, especially in recent years, have reported changes in $CD4^+$ T cells and their subpopulations in PD in the periphery. Some authors have shown decreases in $CD4^+$ cells and their subsets [Baba et al., 2005; Niwa et al., 2012; Saunders et al., 2012; Stevens et al., 2012; Chen et al., 2015; Hu et al., 2018]. Others have found increases in the numbers of $CD4^+$ cells, as well as their Th1 and Th17 subpopulations [Grozdanov et al., 2014; Yan et al., 2021; Idova et al., 2021], but decreases in Th2 and Treg in the peripheral blood of PD patients [Sommer et al., 2016; Chen et al., 2017; Kustrimovic et al., 2018]. An important item in PD is a change in the ratio of pro- and anti-inflammatory $CD4^+$ T cell subpopulations, whereby decreases in circulating Th2, Th17, Th1/Th17, and Treg lead to increases in the Th1/Th2 and Th17/Treg ratios [Chen et al., 2015; Kustrimovic et al. al., 2018; Li et al., 2021b]. In all cases, imbalance of $CD4^+$ T cell subsets and dysregulation of Treg were associated with the severity of the clinical manifestations of the disease

[Kustrimovic et al., 2018; Magistrelli et al., 2020; Chen et al., 2021; Yan et al., 2021].

Neurotransmitters are known to influence the function of neurons, microglia [González et al., 2015], and immune cells [Idova et al., 2012; Alperina, 2014; Kawano et al., 2018]. Neurotransmitter dysregulation in PD, which is associated with insufficiency of the DA system and disruption of its interaction with other neurotransmitter systems (glutamatergic, GABAergic), can alter the function of $CD4^+$ T cells and contribute to increased neuroinflammation [González et al., 2015]. DA D2 and D3 receptors are expressed on $CD4^+$ T cells and are involved in the mechanisms of neuroinflammation and neurodegeneration [González et al., 2013; Liu et al., 2021]. DA D3 receptors promote cell activation and acquisition of the Th1 inflammatory phenotype by taking part in the production of IFN-γ by $CD4^+$ T cells in humans. D3 receptor deficiency protects against the death of DA neurons and reduces microglial activation in an MPTP-induced model of PD [González et al., 2013]. In contrast, D2 knockout mice exhibited more severe DA neurodegeneration, motor deficits, microglial activation, and a shift in $CD4^+$ T cells towards the Th1 and Th17 phenotypes in response to administration of MPTP [Liu et al., 2021]. These data provide evidence that D2 receptors expressed on $CD4^+$ T cells protect against neuroinflammation and neurodegeneration in PD and need to be considered when developing therapeutic strategies to reduce the symptoms of PD.

Activated microglia induce the expression of MHC class I molecules by human catecholaminergic neurons, increasing the susceptibility of DA neurons to death in the presence of cytotoxic T lymphocytes [Cebrián et al., 2014].

There is now evidence that the progression of PD is associated with changes in the phenotypes of peripheral blood lymphocytes, including subsets of $CD4^+$ cells, which are different in nature from those in another neurodegenerative disease, Alzheimer's disease [Garfias et al., 2022]. Progression of PD involved significant decreases in activated $CD4^+CD69^+$ and $CD8^+CD69^+$ T cells, T cells susceptible to apoptosis, and some regulatory populations – $CD19^+CD5^+IL10^+FoxP3^+$ and $CD4^+FoxP3^+CD25^+CD45RO^+$. Progression of Alzheimer's disease is associated with a lower percentage of $CD4^+CD38^+$ cells and a higher percentage of effector CD4 cells at baseline [Garfias et al., 2022]. However, it remains unclear how specific this phenomenon is for PD relative to other neurodegenerative diseases.

Cell composition can be dynamic; for example, the numbers of naïve $CD4^+$ and $CD8^+$ T cells were significantly reduced in patients at the early clinical stage of PD, with an increase in central memory $CD4^+$ T cells, while there were increases in the numbers of $CD4^+$Th17, $CD4^+$Th2, and $CD8^+$ T cells, producing IL-17, IL-4, IFN-γ respectively. However, the contents of Th1 and Treg cells did not undergo any significant changes [Yan et al., 2021].

The $CD4^+$Th17 effector cell population producing IL-17, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor is involved in autoimmune and neurological diseases. A key function of IL-17, a major Th17 cytokine, is that of mobilizing myeloid cells in peripheral immune organs to enter the CNS, where they produce autoimmune diseases [McGinley et al., 2020]. Recent evidence implicates Th17 and the cytokine IL-17A in the death of DA neurons and, thus, in the pathogenesis of PD [Sommer et al., 2018; Chen et al., 2020; Shi et al., 2022]. And although the mechanisms of the influence of Th17 cells on neurodegenerative processes remain to be fully established, they appear to be due to influences on cells resident in the brain, with increased activation of microglia, recruitment of other types of immune cells to the CNS, and activation of the NF-kB cascade through the IL-17 signal pathway [Chen et al., 2020; Shi et al., 2022]. It is possible that this process occurs by means of a direct interaction between lymphocyte functional antigen (LFA-1) on Th17 and intercellular adhesion molecule (ICAM-1) on neurons or via IL-17 produced by the cells [Sommer et al., 2018].

Data on the content of Th17 cells in patients with PD are quite contradictory, showing both an increase in their number in peripheral blood [Chen et al., 2017; Sommer et al., 2018] and a decrease compared to healthy individuals; this may be associated with the dynamic nature of changes in the levels of these cells [Kustrimovic et al., 2018]. Thus, the greatest increase in the Th17 content in the circulation is mainly observed in the early clinical stages of the disease [Chen et al., 2017; Sommer et al., 2018].

Studies of interactions between the level of Th17 cells and indicators of the clinical signs of PD have identified relationships with the non-motor manifestations of PD, particularly the severity of cognitive impairment and dementia [Kalia and Lang, 2015].

Regulatory $CD4^+CD25^+FoxP3^+$ T cells, previously known as T suppressor cells, are involved in regulating immune and inflammatory processes and play important roles in a number of neuropathologies, including PD [Reynolds et al., 2007, 2010; Fuzzati-Armentero et al., 2019; Álvarez-Luquín et al., 2019; Li et al., 2021b]. However, the question of their contribution to the pathogenesis of PD still remains controversial.

In vitro studies have shown that $CD4^+CD25^+$Treg cells can suppress microgliolysis [Kannarkat et al., 2013] and experimental models have demonstrated their ability to limit the neurodegeneration of DA neurons [Reynolds et al., 2007; Huang et al., 2014].

Decreases in the peripheral levels of these cells are associated with a phenotypic shift of microglia from an anti-inflammatory ($CD206^+$) to a proinflammatory ($CD32^+$) phenotype, increased neuron death in the SN, and induction of a chronic neuroinflammatory state, suggesting that Treg have an important modulatory role in neurodegenerative processes [Kannarkat et al., 2013]. Particular importance attaches not so much to the level of Treg cells itself, but to their ratio with other T cells. Thus, decreases in periph-

eral blood Treg levels in patients and experimental mouse models of PD from control levels were demonstrated on the background of increases in the contents of proinflammatory Th1 and Th17 cells [Reynolds et al., 2007; Álvarez-Luquín et al., 2019; Li et al., 2021b]. Depletion of Treg cells aggravated experimentally induced PD, whereas neutralization of Th1-produced TNFα ameliorated disease. Transfer of Treg into experimental animals with PD reduced disease severity, providing more than 90% protection of the nigrostriatal system [Reynolds et al., 2007; Li et al., 2021b], while transfer of Th1 or Th17 increased neurodegeneration [Reynolds et al., 2007, 2010; Li et al., 2021b].

$CD4^+CD25^+$ Treg, like other populations of regulatory cells, express genes encoding DA receptors, and this is particularly important given that L-DOPA and DA receptor agonists are used in the treatment of PD [Arce-Sillas et al., 2019].

T cells with the CD8 phenotype play an important role in the pathogenesis of numerous CNS disorders [Sulzer et al., 2017; Lindestam Arlehamn et al., 2020; Galiano-Landeira et al., 2020; Yan et al., 2021]. Thus, analysis of T cells showed a significant increase in the number of $CD8^+$ T lymphocytes in the SN of patients with PD as compared with a control group, while the density of these cells correlated with neuron death and depended on the stage of disease. The entry of cytotoxic $CD8^+$ T cells able to contact DA neurons into the SN is believed to be an earlier pathogenic event than α-syn aggregation and neuron degeneration [Galiano-Landeira et al., 2020].

It should be noted that the presence of $CD8^+$ T cells containing different sets of cytolytic enzymes (granzymes A, B, and K) and/or proinflammatory cytokines is typical of the early and late clinical stages of the disease [Galiano-Landeira et al., 2020]. When stimulated, $CD8^+$ T cells can expand the molecular repertoire of glutamate release from vesicles to include glutaminase, which is required for generating glutamate and its transporters [Melzer et al., 2013], and may thus play a key role in immune-mediated neurodegeneration [Galiano-Landeira et al., 2020].

Significant increases in $CD8^+$ T cells recognizing α-syn proteins and producing IFNγ, which is known to enhance the cytotoxic properties of cells, have been found in PD, and this potentially contributes to immune disorders in the disease [Sulzer et al., 2017; Lindestam Arlehamn et al., 2020 ; Yan et al., 2021]. At the same time, increased IFNγ expression is known to be associated with microglial activation, death of DA neurons in the SN, and motor disorders [Barcia et al., 2011; Chakrabarty et al., 2011]. DA neurons can express MHC class I genes in response to IFNγ, making them susceptible to the effects of cytotoxic $CD8^+$ T cells [Cebrián et al., 2014]. Thus, increases in IFNγ-producing cytotoxic $CD8^+$ T cells may contribute to both neuroinflammation and neuron damage in PD.

Studies in recent years have shown that not only $CD4^+$ T cells, but also $CD8^+$ T cells producing IL-10, have a regulatory function. The functional activity of the $CD4^+CD25^+$ and $CD8^+CD25^+$ Treg populations in PD patients not taking DA medications is reduced as compared with that in healthy individuals [Álvarez-Luquín et al., 2019]. As PD is associated with chronic inflammation linked with an inadequate anti-inflammatory response, it has been hypothesized that an imbalance between these processes may, at least in part, underlie the pathogenesis of PD.

Studies using single-cell RNA sequencing (scRNA-Seq) showed that, as compared with controls, the proportion of $CD8^+$ T cells is increased and the number of $CD4^+$ T cells and the CD4/CD8 ratio are decreased in the peripheral blood and CSF of patients with BP; this may indicate the presence of immunodeficiency or autoimmune processes [Wang et al., 2021]. Other studies have shown increases in the levels of $CD3^+$ T cells and $CD4^+$ T cells, with a constant number of $CD8^+$ T cells, leading to a significant increase in the $CD4^+/CD8^+$ T cell ratio, while a negative correlation was noted between the content of $CD4^+$ T cells and the stage of disease [Chen et al., 2021].

Thus, both populations of T cells ($CD4^+$ and $CD8^+$), their individual subpopulations, and the ratio between them make important contributions to the mechanisms of neuroinflammation and neurodegeneration in PD.

B cells are an integral part of the adaptive immune system and the only cell type capable of secreting antibodies; they also produce pro- and anti-inflammatory cytokines involved in the regulation of immune and inflammatory responses [Cyster et al., 2019; Ahn et al., 2021].

Studies in recent years have elucidated the role of B cells in the mechanisms of development of a number of neurological disorders – by promoting glial activation, they can contribute to the pathogenesis of neurodegenerative diseases, including PD [Sabatino et al., 2019]. $\alpha\text{-syn}^{-/-}$ mice exhibited defects in B cell-mediated immune responses [Xiao et al., 2014], while the absence of both T and B cells in RAG2 knockout mice resulted in decreases in DA neuron death and behavioral disorders on induction of PD with MPTP [Benner et al., 2008; Brochardet et al., 2009; Lira et al., 2011].

B cells, unlike T cells, have not been detected in the human brain [Brochard et al., 2009; Yan et al., 2021], though they have been found in the brain in animal models of PD [Theodore et al., 2008]. It has been suggested that B cells may be involved in neuroinflammation via peripheral immune mechanisms, including cytokine and antibody production.

PD patients are known to have elevated levels of anti-α-syn antibodies in the blood and CSF [Horvath et al., 2017; Akhtar et al., 2018]. Studies in an MPTP mouse model of PD demonstrated production of natural antibodies to nitrated α-syn [Benner et al., 2008]. IgG deposits are detected on Lewy bodies and DA neurons in the brains of PD patients and can cause selective death of DA neurons [Chen et al., 1998; Orr et al., 2005]. Although these data indicate that humoral immunity potentially plays a role in the development of PD, the relative contribution of peripheral B cell subtypes to the etiology of PD remains unclear.

Clinical and experimental data on B cells in the periphery in PD are quite contradictory – from the absence of any change in their content [Zhang et al., 2014; Jiang et al., 2017; Cen et al., 2017; Zhanaeva et al., 2020] to reductions from the healthy control level [Bas et al., 2001; Gruden et al., 2011; Stevens et al., 2012; Niwa et al., 2012].

Studies using transgenic A53T mice expressing a mutant α-syn gene showed that the percentage of $CD19^+$ B cells decreased in young (two months old) mice on the background of increases in $CD3^+$ T cells and $CD4^+$ Th cells, while the $CD19^+$ B cell content in ~~in~~ old mice was equal to that in controls [Idova et al., 2021].

The peripheral blood $CD19^+$ B lymphocyte level in patients with idiopathic PD was no different from that in healthy individuals in a general group consisting of individuals of both sexes, though significant differences were found in women, these differences depending on the stage of disease [Zhanaeva et al., 2020]. In addition, the content of B cells in women with PD was significantly higher than that in men, while healthy men and women showed no difference in the number of B cells. Other data indicate that sex-related differences in B cell levels were seen not only in patients with PD, but also in healthy individuals [Cen et al., 2017]. The incidence of PD in men is about twice that in women, and there are sex-related differences in the development of PD (involvement of D1 and D2 receptors, expression of cytokines in the brain, sensitivity to neurodegenerative stimuli, response to therapy, etc.) [Cerri et al., 2019]. A relationship between the percentage of B cells and the UPDRS indicators was established, pointing to a negative correlation between disease severity and B cell content as a predictor of PD progression [Cen et al., 2017].

Even with unaltered B cell levels, the structure of B cell subpopulations has been shown to undergo significant changes in PD, with increases in some B cell subtypes while others are decreased or unchanged [Zhanaeva et al., 2020; Yan et al., 2021; Wang et al., 2022].

Comprehensive analysis of the characteristics of peripheral B cells has provided new insights into the humoral immune response in the pathogenesis of PD [Wang et al., 2022]. Single-cell RNA and B cell receptor sequencing has revealed significant increases in memory B cells and decreases in naïve B cells in PD patients as compared with healthy controls. Increases in IgG and IgA isotypes and more frequent cases of recombination with switching of Ig classes have also been seen in PD.

Clinical studies have demonstrated significant increases in the number of TNF-α-producing B cells, this cytokine being a biomarker of the risk of developing PD and a candidate for identifying PD at the prodromal stage [Clark and Vissel, 2018; Majbour et al., 2020, Yan et al., 2021].

Regulatory B cells (Breg), discovered relatively recently, are regarded as a new subpopulation involved in inflammatory, autoimmune, and neurodegenerative processes [Kessel et al., 2012; Rosser and Mauri, 2015; Sabatino et al., 2019; Álvarez-Luquín et al., 2021]. Data have been obtained showing that Breg have the ability to produce anti-inflammatory cytokines IL-10, IL-35, and TGFβ, which affect Treg, Th1, and Th17 at different stages of the development of the inflammatory response [Kessel et al., 2012; Rosser and Mauri, 2015].

There are also some isolated studies on changes in the content and function of $CD19^+CD25^+$ regulatory B cells (Breg) in PD patients [Álvarez-Luquín et al., 2019, Zhanaeva et al., 2020; Li et al., 2021a]. In contrast to healthy individuals, increases in the number of $CD19^+CD25^+$ Breg were detected in the peripheral blood of patients with idiopathic PD in a mixed-sex group and in a women-only group, and this was greatest at disease stage III [Zhanaeva et al., 2021]. Another study, conversely, found decreases in the content of the Breg subpopulation in patients with PD, while the proportion of proinflammatory B cells producing cytokines TNFα and GM-CSF increased, leading to a proinflammatory shift in the B cell response. At the same time, the level of follicular Th decreased, which correlated with B cell impairment and indicated an aberrant interaction of these cells in PD [Li et al., 2021a].

The data presented here on changes in the composition of peripheral B cells and their function in PD and the levels of Ig and cytokines produced by these cells in the periphery and brain indicate that B lymphocytes and their subpopulations may contribute to the pathogenesis of PD.

Immunoinflammatory Therapeutic Approaches to the Treatment of PD. Clinical treatment of PD is based mainly on use of DA drugs, which counter the deficiency of the DA system, though only ameliorating particular disease symptoms. The long process of neurodegeneration as the disease progresses leads to unresponsiveness to DA therapy. An active search is therefore under way for new strategies targeting individual components of the pathogenesis of PD. A significant number of experimental studies and initial clinical developments address mainly suppression of the neuroinflammatory process using a wide variety of drugs known in practice such as ibuprofen, which has a moderate protective effect in relation to DA neuron death and reduces the risk of developing PD [Chen et al., 2003; Gao et al., 2011; Tan et al., 2020; Wang et al., 2021; Lai et al., 2022; Xu et al., 2023].

Proinflammatory cytokines can act as a target element of neuroinflammation; in particular, inhibition of TNFα has a neuroprotective effect.

Recent work has used rhythmic transcranial magnetic stimulation (rTMS) to treat PD. This fairly new method produces positive clinical changes on the UPDRS on stimulation of two areas of the cerebral cortex (the motor and left dorsolateral prefrontal cortex), which is accompanied by decreased production of the proinflammatory cytokines IFNγ and IL-17A [Aftanas et al., 2018].

Exposure of microglia to various drugs (pexidartinib, minocycline, fingolimod, rosiglitazone, pioglitazone, etc.) leads to depletion of these cells, accompanied by decreased

accumulation of pathological α-syn aggregates, as well as a reduction in DA neuron death [Lai et al., 2022].

Actions on inflammasomes produce positive effects; the drug papaverine (PAP), a selective phosphodiesterase 10A inhibitor, inhibited α-syn aggregation and protected DA neurons from death, while IZD174, an inhibitor of NLRP3-containing inflammasomes, reduced the α-syn level.

Synuclein aggregation results from decreased clearance. In vivo and in vitro experiments have shown that anti-α-syn autoantibodies in the body facilitate its clearance, reduce protein aggregation, and reduce neuron damage. Use of monoclonal antibodies in passive and active immunization reduced blood α-syn levels in animals in preclinical studies [Wang et al., 2021]. Decreases in α-syn aggregation can also be achieved by enhancing its clearance by other means [Baird et al., 2019].

As dysfunction of the immune system involving different T-cell populations plays an important role in the onset and progression of the disease, targeted immunotherapy addressing T cells may be more promising and successful in reducing the risk of developing PD.

Using the T cell response as a target for therapy is attractive in that measures can be assessed peripherally, with the T cells subsequently migrating to the brain. This should primarily be immunosuppressive therapy, with the goal of reducing the numbers of peripheral T cells and $CD4^+$ cells to reduce the penetration of these cells into the brain, where they provoke neuroinflammation and neurodegeneration. Another approach consists of increasing the population of $CD4^+CD25^+Foxp3^+$ T-reg cells, either by transfer of the cells themselves or by giving granulocyte macrophage colony-stimulating factor (GM-CSF). This factor was shown in clinical trials to be well tolerated by patients and an to improve motor function [Baird et al., 2019; Lindestam Arlehamn et al., 2020]. Anti-CD3 monoclonal antibodies (CD3mAb) and the neuropeptide hormone vasoactive intestinal peptide (VIP) are also able to induce T-reg differentiation and reduce neuroinflammation. Both drugs have shown positive effects in animal studies, though to date there are no clinical trial protocols. In addition, the situation is not entirely straightforward, as T-reg cells may be elevated in PD [Idova et al., 2021] and may undergo transdifferentiation into Th type 17, which are involved in the autoimmune mechanisms of PD pathophysiology, as discussed above.

Th17, which are elevated in the circulation, can be targeted mainly in the early stages of the disease [Sommer et al., 2018]. Blockade of the development of these cells, as well as the interaction of LFA-1 receptors on Th17 and ICAM-1 receptors on DA neurons or the interaction of IL-17 with IL-17 receptors, yields positive therapeutic effects in PD [Prots and Winner, 2019].

Considering all the targets and state-of-the-art approaches to the treatment of PD, it should be noted that their development is still in the preclinical and early (1 and 2) clinical phases, and as no clinical trial has yet been completed, these treatments cannot be used in practice. However, when trials are completed, multitarget therapy addressing a variety of pathogenetic components can be seen as one of the most promising approaches to the treatment of PD.

Conclusions. The mechanisms underlying the death of DA neurons and the intraneuronal accumulation of aggregated α-syn, which are the main pathological signs of PD, are not yet fully understood. Neuroinflammatory processes are important factors in the development of many diseases associated with neurodegeneration, such as Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis, as well as PD. Neuroinflammation in PD is accompanied by activation of microglia, infiltration of T cells (CD4 and CD8 T lymphocytes) into the CNS, and increases in the contents of proinflammatory cytokines/chemokines in the cerebral parenchyma and CSF and in the periphery.

Microglial cells play a central role in neuroinflammation by promoting a neurotoxic or neuroprotective microenvironment, thereby controlling neuron survival. Microglial function is regulated by cell-to-cell interactions between neurons, astrocytes, and various immune cells which enter the brain when the BBB is compromised.

Up-to-date clinical and experimental data provide convincing evidence that, in addition to neural events, the mechanisms of development of PD include an immune component involving innate and adaptive immunity. The role of T cells in the development of PD is increasingly recognized. A decrease in the death of DA neurons has been demonstrated in conditions of T cell deficit; these cells, in contrast to B cells, penetrate the brain and, infiltrating the compact zone of the SN and making contact with DA neurons, take part in activating microglia, and they also release proinflammatory cytokines with neurotoxic effects. This process is mediated by $CD4^+$ and $CD8^+$ T cells, which have cytotoxic functions and, as a result of contact with neurons and/or IL-17 production, produce, in particular, IFNγ, which enhances cell cytotoxicity, and Th17; this is also accompanied by decreases in Th2-type cells and Treg cells. Changes in immunity in response to extracellular α-syn may play a critical role in modulating the progression of PD. Acting via specific antigenic epitopes, α-syn is able to activate T cells involved in immune processes, which leads to neurodegeneration of DA neurons. α-syn-specific T cells have been shown to be present in most PD patients and to mediate subsequent autoimmune reactions. As damaged neurons accumulate, pathology-associated α-syn T cells can be detected before motor impairment is detectable and before diagnosis, and this provides an opportunity for early detection of the disease.

It may be that T cell-induced inflammation mediating DA neurodegeneration in PD is initiated in the intestinal mucosa and is largely dependent on the composition of the intestinal microbiota. This is supported by evidence that the T cell response against Lewy bodies is initially limited to the intestinal mucosa but later spreads to the brain [Campos-Acuña et al., 2019].

It should be noted that the ratio of subsets of different populations of immune cells (monocytes, T- and B-cells) detected in the periphery in recent years varies significantly depending on the dynamics of development and severity of disease. The early stages of PD, characterized by the greatest cellular changes, with increased expression of TLR and proinflammatory cytokines, are potentially the most important for immunotherapy and neuroprotection. The prevalence of PD and the severity of the disease create the need for new therapeutic approaches targeting immunological cellular and molecular indicators. As dysfunctions of the innate and adaptive immune responses are the main components of the pathogenesis of PD, the possibility of combining conventional therapy with immunomodulatory interventions able to restore immunological homeostasis and lead to neuroprotective outcomes has become clear. This requires knowledge of the fine mechanisms of development of PD and its specific biomarkers, especially in the early stages of disease.

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