Chapter 6

Is Chronic Systemic Inflammation a Determinant Factor in Developing Parkinson's Disease?

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Additional information is available at the end of the chapter

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Abstract

The etiology of Parkinson's disease (PD) is complex and involves numerous risk factors as environmental and hereditary. Nevertheless, recent studies have established that systemic inflammation and neuroinflammation are both present in the prodromal phase and sustained during the progression of the disease. Evidence suggests that the activation of the peripheral immune system exacerbates the brain inflammatory response, which may initiate or enhance neurodegenerative processes. Understanding the impact of chronic systemic inflammation in the neuroinflammation and the progression of the disease will provide a broader view of the etiology and pathology of PD. In this chapter, we review the role of the chronic systemic inflammation in neuroinflammation and its effect on PD, considering cell types, molecular, and inflammatory mediators that predispose to the development of the disease.

Keywords: Parkinson's disease, chronic systemic inflammation, neuroinflammation, microglial activation, pro-inflammatory cytokines

1. Introduction

The contribution of systemic inflammation in the progression of several neurodegenerative diseases slightly has been studied. Inflammatory processes and activation of microglia are both important components in the pathogenesis of many neurodegenerative diseases such as Parkinson's disease (PD). Data support that microglial age-related cell changes induce cytotoxicity; this may contribute to the onset of neurodegenerative changes.

Indeed, low levels of chronic inflammation are associated with age-related diseases, including atherosclerosis, cardiovascular diseases, diabetes, and PD [1]. This phenomenon is caused by a persistent antigenic response and oxidative stress accompanied by reduced ability to counteract with a variety of stress factors, as well as a progressive increase in the pro-inflammatory state [2].

The etiology of PD is complex and involves numerous risk factors as environmental and hereditary. Nevertheless, recent studies have established that systemic inflammation and neuroinflammation are both present in the prodromal phase and sustained during the progression of the disease. Evidence suggests that the activation of the peripheral immune system exacerbates the brain inflammatory response, which may initiate or enhance neurodegenerative processes. Understanding the impact of chronic systemic inflammation in the neuroinflammation and the progression of the disease will provide a broader view of the etiology and pathology of PD. In this chapter, we discuss the role of the chronic systemic inflammation in neuroinflammation and its effect on PD, considering cell types, molecular, and inflammatory mediators that predispose to the development of the disease.

2. Neuroinflammation

A few decades ago the central nervous system (CNS) was considered an immunologically privileged site, a feature that has been attributed mainly to the presence of the blood-brain barrier (BBB), the low expression of major histocompatibility complex class II (MHCII), and the lack of brain lymphatic vessels [3].

Under systemic or endogenous pathological conditions, brain immune and glial cells start local inflammatory events, a situation named neuroinflammation, which is a mechanism of host defense that aims to restore the structure, recover normal functions, and insult neutralization [4].

Several hypotheses have been postulated on the possible causes of neurodegeneration in PD patients, which include genetic factors, environmental toxins, mitochondrial dysfunction, and cell death associated with free radicals [4, 5]. However, now research has focused on neuroinflammation as possible neurodegeneration activator in PD as epidemiological data indicate that is present even during the asymptomatic phase of the disease [6].

The main neuroinflammatory characteristics present in PD are the presence of activated microglia and reactive astrocytes; participation of the adaptive immune system; increased immune molecules such as cytokines, chemokines, among others; and increased oxygen and nitrogen reactive species concentration (ROS/RNS). These features can lead to the impairment of the BBB [7].

3. The blood-brain barrier

The BBB is a cellular barrier that regulates the environment of the CNS of vertebrates. It represents the border between CNS capillaries and extracellular fluid of neurons and glial cells,

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and ensures specific brain homeostasis, allowing proper function of neurons [8]. Although the BBB becomes more permeable during systemic inflammation [9], the total area of the microvasculature that composes the BBB in the adult human brain is 12–18 m^2 [10] and is the primary interface for the brain-blood exchange.

The primary function of the BBB is to provide a stable microenvironment for neural function. At first, it provides optimal concentrations of ions for neural communication, due to the functional combination of channels and transporters specific ions. For example, in mammals, the plasma concentration of potassium is 4.5 mM; however, in the cerebrospinal fluid (CSF) and the interstitial fluid, the levels range between 2.5 and 2.9 mM [11, 12]. Also, brain calcium and magnesium levels, and the pH are actively regulated by the BBB [13–15].

Moreover, although the peripheral nervous system and CNS use the same neurotransmitters, the BBB impedes the free flow and maintains the concentrations to avoid phenomena such as excitotoxicity [16, 17]. Similarly, the CSF protein content is lower than that of blood plasma. High levels of proteins such as albumin, prothrombin, and plasminogen can activate apoptotic cascades, therefore, be locally harmful to the nervous tissue [18–20].

The main elements that conform the BBB are endothelial cells, pericytes, astrocytes (specifically astrocytic foots), neurons, microglia cells, and the extracellular matrix. The close interactions between these components form the neurovascular unit [21] (**Figure 1**).

The endothelial cells of the BBB differ from the rest of the endothelial cells because they present tight junctions, low vesicular transport, and multiple transporters, restricting and selecting molecule flow [22]. Transmembrane tight junctions proteins (occludins, claudins 1–20 and JAMs) seal the intercellular space of endothelial cells and interact intracellularly with scaffold proteins (ZO-1, ZO-2, and ZO-3), and other cytoskeletal proteins. In adherens junctions, cadherins stabilize the adhesion between endothelial cells and catenin binds the cadherin to the cytoskeleton [23].

Through analysis of the microvasculature of the brain, it showed that astrocytic foot forms a thin film on the outer surface of the endothelium, suggesting that the astroglia is responsible for the development and specialization of brain endothelial phenotype [16]. An example that illustrates this point is the transforming growth factor-β (TGF-β) and angiopoietin-1 produced by astrocytes, which increases the expression of tight junction proteins and decreases the permeability of H3-Sucrose [8].

On the other hand, pericytes share the basement membrane with the endothelial cells of capillaries, venules, and arterioles, stabilizing the blood vessel wall. Also, pericytes present receptors for catecholamines, angiotensin II, vasoactive intestinal peptide, vasopressin, and endothelin-1 that prevent pericyte apoptosis rates in coculture of endothelial cells with astrocytes [22].

Multiple CNS pathologies such as hypoxia, ischemia [24], edema [25], and neurodegenerative diseases such as Alzheimer's, PD and multiple sclerosis [26–28] involve some degree of BBB dysfunction. An increased BBB permeability facilitates entry of macromolecules such as albumin into the CNS [29] and changes in blood vessels [30] in patients with PD. These changes

of BBB permeability contribute to neuronal death in MPTP-intoxicated animal models of PD [31, 32].

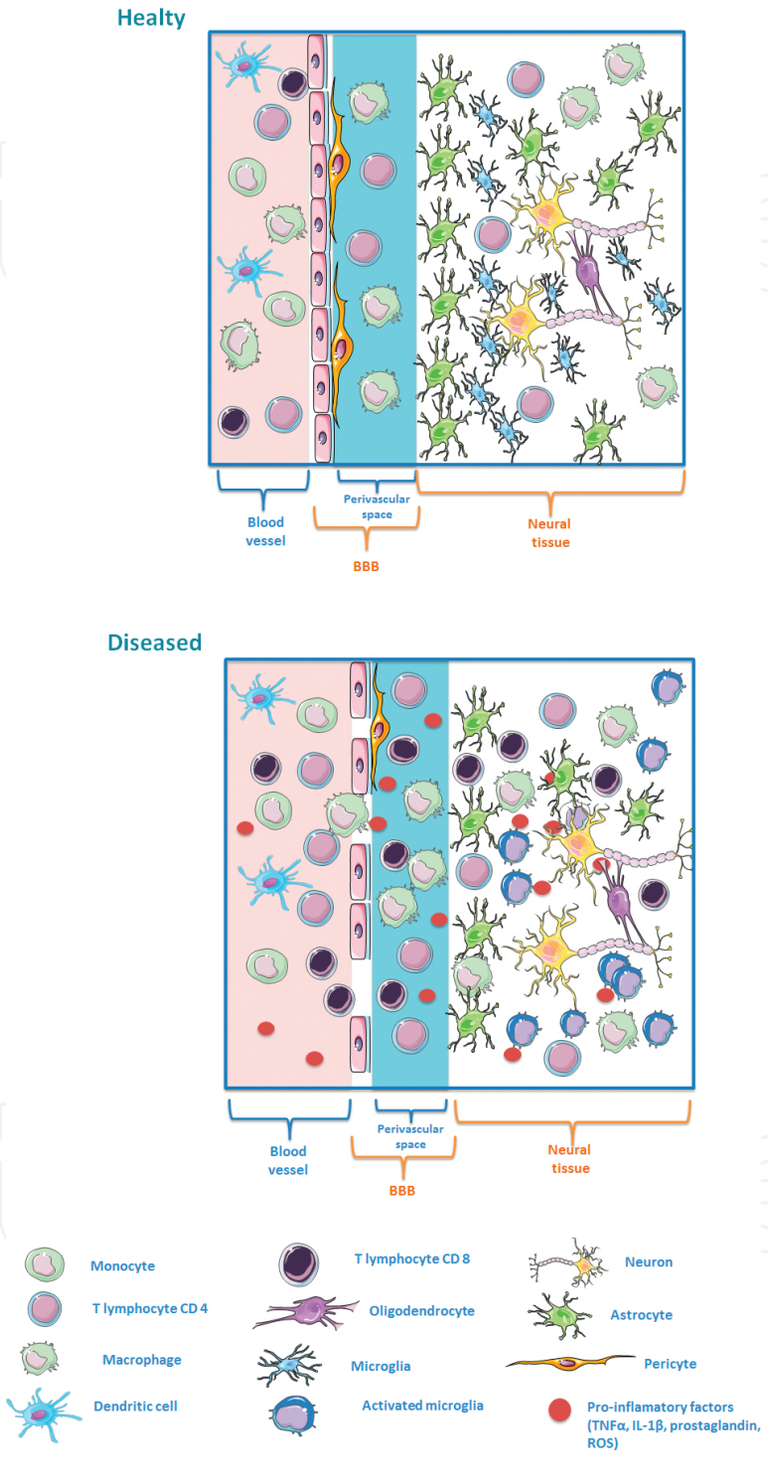

Figure 1. Under physiological conditions, astrocytes and neurons modulate the activation of the microglia. Peripheral immune cells maintain immune surveillance of brain parenchyma and perivascular space, and CD4+ T cell and macrophages could enter across of intact BBB into the CNS. But under systemic inflammation conditions, peripheral immune cells can penetrate the BBB and contribute to neuroinflammation.

One of the main evidence that involves BBB changes in patients with PD stems from a study of positron emission tomography (PET) that showed an increase of the [11C] verapamil capture in the midbrain of PD patients suggesting a decrease of P-glycoprotein [33]. Also, it has been proposed that in these individuals developing changes in the BBB permeability, increased traffic of iron and magnesium, both involved in the PD pathogenesis [34].

There is growing interest in the study of inflammation as a pathogenic mechanism of PD, which involves BBB properties alterations as shown in several experimental models [35]. These events facilitate the establishment of neuroinflammatory phenomena (**Figure 1**). Regardless of whether these developments are cause or consequence of neuronal death in PD, the attention of researchers focuses on identifying new therapeutic targets for alternative therapies in the treatment of this disease.

4. Brain-immune cells response in Parkinson's disease

4.1. Microglia: the major surveillance cell in the CNS

Microglial cells are vital in maintaining an immune homeostasis in the CNS; these cells are the first defenders against infectious agents and injury-related products in the CNS. Similar to tissue macrophages, microglia survey the brain for pathogens and support CNS homeostasis and plasticity, by guarding and remodeling synapses [36].

Under physiological conditions, astrocytes and neurons maintain the microglia in a quiescent or non-activated state [37, 38]. Non-activated microglia constitutively expresses low levels of HLA-DR in the healthy human brain [39] and MHCII in the rodent brain [40]. In this state, microglia mainly maintain brain homeostasis with astrocytes. Nevertheless, activated microglia display more molecular markers of an antigen presentation cell such as MHCII, CD80, CD86, CD40, CD11a, CD54, and CD58 [41, 42]. These properties show the capability for antigen presentation of this cell and thus its function of immune surveillance of the brain. Microglia have all the machinery necessary to detect any foreign molecule that accesses the CNS parenchyma and can rapidly mount a potent inflammatory response. After immune stimuli, such as a viral infection or brain injury, microglia cells quickly activate [43, 44] and acquire a compact phenotype. They upregulate several surface receptors such as receptors for neurotransmitters, cytokines, and chemokines, as well as pattern-recognition receptors [45–47]. Several TLRs are expressed on the microglial surface, including TLR2, TLR4, and TLR6 [48, 49].

Microglia also respond and propagate inflammatory signals initiated at the periphery, by activating and producing pro-inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor alpha (TNFα) [50, 51](**Figure 2**). These cytokines are indispensable for the induction and maintenance of the CNS inflammatory state. They also promote the release of secondary inflammatory mediators including prostaglandins and nitric oxide (NO) [52–54]. Also, they facilitate the production of reactive oxygen species (ROS) through the induction or activation of NADPH and NO release [55, 56]. Though the activation of microglia and the

production of cytokines are transient, once the immune insult is resolved, the microglia return to a surveying state.

Similar to peripheral macrophages, microglial exposure to IFNγ or TNFα, or stimulation by microbial agents such as LPS, or other TLR-agonistic compounds or pathogen-associated molecular patterns, would establish in microglia a "classical" macrophagic activation with an M1 phenotype. These cells are defense-oriented, release pro-inflammatory and cytotoxic factors. Cytokines, such as IL-4 or IL-13, instead facilitate an "alternative" activation of macrophages, also known as M2 phenotype [57]. Recent studies proved that brain microglia display a distinct profile that is not present in microglial cell lines and differ from M1 or M2 polarized microglia, but rather implicate genes associated with nervous system development [58].

During aging or in some pathologies such as Alzheimer's disease, microglia display a heterogeneity analogous to systemic tissue-resident populations [59, 60]. These studies showed that early in disease progression, microglia develop an altered inducible "activated" state, which functionally differs from steady state microglia. This activation state is further subdivided into classical M1 and alternative M2 state [61, 62].

More interestingly is that in neurodegenerative diseases, microglia can get overactivated resulting in reactive microgliosis, and this might induce neurotoxicity, perturbation of the neuronal network, maladaptive plasticity, and leading to tissue damage [63]. In PD, microglia can release pro-inflammatory cytokines, such as IFNγ, IL-1β, TNFα, IL-2, and IL-6 [64], increases the levels of TNFα receptor R1 (p55), bcl-2, soluble Fas, caspase-1 and caspase-3, which may contribute to the dopaminergic neurons degeneration [65, 66]. In turn, dopaminergic neuronal death may trigger microglial activation through the loss of the neural inhibitory CD200 signaling, exposure to α-synuclein, through binding of neuron-bound complement or antibodies, etc. [67, 68].

4.2. Astrocytes

Astrocytes are the most abundant glial cells of neuroectodermal origin that preserve brain homeostasis and neuronal functions, participate in maintaining and inducing the BBB, as well as in nervous tissue repair. Also, they significantly regulate the immune response and express a set of pattern-recognition receptors involved in innate immune response such as TLRs, mannose receptors, scavenger receptors, and some components of the complement system [69]. Astrocytes have a strategic location close to other glial cells and blood vessels and form a connection between the blood vessels and the brain parenchyma. Moreover, astroglia can be activated by pattern-recognition receptors ligands or exposure to IFNγ; increasing the expression of the glial fibrillary acidic protein (GFAP), MHCII, costimulatory molecules (CD80, CD86, CD40), and adhesion molecules [69]. They possess the ability to secrete cytokines such as IL 12 and chemokines (CCL2, CCL19, CCL20, and CXCL10) that promote changes in BBB permeability and favor thus an inflammatory-type response TH1 [69–72]. However, its role as antigen presenting cell is controversial, and it is thought that their participation is secondary [3].

Most findings indicate that microglial cells are the main mediators of neuroinflammation in the PD, but the presence of reactive astrocytes in the substantia nigra of PD patients is a constant pathological feature [73]. The increased GFAP expression observed suggests not only a morphological change but also a functional shift in this type of cell [74]. This phenomenon is consistent with the decreased production of trophic factors as derived neurotrophic factor glia and ciliary neurotrophic factor, both substances generated by astrocytes under normal physiological conditions [74, 75], and this reactivity is proportional to damage dopaminergic neurons [76].

Astrocytes can detect neurons with α-synuclein accumulation (the main component of Lewy bodies) and can be activated as a measure of neural protection. A recent study showed that neural α-synuclein is transferred and accumulated in astrocytes and induces activation of genes associated with the immune response. In these conditions, astrocytes express cytokines such as IL-1α, IL-1β, IL-6, IL-18, and colony stimulating factor 1, 2, and 3 [6], chemokines type CC, CXC, and type CX3C [69].

Also, intercellular adhesion molecule 1 (ICAM-1) positive astrocytes are present in the substantia nigra of PD patients; it is possible that they attract reactive microglia to the site of injury since microglial cells expressing the LFA-receptor 1 in the same place are found [77]. The action of α-synuclein on astrocytes is thought to occur via receptors, but the identity of these receptors is currently unknown [5].

5. Peripheral immune cells participation in Parkinson's disease

5.1. Macrophages and dendritic cells

The phagocytic cells such as macrophages are restricted to the perivascular space, leptomeninges, and choroid plexus. Macrophages constitutively express MHCII, CD11b, and CD45, which can help distinguish the microglia since it has a low expression of CD45 in the inactivated state [70]. In the healthy brain, the primary function is immune surveillance, antigen capture, and presentation locally and in the cervical lymph nodes. In the case of a lesion, macrophages participate as antigen presenting cells, in phagocytosis and secretion of proinflammatory cytokines (IFNγ, TNFα, IL-12) and chemokines (CCL2, CCL3) favoring chemotaxis and inflammation [78, 79]. Also, peripheral macrophages and brain microglia can secrete inflammasome components (caspase-1, IL-1β, and IL-18) that can induce neurotoxicity [78, 79]. In contrast, macrophages also have a regulatory role since they can produce anti-inflammatory and neurotrophic factors as nerve growth factor [80].

Dendritic cells (DCs) can be found primarily in the choroid plexus and meninges [81]. However, they have also been identified in regions lacking BBB such as the circumventricular organs, in sites of postnatal neurogenesis, in the perivascular space and even forming part of the glia limitans of the BBB [82, 83]. They are classified into two main groups (lymphoid and myeloid) and are assorted into several subpopulations due to cell expressing markers. The main attributed function in the CNS is immune surveillance, antigen capture, and delivery to

the cervical lymph nodes, and antigen presentation [84]. However, they also have an important role in inflammation by producing cytokines such as IL-23, IL-1β, IL-12, TNFα, and IFNγ also IL-10 [81].

After recognizing molecules associated with inflammation, damaged tissue, or autoantigens, the DCs migrate to sites of inflammation and to lymph nodes to activate T cells and thus connect the innate immune response and the adaptive immune response. There is little evidence of the involvement of the DCs in the pathogenesis of PD, but they are recruited from the blood to the brain where they prime T cells and contribute to the neuroinflammation. A decrease in the number of peripheral DCs, mainly myeloid, associated with the increased severity of cognitive and motor symptoms of the disease [85]. Additionally, it has been reported that DCs treated with neuromelanin (the pigment present in dopaminergic neurons) acquire a mature phenotype, produce IL-6 and TNFα, and can stimulate T cell proliferation [86].

5.2. Lymphocytes

Leukocyte trafficking into the CNS is a highly regulated process, which protects the brain from a generalized inflammatory phenomenon that could significantly compromise the homeostasis required for neural functions [87, 88].

Interestingly, the cellular immune surveillance in the healthy human brain differs among CNS regions and the greatest numbers of immune cells are located in brain regions where the tight junction barrier of the BBB is reduced, such as the circumventricular organs and the ventrorostral areas of the medulla oblongata [89].

In healthy humans, predominantly activated central memory T cells that expressed high levels of CCR7, CXCR3, and L-selectin are found in the choroid plexus, the subarachnoid space, and the CSF [90]. Also, P-selectin facilitates migration of T cells into the CSF of mice and healthy humans. Furthermore, P-selectin, E-selectin, and ICAM-1 have been detected in vessels of the choroid plexus and subarachnoid space in humans [91].

Under physiological conditions, the immune surveillance in the perivascular space, with the participation of T cells that cross the vessel wall of postcapillary venules, however, progress towards the brain parenchyma dependent antigen presentation by perivascular macrophages or DCs [3, 83]. Questions have been raised whether the antigen specificity of T cells is a prerequisite for easy transit to the CNS. Still, several studies have transferred reactive T cells against neural antigens or irrelevant antigens to animals, and both types infiltrate the perivascular space similarly, though antigen specificity is required for final access to the brain [87, 92].

Given the evidence of the role of T cells in the maintenance of brain homeostasis, these could be implicated in the initiation and progression of PD. In this regard, PD patients and animal models of PD present infiltrating T CD4+ and CD8+ cells in the substantia nigra [93, 94] and decreased blood naive T lymphocytes [64, 95, 96]. Similarly, patients with PD have a cytotoxic response by T cell due to a change in the proportion of markers CD4:CD8 and the increase in the secreted IFNγ production versus IL-4 by lymphocytes [95, 97].

Other changes in peripheral blood lymphocytes of patients with PD have been reported, and lymphocytes from patients with PD have a higher incidence of micronuclei, DNA breaks, and oxidized purine bases [98]. Interestingly, levodopa treatment appears to reduce DNA damage in lymphocytes of these patients [99]. Furthermore, apoptotic markers, caspase-3, and the activity of Cu/Zn superoxide dismutase are increased in lymphocytes from patients with PD [100]. The increased levels of apoptosis and DNA damage could be indicative of a fundamental process pathogenic that involves oxidative stress, specific immune responses, and/or intrinsic factors such as genetic.

B cells are antibody-secreting cells of the immune system and the key mediators of the humoral response [101].

Patients with PD display antibodies against α-synuclein as well as against other epitopes from the CNS [102, 103]. Nevertheless, the presence of antibody producing B cells in the CNS of PD patients has not been reported [93, 94] despite the decrease in peripheral B lymphocytes [95, 96]. Deletion of the B cell counts in autoimmune diseases and other inflammatory diseases are secondary to reduced circulating memory B cells, which can be related to an inflammatory process or cellular activation [104, 105]. These events can occur in the substantia nigra in PD and that could explain the B cell decrease in the periphery of these patients.

6. Main cytokines and chemokines involved

Cytokines are proteins with pleiotropic actions that mediate many of the functions of immune cells and are mainly secreted by immune cells but also parenchyma brain cells. Multiple cytokines (IFNγ TNFα, IL-1β, IL-6, IL-18, IL-4, IL-10, IL-11, IL-13, TGF-β, IL-17, and IL-23) are found in the CNS, even under physiological conditions [106, 107].

It has been shown that PD patients present increased plasma cytokines such as IL-2, IL-4, IL-6, IL-10, TNFα, and IFNγ [108, 109]. Also, high levels of these cytokines and other inflammation markers are related to the risk of idiopathic PD [110]. Postmortem studies have found over-expression of pro-inflammatory cytokines (IL-1β TGF-α, IFNγ, and IL-6) in CSF and nigrostriatal regions of PD patients [111, 112]. Also, proteins of the complement system are found associated with extra-neuronal Lewy bodies [113]. As mentioned earlier, genetic factors are strongly related to the PD, polymorphisms of IL-8, IL-17, and IL-10 genes are associated with the risk of developing sporadic PD [114]. The findings suggest that activation of the immune response occurs in association with or in response to the Lewy bodies' formation [115].

Chemokines, which play important roles in neuroinflammation as mediators of leukocyte infiltration, are among the most important inflammatory factors [116]. They are proteins mediating the response and traffic of leukocytes and are classified into four subfamilies: C, CC, CXC, and CX 3. In the CNS, chemokines are mainly produced by glial cells and its primary function is chemotaxis or attraction of leukocytes to the damaged area promoting inflammation. The main CNS chemokines are monocyte (CCL2, CCL3, CCL4), lymphocyte (CCL5) chemoattractant, IFNγ-induced (CXCL10), among others [117, 118].

A prominent member of the chemokine family is CXCL12 or stromal-derived factor-1 alpha (SDF-1a) and its receptor CXCR4. Both CXCL12 and CXCR4 are constitutively expressed and modulate a variety of CNS functions, including neurogenesis [119], axonal growth [120], pain [121], and neurotransmission [122]. High expression of CXCL12 and CXCR4 is present in the rodent substantia nigra [123] and modulate dopamine transmission [124]. In the human substantia nigra, CXCR4 immunoreactivity was high in dopaminergic neurons [125].

Regarding PD, patients show elevated levels of CCL5 in the serum, and its concentrations are higher in patients with greater severity of symptoms [109]. Interestingly, the substantia nigra of patients with PD exhibited higher expression of CXCR4 and CXCL12 than control subjects despite the loss of dopaminergic neurons. This effect was accompanied by an increase in activated microglia [125].

We can finally say that levels of CCL2 expressed by peripheral blood mononuclear cells were higher in PD patients than in healthy control. CCL2 levels are also correlated with the Unified Parkinson's Disease Rating Scale (UPDRS)-III and Hoehn-Yahr stage [109]. Moreover, a recent study showed that elevated CCL2 CSF levels were associated with more severe symptoms of depression in PD patients [126].

7. Contribution of systemic and neuroinflammation in Parkinson's disease development

The contribution of systemic inflammation in the progression of several neurodegenerative diseases has been slightly studied. Inflammatory processes and activation of microglia are both important components in the pathogenesis of many neurodegenerative disorders such as PD; epidemiological evidence suggests an association between neuroinflammation and PD [35].

The PD, such as other neurodegenerative diseases, is associated with aging, which is related to increased formation of ROS predisposing the cell to damage and dysfunction. The evidence points to a relationship between oxidative stress and inflammation in the excessive production of free radicals that can induce an inflammatory response [1].

7.1. Cytokines contribution

Several studies have reported increases and decreases in the levels of pro-inflammatory cytokines and neurotrophins in the brain of PD patients [127], suggesting that neurons could be more susceptible to neuroinflammation and apoptosis, thus contributing to the pathogenesis of PD.

High levels of TNFα, IL-1β, IL-2, IL-4, IL-6, TGF-α, TGF-β1, and β2 have been detected in the brain parenchyma or CSF of PD patients [94, 128–130]. In accordance, the activated microglia can be a source of pro-inflammatory cytokines since in the substantia nigra of PD patients microglial overactivity was observed [46, 131–135]. An additional source of pro-inflammatory cytokines is the presence of CD8+ T lymphocytes in the vicinity of degenerating neurons

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[94]. Cytotoxic T CD8+ is directly neurotoxic in autoimmune and aging-associated neurodegenerative disorders of the CNS [136]. This observation suggests that an infiltration of immune cells through the BBB may also contribute to the pathophysiology of PD. In this regard, peripheral blood mononuclear cells from PD patients express significantly higher levels of CCL2, CCL3, CCL5, IL-8, IFNγ, IL-1β, and TNFα after LPS stimulation than in healthy subjects [109].

It is possible that as well local as peripheral pro-inflammatory cytokines contribute to the loss of the BBB integrity facilitating the entrance of peripheral immune cells into the CNS. The role of peripheral immune cell traffic into the brain and its relevance in PD have not been extensively explored, but some studies show the implication of CD4+ T cells since mice lacking CD4+ cells are protected from MPTP-induced nigrostriatal neurons degeneration [93].

7.2. Microglia priming

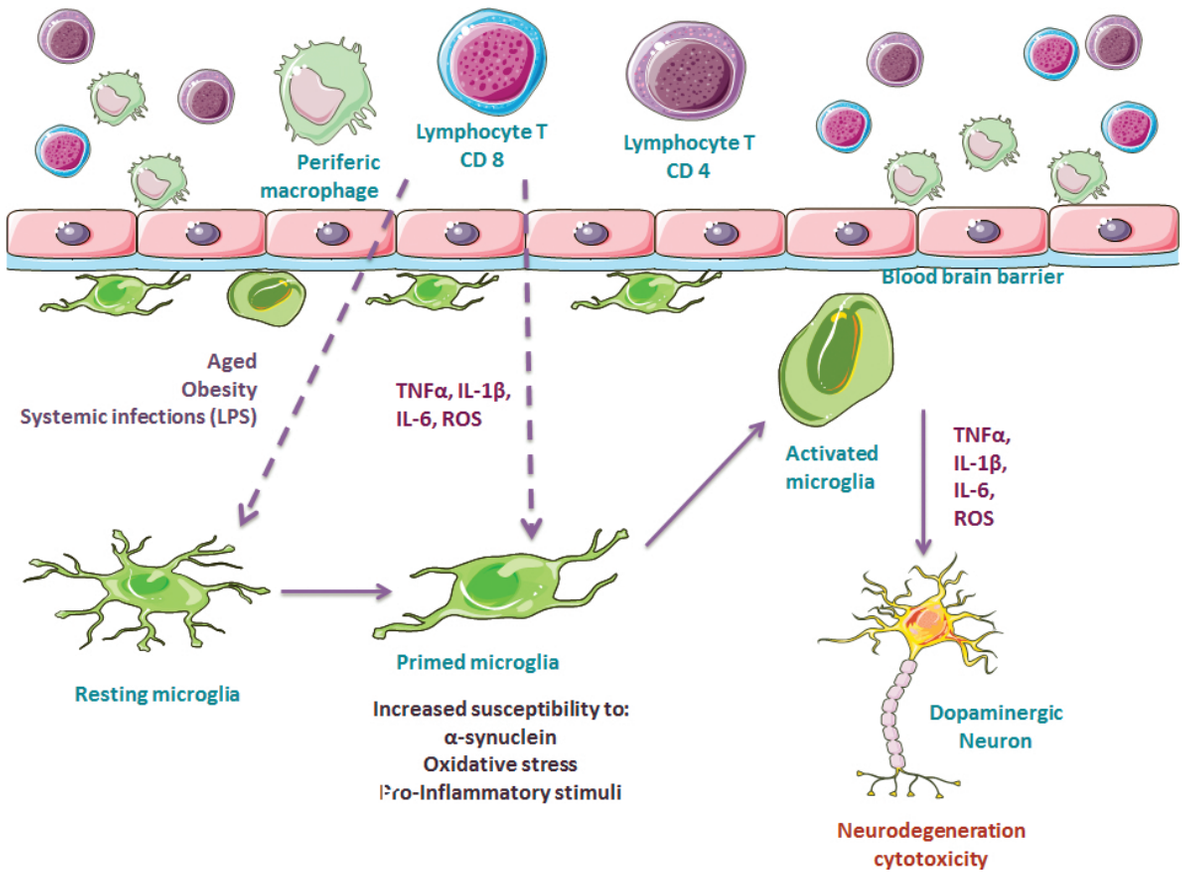

Figure 2. The relationship between peripheral inflammation and neuronal loss in PD. Neurodegenerative diseases present microglial activation as the chief hallmark, which can change its morphology from resting towards an activated or primed shape. The intermediate stage, "primed microglia," describes the atypical microglial stage, which precedes a further neurotoxic microglial activation as a consequence of a secondary pro-inflammatory stimulus. This intermediate stage could be a consequence of pro-inflammatory stimuli evoked by obesity, aged, or a systemic infection. Activated microglia releases pro-inflammatory cytokines which can act on dopaminergic neuronal integrity.

Primed microglia is the state when microglia respond to a secondary inflammatory stimulus with an exaggerated inflammatory response; this form of microglia contributes significantly to neuroinflammation and death of dopaminergic neurons (**Figure 2**). A recent study reported that a single paraquat exposure induced microglia activation with induction of the NADPH oxidase. If this activation was blocked with the anti-inflammatory drug minocycline, subsequent exposures to the paraquat failed to cause oxidative stress and neurodegeneration [137]. Also, systemic LPS administration resulted in rapid brain TNFα increase that remained elevated for 10 months activating microglia and secondarily increasing the expression of brain pro-inflammatory factors (i.e., TNFα, CCL2, IL-1β, and NF-κB). Further, tyrosine hydroxylase-immunoreactive neurons in the substantia nigra are reduced after LPS exposure and these data demonstrate that peripheral inflammation can activate brain microglia to produce chronically elevated pro-inflammatory factors, favoring a progressive loss of dopaminergic neurons of the substantia nigra [138].

Other works showed that priming of microglia with LPS predisposes susceptibility of dopaminergic neurons to neural toxins such as paraquat and 6-hydroxydopamine (6-OHDA), favoring the secretion of IL-1β, triggering the loss of these neurons, and suggesting a close relationship between neurodegeneration and inflammation [139, 140].

Therefore, microglial priming may in part regulate microglial phenotype and shift microglial activities from neuroprotective to neurotoxic (i.e., from trophic factor synthesis to production of ROS/RNS, among others), leading to hasten the death of vulnerable neuronal populations [141, 142].

Increased susceptibility to inflammation-induced nigral degeneration was shown in Parkin-deficient mice treated chronically with intraperitoneal low-dose of LPS, mice developed neuroinflammation and selective loss of dopaminergic neurons of substantia nigra [143].

Also, the systemic co-administration in mice of LPS and α-synuclein significantly increased IL-1β, IL-6, and TGF-β mRNA when compared with animals treated with α-synuclein alone. These observations suggest that any activator of the innate immune system, such as a peripheral pathogen, will alter the pathogenesis of PD by generating a transient pro-inflammatory environment that is likely to accelerate neurodegeneration [144].

7.3. What role plays aging?

Many age-related changes affect the CNS, contributing to both oxidative stress and inflammation deterioration of certain functions; thus, these processes singly and collectively affect neuronal viability and increase vulnerability. Data support that microglial age-related cell changes induce cytotoxicity, and this may provide to the onset of neurodegenerative changes. It has been observed that basal mRNA expression of markers of activated microglia such as CD11b and Iba-1 was higher in the aged hippocampus when compared to the adult [145]. Moreover, aging increased macrophage infiltration in the brain, with increased expression of IFNγ and the TLR4 agonists, high-mobility group protein B1 (HMGB1) [146].

Microglia seem to be activated at baseline in the elderly [94]. Furthermore, microglial cells obtained from aged mice developed lipofuscin granules, reduced the complexity of process-

es ramification, and increased mRNA levels of several pro-inflammatory cytokines (TNFα, IL-1β, and IL-6) as well as several anti-inflammatory cytokines (IL-10 and TGF-β) when compared with young mice. Also, when a pro-inflammatory stimulus is performed by a single dose of LPS, expression of TNFα IL-1β, IL-6, and IL-10 is increased but not of TGF-β [147]. These elevated cytokine levels may modify the microglial function and predispose microglial cells to become cytotoxic and cause neurodegenerative changes [148].

Upon aging, there are hormonal, immunological, and fatty changes that lead to a chronic inflammatory state [149]. These changes promote cognitive, cardiac, neuronal deterioration, and the occurrence of vascular events. However, if pro-inflammatory molecules outgrow anti-inflammatory responses, an imbalance occurs establishing a chronic inflammatory state [1, 150]. Therefore, this apparent imbalance in innate immune responses and pro-inflammatory molecules present in aging leads to a low-grade chronic inflammatory condition commonly present in elderly [150].

In this context, obesity results in a chronic inflammatory environment and may be associated with increased systemic oxidative stress. Levels of pro-inflammatory cytokines, such as IL-6 and TNFα, are significantly higher in obese subjects than in lean subjects [151, 152]. It becomes relevant since mortality was higher in obese animals than in control mice in the MPTP mice model, suggesting that obesity may increase the vulnerability of dopaminergic neurons to MPTP via increased levels of ROS and pro-inflammatory cytokines [153].

8. Conclusions

In recent decades, has deepened in the study of neuroinflammation as an important factor in etiology and development of PD, finding enough evidence to affirm that neuroinflammation is an adverse process for neuronal survival and function of individuals with this disease.

The immune system continues to undergo changes throughout life. The evidence shows that chronic inflammatory conditions caused by infectious, degenerative diseases or conditions such as aging and obesity, contribute to the establishment of neuroinflammation and the development of neurodegenerative phenomena, mainly in microglia rich brain regions, as the substantia nigra.

The full impact of systemic inflammation on brain immune changes remain poorly understood. The existence of a close association between systemic inflammation and neuroinflammation is evident in the progression of neurodegenerative disorders.

The cross-talk between immune cells and nervous system, especially microglia, is of particular importance in damage processes that precede PD. Based on current evidence, blocking microglia-derived inflammatory mediators or modulating the peripheral immune cells may be potentially useful therapies. However, it is important to explore in parallel the cellular, molecular and functional changes occurring during systemic inflammation, and thus, it may be possible to analyze the implications of this inflammation in recent Parkinson development.

Although research has been extensive, it is necessary to deepen this area of knowledge, especially in countries with a high number of individuals with obesity or metabolic syndrome, to assess and reduce the risks of increasing prevalence of PD and other neurodegenerative diseases.

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