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## Physiology and Pathology of Neuroimmunology: Role of Inflammation in Parkinson's Disease

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### Abstract

Parkinson's disease (PD) is a neurodegenerative disease that affects 1% of the population aged 65 and over and is the second most common neurodegenerative disease next to Alzheimer's disease. Interneuronal proteinaceous inclusions called Lewy bodies (LB) and a selective degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNPC) are the main features of PD pathology. The most common clinical manifestations are rigidity, tremor, bradykinesia, postural instability, sleep disorders, alterations in gait, smell, memory, and dementia. Genetic and environmental factors are involved in PD, and, recently, oxidative stress, proteasome-mediated protein degradation, and inflammation have acquired relevance as major mechanisms of neuronal dysfunction. Increased levels of reactive oxygen and nitrogen species in the brain contribute to greater vulnerability of proteins to nitro-oxidative modification and to greater degrees of aggregation. These protein aggregates contain a variety of proteins of which  $\alpha$ -synuclein appears to be the main structural component. Interestingly,  $\alpha$ -synuclein can be secreted by neuronal cells and may lead the initiation and the maintenance of inflammatory events through the activation of microglia, which contributes to dopaminergic neuron depletion. New evidence also suggests that PD may be the result of an autoimmune response in which the immune cells recognize the neurons as foreign elements and would act against them, causing their death.

**Keywords:** Parkinson's disease, physiology, pathology, neuroimmunology, inflammation

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## 1. Introduction

The central nervous system (CNS) has traditionally been considered immunologically privileged due to the protection conferred by the blood-brain barrier; it lacks lymphatic vessels and is devoid of dendritic cells, and the parenchyma cells do not express major histocompatibility complex (MHC) class-I antigen-presenting molecules. However, the CNS can modulate the immune response and limit inflammation-induced tissue damage [1]. Neurons of the CNS are actively involved in control of the immune response by modulating the function of glial cells and T lymphocytes. There are mechanisms involved in the control of the immune response: the direct contact through membrane glycoproteins (CD22, CD47, CD200), neural cell adhesion molecules (NCAM or CD56), intercellular cell adhesion molecule-1 (ICAM-1), semaphorins and cadherins, and the mechanism independent of cell-cell contact that involves the expression of the Fas ligand or CD95L, which promote apoptosis of microglial cells and T lymphocytes. The immune system is not a completely autonomous system since the lymphoid organs are innervated by cholinergic, catecholaminergic, and peptidergic neurons and other neurons [2]. Thus, the nervous system and the immune system can interact not only through the hypothalamic-pituitary-adrenal axis, whose activation leads to the synthesis of corticosteroids that inhibit the immune response, but can also do so through neuronal circuits at the central level through the autonomic nervous system (ANS), both sympathetic and parasympathetic, which, through sensory and effector circuits, transmit impulses that reflexively induce the implementation of an anti-inflammatory response. In physiological conditions, the sensory and afferent fibers of the ANS travel in the vagus nerve from the peripheral tissues to the CNS to provide information about tissue function or, on the contrary, about the existence of injury within tissues that leads to the development of a cytokine-induced inflammatory process. The afferent sensory stimulus triggers a response in the CNS that includes the signs and symptoms of the disease and the efferent sympathetic pathway, called the cholinergic anti-inflammatory reflex, which, through the vagus nerve, inhibits the synthesis of pro-inflammatory cytokines and thus limits or prevents tissue damage produced by these mediators.

Pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, produced during the activation of innate immunity cells in peripheral tissues, are able to modulate the activity of CNS neuronal circuits through specific receptors expressed by neurons of the hypothalamus and other regions of the brain. In this way, a response is characterized by the transmission of action potentials that trigger local and systemic symptoms and signs of the disease syndrome, which are then controlled by the cholinergic and anti-inflammatory vagal route. This CNS response leads not only to control the progression of the inflammatory process in the peripheral tissue but also to prevent eventual immune-mediated tissue damage. Thus, the immunological activation of this neuronal circuit confers protection against tissue damage by inhibiting the release of cytokines during infection, autoimmunity, shock, and other inflammatory syndromes in the CNS.

Parkinson's disease is a neurodegenerative disease characterized by an early loss of dopaminergic neurons in the substantia nigra pars compacta, located in the basal ganglia. The resulting deficiency of dopamine leads to a movement disorder characterized by classic motor symptoms (rigidity, resting tremor, bradykinesia, and postural instability), as well as non-motor symptoms which may often appear even years before the diagnosis of the disease. The gold standard for the diagnosis of PD is still an autopsy demonstrating degeneration of the substantia nigra and, in most cases, evidence of Lewy bodies (abnormal aggregates of  $\alpha$ -synuclein protein). The association between Lewy pathology and the pathogenesis of the disease is poorly understood and is not limited to the brain, but it can also be found in the spinal cord and peripheral nervous system (including the vagus nerve, sympathetic ganglia, cardiac plexus, enteric nervous system, salivary glands, adrenal medulla, cutaneous nerves, and sciatic nerve). Moderate loss of neurons of the substantia nigra is also present in early stages of the disease. In addition, neuronal loss in PD occurs in many other brain regions including the locus coeruleus, Meynert's basal nucleus, pedunculopontine nucleus, raphe nucleus, dorsal motor nucleus of the vagus, amygdala, and hypothalamus [3]. Hence, the varied symptomatology of the disease is now conceptualized more like a syndrome than as a disease itself.

Commonly, deterioration of the sense of smell is one the earliest symptoms of PD. It usually manifests as a partial reduction in the ability to discriminate or perceive odors, and this occurs due to changes in the  $\alpha$ -synuclein protein of the dorsal motor nucleus of the vagus and olfactory bulb [4, 5]. On the other hand, a prospective study showed that 40 of 78 relatives of patients with PD had hyposmia at the start of the study, and 4 of them developed the disease after 2 years [6].

Mood disorders such as anxiety, depression, and personality changes have often been linked to early stages of PD. In fact, depression is a major contributor to poor quality of life, future disability, and average survival to the disease [7]. Depression has been linked to multiple neurotransmitter dysfunctions, including dopamine, serotonin, and noradrenaline. About 35% of the patients with PD had clinically significant symptoms of depression over the course of the disease, and depressive symptoms precede motor symptoms in 30% of the patients. The incidence of depression appears to increase during the last few years prior to the diagnosis of PD. In addition, more than 30% of the patients have cognitive impairment in the early stages of the disease. In early stages, the cognitive impairment is mild, is non-amnesic, and has a frontal subcortical pattern, whereas the progress toward dementia is due to the damage to the posterior cortical areas. Alterations of working memory and difficulties understanding complex grammatical structures may also be present [8].

Sleep disorders such as excessive daytime sleepiness or rapid eye movement (REM) sleep behavior disorder (RBD) are commonly identified even many years before the diagnosis of the disease has been made. In RBD, the subject loses the characteristic atony of the REM phase in which all body muscles except for the ocular muscles are paralyzed. These patients make body movements in apparent response to the content of their dreams. It has been demonstrated that over 50% of the people with RBD will develop the disease in a period of 10–15 years [9]. Therefore, many authors argue that RBD is by far the strongest available clinical predictor of neurodegenerative disease associated with  $\alpha$ -synuclein accumulation in the brain. Other early symptoms are gastrointestinal problems such as reduced intestinal transit, constipation, and changes in the intestinal microbiota. These symptoms have been observed as early as 20 years before the onset of the motor symptoms [10, 11].

Excess saliva, which often causes drooling, has been recognized as a feature of the disease since James Parkinson initially described the syndrome in 1817. Although it is not a dangerous symptom, it can be embarrassing in the social context and thus became very annoying for the patient and the caregivers. Interestingly, this problem is not due to saliva overproduction, since people with PD usually generate less saliva than normal [12]. Bladder control dysfunction is another autonomic dysfunction found in PD patients, probably caused by brain stem deterioration.

## 2. Physiology of the basal nuclei

The functional organization model of the basal nuclei assumes that the connections between the basal nuclei (BN), the cerebral cortex, and the thalamus form parallel and separate circuits. The sensory-motor and association areas of the cerebral cortex send glutamatergic excitatory projections to the sensory-motor and associative regions of the striatum, which projects through two striatal pathways to the exit of BN (globus pallidus internus (GPi)/globus pallidus externa (GPe) and substantia nigra pars reticulata (SNR)). The direct pathway, which facilitates the initiation and execution of voluntary movement, originates from the inhibition through gamma-aminobutyric acid (GABA) and substance P (SP) of the inhibitory striatal neurons, thus triggering the thalamus disinhibition. In the indirect pathway, the activation of the inhibitory striatopallidal projections, through GABA and enkephalins, suppresses the activity of GPe neurons, thus inhibiting the subthalamic nucleus (STN). The STN reaches the thalamus through glutamatergic projection. Therefore, when activated, it produces an excitatory action. Its inhibition through the GPe in the indirect pathway in turn increases its inhibition over the thalamus. In addition, the high discharge frequency of most pallidal neurons exerts a tonic inhibition on the STN.

During the execution of a specific motor act, movement-related neurons in the GPi/GPe and SNR present a phasic increase or decrease in their spontaneous discharge frequency. The phasic decrease plays a crucial role in motor control by inhibition of the ventral lateral (VL) nucleus of the thalamus, facilitating cortical initiated movements, and the phasic increase seems to have the opposite effect. The direct and indirect pathway inputs on the GPi/GPe and the SNR neurons are not fully described. However, it is possible that the direct and indirect inputs that are selectively and cooperatively activated, in relation to a cortically initiated movement, can be directed to the same group of neurons. This enables the entrances of the indirect pathway to downregulate a movement that was reinforced by the direct pathway. Another possibility is that the inputs of the direct and indirect pathways associated to a specific movement are directed to different neuronal groups, playing a double role in the cortical modulation of movement by reinforcing a selected motor model by the direct route and suppressing a conflictive one by the indirect pathway. The nigrostriatal dopaminergic projection exerts opposing effects on the striatal efferent pathways. It seems to have an excitatory effect on the striatal neurons of the direct pathway and an inhibitory effect on the indirect pathway. Thus, the action of the DA on the striatum reinforces the cortical activation of the circuit, facilitating the conduction through the direct pathway which has

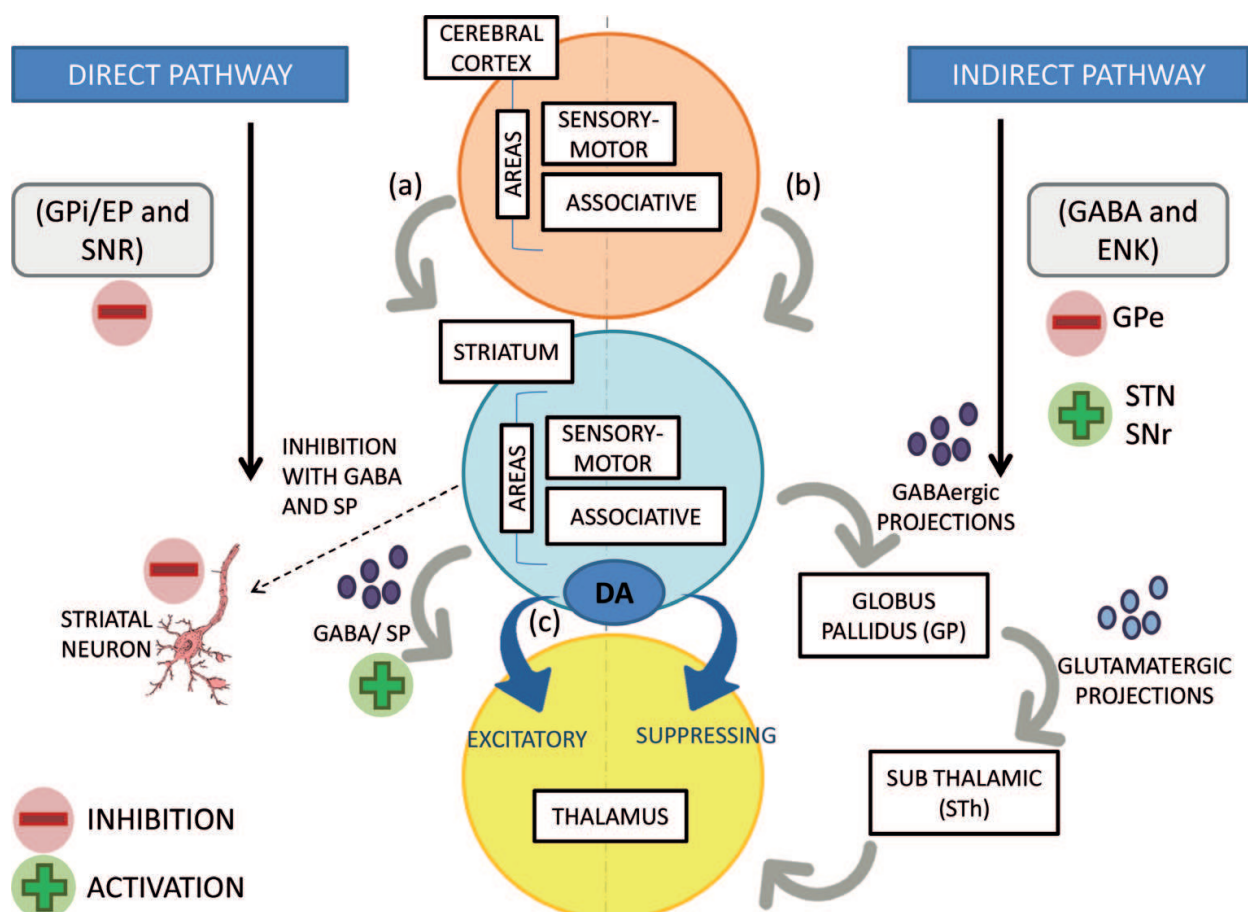


an excitatory effect on the thalamus and suppressing conduction through the indirect pathway that has an inhibitory effect on the thalamus (**Figure 1**) [13].

## 2.1. Basal nuclei and the movement control

Basal nuclei are part of the cortico-subcortical circuits involved in the programming and execution of movement, as evidenced by the profound alterations in movement in the diseases in which BN are affected [14]. A number of studies have been published on the action of the various neurotransmitters integrated in the BN and their specific role. These studies have helped to understand the role of neurotransmitters involved in the organization of movement as well as the interactions of each of the nuclei that form part of the BN [15–18].

The striatum is one of the main structures involved in the rotational behavior; it receives an important afferent projection of the neurons and through the nigrostriatal pathway reaches



**Figure 1.** Physiology of basal nuclei (direct and indirect pathways). Functional organization of the basal nuclei has lead to the postulation of a model assuming connections between cerebral cortex, thalamus and basal nuclei. (a) direct pathway is originated by inhibition of striatal neuron with GABA and SP, their activation leads to a disinhibition of the thalamus. (b) the indirect pathway (inhibitory with GABA and ENK) reaches first to (GP) through a GABAergic projection then to STh through a glutamatergic projection. (c) the action of the DA on the striatum reinforces the cortical activation of the circuit, facilitating the conduction of the “direct path”, which has an excitatory effect on the thalamus or suppressing conduction through the “indirect pathway” that has an inhibitory effect on the thalamus.

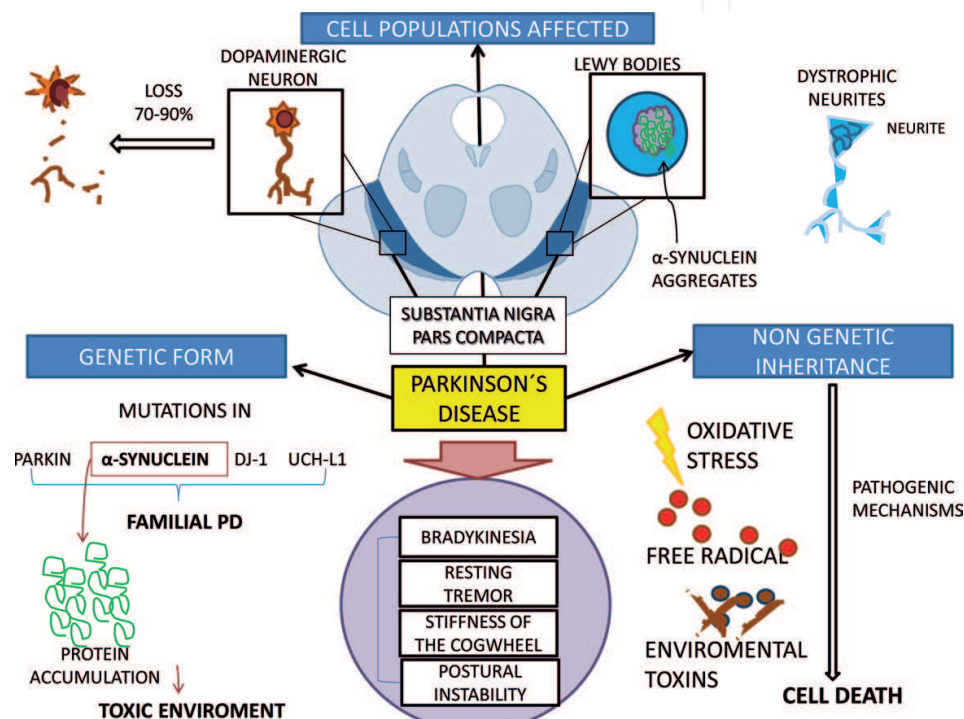
the GABAergic neurons of the SNR. The rotational behavior is influenced by the CNS dopaminergic and the SNR GABAergic neurons [19]. Posture control is also attributed to the nigrostriatal dopaminergic neurons of the CNS and the non-dopaminergic neurons of the SNR. The unilateral lesion of the nigrostriatal projection with 6-hydroxydopamine produces a dramatic asymmetry with a tendency of the animal to rotate toward the injured side (homolateral rotation). On the other hand, unilateral electrolytic lesions of the SNR induce a rotation preference toward the uninjured side (contralateral rotation), indicating the existence of non-DA neurons that originate from or across the SNR. Unilateral injection of SNR with kainic acid produces spontaneous contralateral rotation, maintaining a relative integrity of the CNS and a low reduction of serotonin but a marked decrease of glutamic acid decarboxylase and catalase in the striatum, which suggests that kainic acid damages the non-dopaminergic (GABAergic and cholinergic) neurons of the SNR. Unilateral intra-nigral injection of ethanolamine-O-sulfate, which produces an endogenous GABA accumulation within the neuron by blocking the enzyme GABA transaminase, also produces contralateral rotations similar to those produced by kainic acid. This suggests that the destruction of GABAergic neurons of the SNR would control rotations in a manner opposite to nigrostriatal dopaminergic neurons. The unilateral lesion of dopaminergic nigrostriatal neurons with kainic acid produces contralateral rotations independent of the action of nigrostriatal dopaminergic neurons which produces a decrease in neurons of the SNR. Thus, the non-dopaminergic neurons of the SNR control rotations and posture in a manner opposite to dopaminergic neurons [19].

Unilateral pedunculopontine tegmental nucleus (PPTg) injury is associated with rotational movement. The unilateral injection of GABA agonists into PPTg triggers rotation and contralateral postural asymmetry. Conversely, injection of GABAergic antagonists has the inverse effect. The stimulation of PPTg with kainic acid produces homolateral rotations which can be blocked by haloperidol (DA antagonist),  $\alpha$ -methyl tyrosine (TH blocker that reduces neuronal dopamine and norepinephrine), and bilateral atropine injections. These data suggest cholinergic-dopaminergic interactions. In unilateral kainic acid lesions in PPTg, slow rotations occur in response to systemic amphetamine: unilateral quinolinate lesions in the PPTg produce a slight homolateral inclination in response to systemic amphetamine. However, bilateral quinolinate lesions have no effect on locomotor activity. On the other hand, lesions of ibotenate produce a slight contralateral inclination with amphetamine. These effects may be due to a loss of a large number of cholinergic and a smaller number of non-cholinergic PPTg neurons after injury with ibotenate [20].

## 2.2. Basal nuclei and Parkinson's disease

The observation that Parkinsonian patients have difficulties initiating movement led to the hypothesis that BN are involved in the automatic execution of learned movements [21]. There are two categories of motor disorders produced by BN alterations: hyperkinetic and hypokinetic. The hypokinetic motor disorders include bradykinesia, akinesia, and/or rigidity. PD is the prototype of the hypokinetic disorders since it is characterized by bradykinesia, increased muscle tone, and slow spontaneous movements [21]. Parkinson's disease is a variable combination of certain signs attributable to BN dysfunction, for which there is no apparent etiology

[22, 23]. The main pathophysiological findings in PD are the degeneration of neuronal bodies (greater than 80%) and an anterograde loss of ascending nigrostriatal axons and of its terminal ramifications reaching the putamen and caudate, which causes a reduction of DA and a significant loss of the dopaminergic neurotransmission. Therefore, the signs of PD are due to a deficiency of DA in BN. Although there are other biochemical alterations, their contribution to the signs and symptoms of PD is unknown [22–25]. But, what causes those neurons to die? Currently, four possible culprits are involved in neuronal loss: (1) excessive free radical production, (2) environmental toxins, (3) premature aging of neurons, and (4) hereditary factors (Figure 2).



**Figure 2.** General pathophysiology of Parkinson's disease. Classic symptoms of PD includes bradykinesia, resting tremor, stiffness of the cogwheel and postural instability manifested only when 70–90% of the dopaminergic neurons have been lost in the pars compacta, also the presence of Lewy bodies (containing eosinophil inclusions containing an aggregated  $\alpha$ -synuclein center, along with other proteins and an area of radiated fibers) and dystrophic neurites are associated with pathological mark of PD. Approximately 10% of patients have a familial PD, with a defined genetic component. mutation in genes,  $\alpha$ -synuclein, parkin (a ubiquitin E3 ligase involved in the degradation of multiple compounds), and DJ-1 (its role is not clearly defined but would be compensatory during oxidative events) are associated with early onset PE, and mutations in UCH-L1 (carboxyl-terminal ubiquitin hydrolase L1, with beneficial activity as hydrolase, but also with potentially harmful ligase activity). in patients without a clear genetic inheritance, pathogenic mechanisms have been more difficult to understand, and a number of factors, including environmental toxins, oxidative stress, and mitochondrial dysfunction.

### 3. General pathophysiology of Parkinson's disease

The classic symptoms of PD (bradykinesia, resting tremor, cogwheel stiffness, and postural instability) are manifested only when 70–90% of the dopaminergic neurons have been



lost in the substantia nigra or when 50% of the nigrostriatal synapses are lost. In addition, extensive extranodal pathology is also observed indicating that other cell populations are also susceptible to neurodegeneration. The presence of Lewy bodies and dystrophic neurites is associated with neurodegeneration and constitutes a pathological distinguishing feature of PD. Lewy bodies consist of rounded eosinophil inclusions which contain an aggregated  $\alpha$ -synuclein center surrounded by other misfolded proteins and an area of radiated fibers. The distribution pattern of these structures correlates with the severity of neurodegeneration. However, not all forms of PD contain Lewy bodies, and, as mentioned later, mutations that affect other proteins such as Parkin generally lack them.

Although only 10% of the patients have familial PD in which a defined genetic dysfunction is identified, this group of patients has allowed us to study the specific risk factors associated with the disease. Mutations in three genes:  $\alpha$ -synuclein, parkin (a ubiquitin E3 ligase involved in the degradation of proteins), and DJ-1 (inhibits the aggregation of  $\alpha$ -synuclein via its chaperone activity and thus protects neurons against oxidative stress) are associated with early onset PD [26–29]. Mutations in the ubiquitin carboxy-terminal hydrolase (UCH-L1) gene are implicated in the pathogenesis of PD. The UCH-L1 protein has hydrolase activity that is protective against neuronal degeneration but also has a potentially harmful ligase activity [30].

$\alpha$ -Synuclein appears to be strongly related to the etiology of PD. The expression of mutant  $\alpha$ -synuclein produces the accumulation of aberrant protein that causes severe neuronal toxicity. However, an elevation of the normal “wild”  $\alpha$ -synuclein protein is sufficient for the development of PD [31]. This suggests that aberrant metabolism of wild-type  $\alpha$ -synuclein could be the cause of the loss of dopaminergic cells in patients who have the nonfamilial form of PD. Although, the idea of establishing  $\alpha$ -synuclein as the main etiologic factor implicated in PD is attractive, caution should be taken because in the studies that have been done that the  $\alpha$ -synuclein region also contained another 17 additional genes that could have certain participation in the pathogenesis of PD [32].

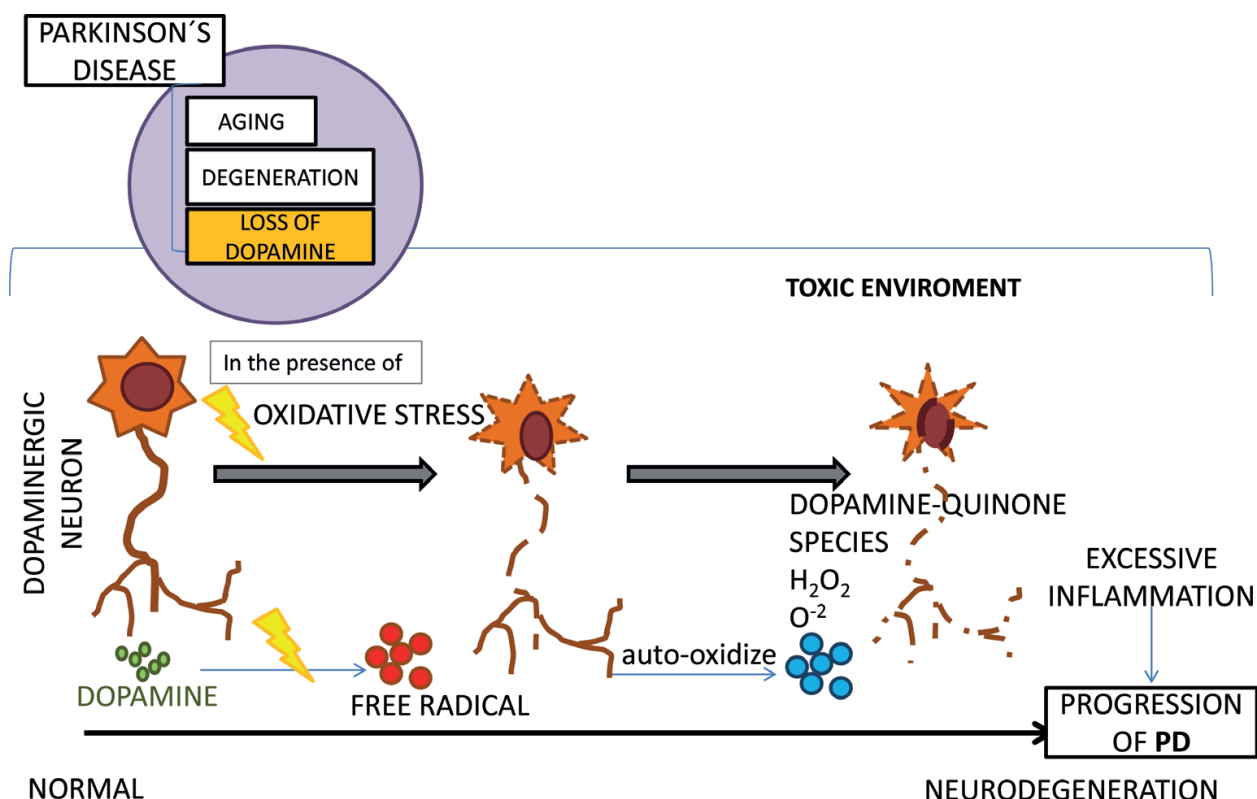
In vitro studies suggest that prefibrillar assemblies represent toxic species of  $\alpha$ -synuclein and that a homogenous population of fibrils, rather than their precursor on-assembly pathway oligomers, is highly toxic to cells. Fibrils have been shown to permeabilize membrane vesicles and to alter calcium homeostasis. Moreover, cells exposed to increasing concentrations of fibrils resulted in the activation of caspase-3 in a concentration-dependent manner and cell death [32, 33]. These inclusions, especially if they are large, may potentially alter intracellular traffic or other functions, leading to cell death. It has been shown that the protofibrillar form of  $\alpha$ -synuclein transiently makes the membranous vesicles permeable and thus alters intracellular homeostasis, which predisposes to cell apoptosis [34]. In experimental models of PD, overexpression of  $\alpha$ -synuclein can kill selectively dopaminergic neurons. Studies using  $\alpha$ -synuclein viral transfection have shown that dopaminergic neurons are considerably more vulnerable to cellular apoptosis than non-dopaminergic neurons in substantia nigra [35, 36]. It has been shown that  $\alpha$ -synuclein toxicity is increased by the generation of oxygen radicals in the presence of dopamine [37] and that dopamine, in vitro, favors the formation of  $\alpha$ -synuclein adducts [38].

#### 4. Parkinson's disease and proteasome

In PD,  $\alpha$ -synuclein-rich Lewy bodies are almost certainly the result of inefficient removal of  $\alpha$ -synuclein. The formation of Lewy bodies would depend on the balance between the tendency of  $\alpha$ -synuclein to aggregate spontaneously and the ability of cells to remove the protein before it reaches its critical concentration [39]. It should be borne in mind that Lewy bodies can represent a defensive response of the organism, whose aim is to avoid the inherent cytotoxicity of the compounds that accumulate in them. Although the connection between poorly folded protein aggregates and neuronal damage is still incomplete, there is evidence in PD, and in other neurodegenerative pathologies, that alteration in the removal of damaged proteins is part of the pathological process. Under physiological conditions the cellular proteins are destined to be destroyed through of the heat-shock proteins (HSPs) and the ubiquitin-proteasome system [40]. These two systems ensure that poorly folded proteins are quickly eliminated. The HSPs targets the proteins to be degraded both by the lysosomal pathway and the proteasome pathway, whereas ubiquitin represents the major proteasome pathway. The ubiquitination is a highly ordered process in which ubiquitin molecules are attached to the lysine residues of a protein through a three-stage enzymatic process (E1–E3). The ubiquitin-tagged proteins are then degraded by the proteasome. Interestingly, proteasome activity in the CNS is reduced in patients with PD [41, 42], and  $\alpha$ -synuclein inhibits proteasome activity in a concentration-dependent manner [42]. It is proposed that an altered ubiquitin-proteasome system can sensitize specific cellular populations to exogenous stress. Studies in cells with alterations in protein folding suggest that dysregulation at the endoplasmic reticulum would be the downstream path responsible for cell death [43]. A reduced proteasome function can affect many cellular functions that normally depend on adequate protein degradation. Also, as previously mentioned, a reduction in the removal of protofibrillary  $\alpha$ -synuclein can be directly toxic since it could alter dopamine homeostasis and increase oxidative stress. In fact, experimental inhibition of the proteasome affects more the dopaminergic neurons than the GABAergic neurons [44].

#### 5. Is inflammation responsible for neurodegeneration in Parkinson's disease, or is it a simple response to neuronal death?

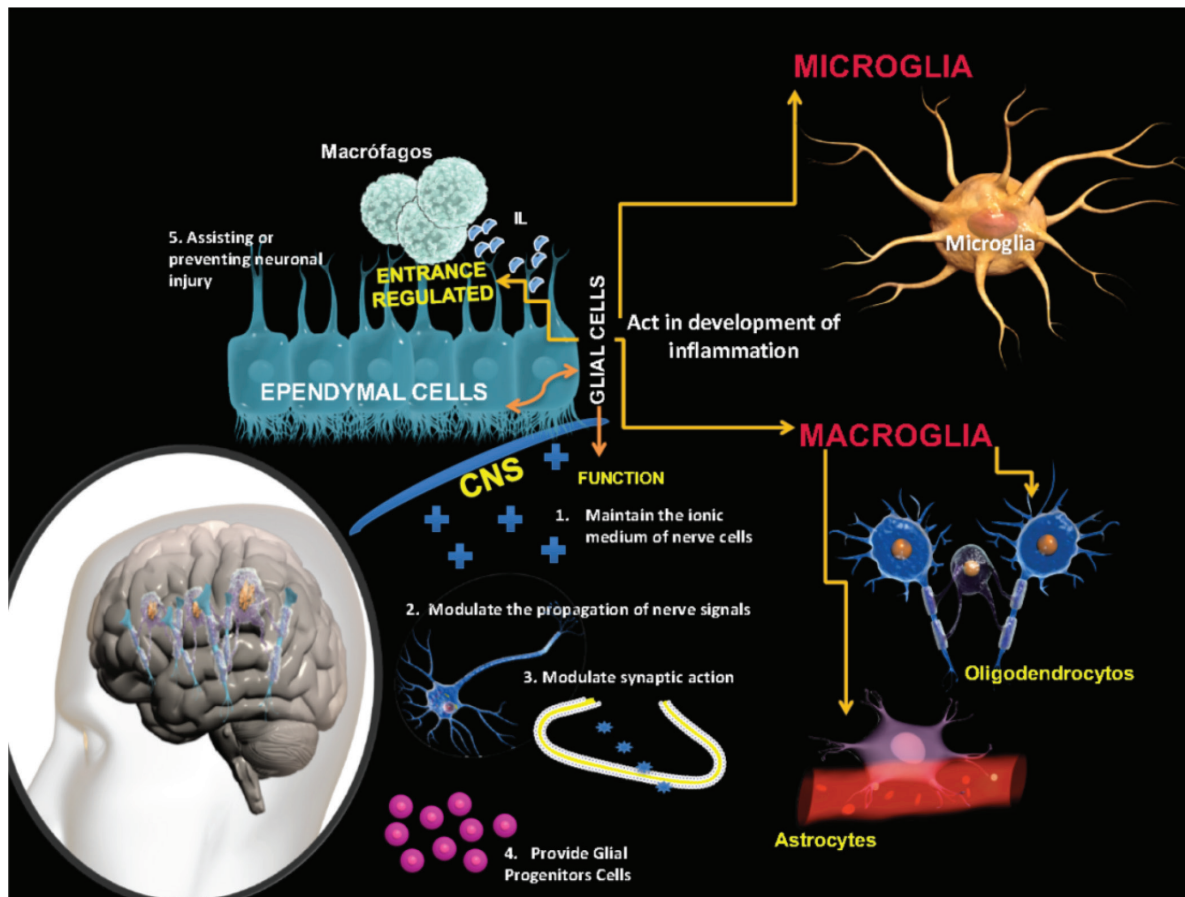
Recent studies demonstrate that excessive inflammation and overactivation of immune cells could play an important role in the onset and progression of this pathology [45]. One of the most striking aspects of neurodegenerative diseases (including PD) is the selective vulnerability of specific neuronal populations. For example, although  $\alpha$ -synuclein is expressed in extensive regions of the CNS, neurodegeneration is mainly restricted to the substantia nigra. Dopaminergic neurons are particularly exposed to oxidative stress because the metabolism of dopamine produces dopamine-quinone species, super oxide radicals, and hydrogen peroxide [46]. Dopamine can also be enzymatically deaminated by monoamine oxidase (MAO) into the nontoxic metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) and hydrogen peroxide [47]. Therefore, metabolism of dopamine can activate apoptotic cascades and neuronal death (**Figure 3**) [47].



**Figure 3.** Inflammation in Parkinson's disease. Dopaminergic neurons are particularly exposed to oxidative stress because the metabolism of dopamine causes a number of molecules that are potentially toxic if not properly removed. Dopamine behaves as a free radical generating compounds that can auto-oxidize to physiological pH forming toxic dopamine-Quinone species, super oxide radicals and hydrogen peroxide. This excessive toxic environment and inflammation can lead to the neurodegeneration and progression of the disease.

Accumulation of reactive oxygen species (ROS) is toxic per se due to the depletion of cellular antioxidants (e.g., vitamin E and reduced glutathione) which increases membrane lipid peroxidation, DNA damage, and alteration in protein folding [47]. In addition to general oxidative damage, there is evidence that the interaction between  $\alpha$ -synuclein and dopamine metabolites determines the preferential neurodegeneration of dopaminergic neurons. Abnormal protein aggregates may produce a chronic inflammatory reaction capable of inducing synaptic changes and neuronal death [48]. In fact, the existence of a chronic inflammation process includes the presence of astrocytes and microglial activation in the brain biopsies of PD patients, especially in the vicinity of the protein aggregates. Furthermore, the compounds released by damaged neurons can induce the production of neurotoxic microglial factors aggravating the neurodegeneration [49]. Neuromelanin is a secreted compound that forms neuromelanin-iron complexes which activate the microglia in vitro, resulting in the release of  $TNF-\alpha$ , IL-6, and nitric oxide. An increase in total iron concentration in the substantia nigra has been reported in PD, although the underlying mechanism is not understood [49]. Accelerated  $\alpha$ -synuclein aggregation in turn may induce the formation of more ROS, and when the dopaminergic neurons are within an oxidative environment, the  $\alpha$ -synuclein accumulation is increased, thereby generating a vicious cycle that leads to neuronal death [50, 51].

Inflammation is a complex cascade of physiological responses to a harmful stimulus from the environment, and the CNS has a specialized immunity through the action of glial cells. Glial cells regulate the innate immunity, constituting the first line of defense whenever an injury or illness occurs. The activation of glial cells can be detected in a wide range of stimuli (**Figure 4**) [52]. Inflammation present in both acute injuries and chronic neurodegenerative diseases occurs in response to an alteration of the CNS, which triggers an innate immune response that activates glial cells (astrocytes and microglia) and stimulates the release of cytokines, chemokines, prostaglandins, complement cascade proteins, ROS, and RNS. An excessive and uncontrolled inflammatory response may be an additional source of damage to the integrity and function of neurons. Neural tissue has very restricted cellular regeneration which makes the CNS extremely vulnerable to immune and inflammatory processes. Inflammation contributes to neuronal loss in neurodegenerative diseases, but it is unknown how inflammation decisively contributes to the chronic progression of these diseases [49–52]. The involvement of glial cells in the inflammatory process and the processes that derive from the activation of these cells are described below.



**Figure 4.** Role of Glia in the inflammatory response. The classification of glia is divided into macroglia and microglia. Their functions are listed from 1 to 5, IL, interleukins; CNS, central nervous system. Pathway builder online tool was used to draw the figure. The original image may be found at [www.QIAGEN.com/es/shop/genes-and-pathways](http://www.QIAGEN.com/es/shop/genes-and-pathways) in conjunction with any use of the IMAGES, either on the IMAGES themselves or in close proximity to the IMAGES, such that QIAGEN's right in the original IMAGES shall be conspicuous.



### 5.1. The role of the glia in the inflammatory response

Glial cells react energetically to any immune stimulus or neuronal damage and play an active role in the development of inflammation. In general, glial cells are generally classified into two groups: microglia (astrocytes and oligodendrocytes) and microglia which have a mesodermal origin. Glial cells differ, do not have synaptic contacts, and have the ability to divide over a lifetime. The main functions of glial cells are to:

1. Maintain the ionic medium of neurons.
2. Modulate the rate of propagation of nerve signals.
3. Modulate synaptic action by controlling the uptake of neurotransmitters.
4. Provide a foundation for neural development.
5. Assist in (or prevent, in some cases) recovery from a neuronal injury [53].

### 5.2. Microglia

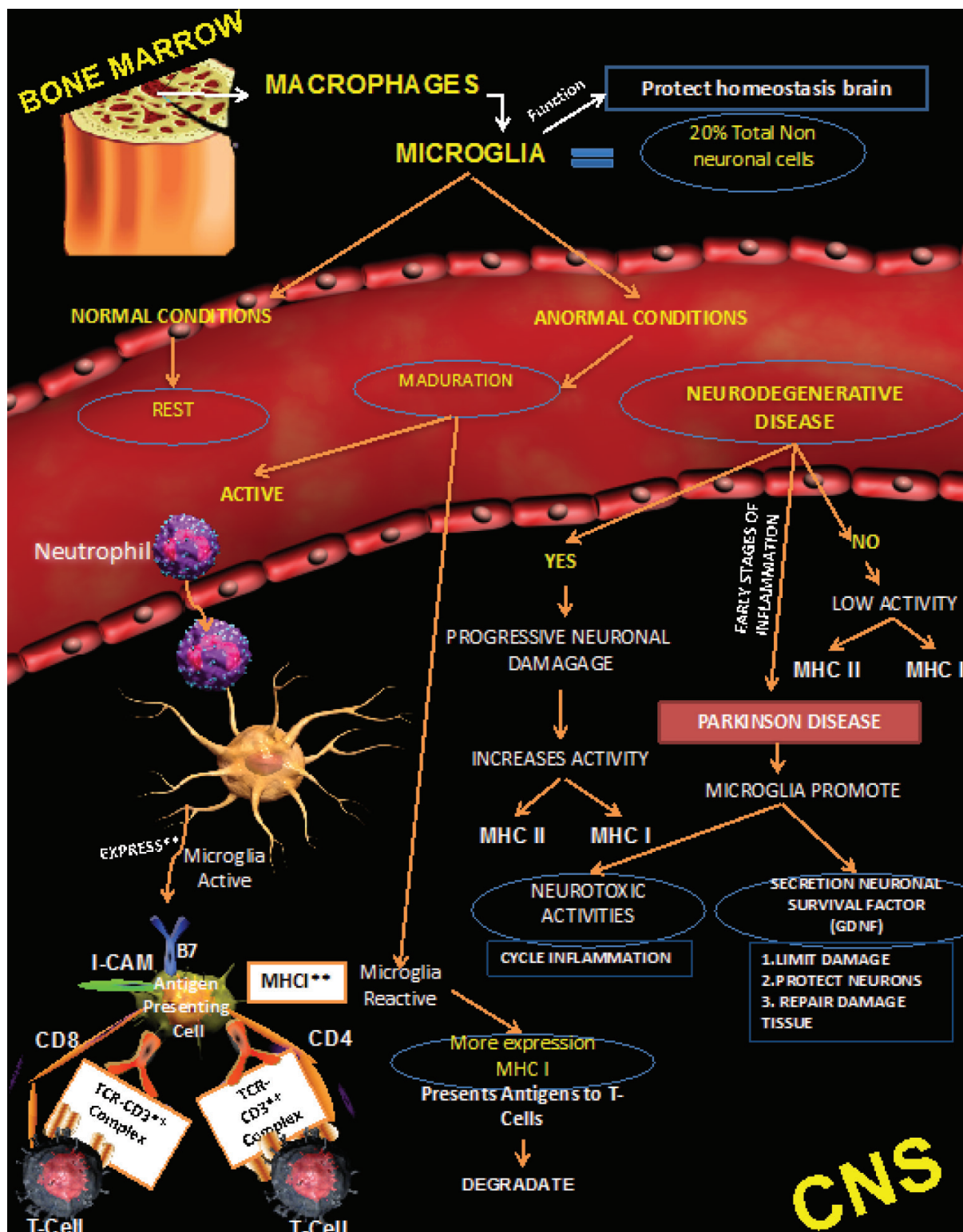
Microglia are specialized macrophages that represent about 20% of the total population of non-neuronal cells and are especially important to protect the integrity and homeostasis of the brain. Microglial cells are activated after an injury or infection (**Figure 5**). Once activated, it is subjected to maturation into two different states: the active and the reactive. The active microglial cells are characterized by being swollen and branched with a large cell body and short projections. They express CR3 complement receptors and histocompatibility complex class-1 (MHC-1). The reactive microglial cells are smaller, are spherical, and lack ramifications. The reactive cells, like macrophages, express the MHC-I and MHC-II and have the ability to present antigens to T. Under normal conditions, the expression of MHC-I and MHC-II is very low, but in almost all neurodegenerative diseases, its expression is increased [54].

The mechanism that regulates the function of microglia in PD is poorly understood. In the early stages of inflammation, the microglia promote secretion of neuronal survival factors such as glial-derived neurotrophic factor (GDNF), in order to limit damage and protect the population of vulnerable neurons of the central nervous system (CNS) and to stimulate the repair of damaged tissue [54]. Moreover, microglia promote neurotoxic activities by producing ROS, RNS, prostaglandin, chemokines, and cytokines. If microglial activation persists for long periods, it could lead to a lack of control of the inflammatory response that gives rise to a cycle of chronic inflammation [55]. Therefore, the microglial activation influences the extent of brain injury following an uncontrolled inflammatory stimulus. Chronic microglial activation is involved in the development and progression of PD [56].

### 5.3. Microglial cells and inflammation

Microglial cells release other inflammation mediators such as galectin-3, a protein which triggers an inflammatory cascade by binding to TLR3 receptor [57]. Under physiological conditions

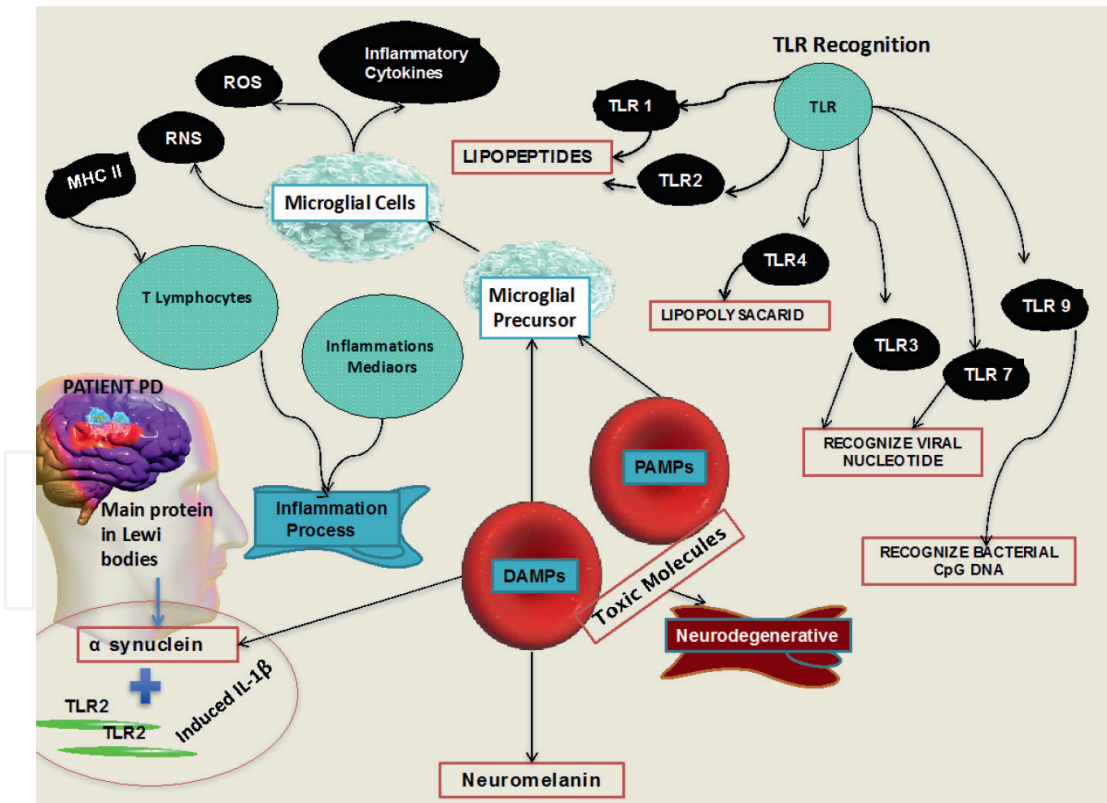




**Figure 5.** Parkinson and microglia. Activation and inactivation of microglia and its effects on Parkinson's disease. MHC, major complex histocompatibility; CD-8, cytotoxic T-cells; CD-4, helper T-cells; TCR-CD3, T-cell receptor of CD3; B7, protein; I-CAM, intercellular adhesion molecule; CNS, central nervous system. Pathway builder online tool was used to draw the figure. The original image may be found at [www.QIAGEN.com/es/shop/genes-and-pathways](http://www.QIAGEN.com/es/shop/genes-and-pathways) in conjunction with any use of the IMAGES, either on the IMAGES themselves or in close proximity to the IMAGES, such that QIAGEN's right in the original IMAGES shall be conspicuous.

damage-associated molecular patterns (DAMPs) are intracellularly sequestered molecules and are hidden from recognition by the immune system. However, under certain cellular stress or tissue injury, DAMPs can either be actively secreted by stressed immune cells or exposed on stressed cells, or they can be released into the extracellular environment from dying cells or the damaged extracellular matrix. DAMPs are recognized by pattern recognition receptor (PRR)-bearing cells of the innate immune system to promote pro-inflammatory pathways [56]. Neuromelanin and  $\alpha$ -synuclein are examples of DAMPs that activate microglia [57]. Recently, it has been demonstrated that  $\alpha$ -synuclein triggers Toll-like receptor (TLR) two in rat microglia and in human monocytes, causing interleukin-1 $\beta$  (IL-1 $\beta$ ) production (**Figure 6**) [58].

Monocytes are a heterogeneous cell population that can be characterized according to CD14 and CD16 expression [59]. In general, CD16<sup>+</sup> monocytes present a more pro-inflammatory profile than CD16<sup>-</sup> monocytes. The CD14<sup>+</sup>CD16<sup>+</sup> monocytes are increased in inflammatory diseases, indicating that imbalance in proportions of monocyte subsets can contribute to their pathogenesis [59]. Indeed, in patients with PD, alterations in cytokine receptor expression in CD16<sup>-</sup> monocytes suggest a preferential recruitment of this monocyte subset into the inflamed brain. Since DAMPs can trigger immune responses in the brain and in peripheral blood cells, circulating monocytes arise as important precursors of microglial cells [59].

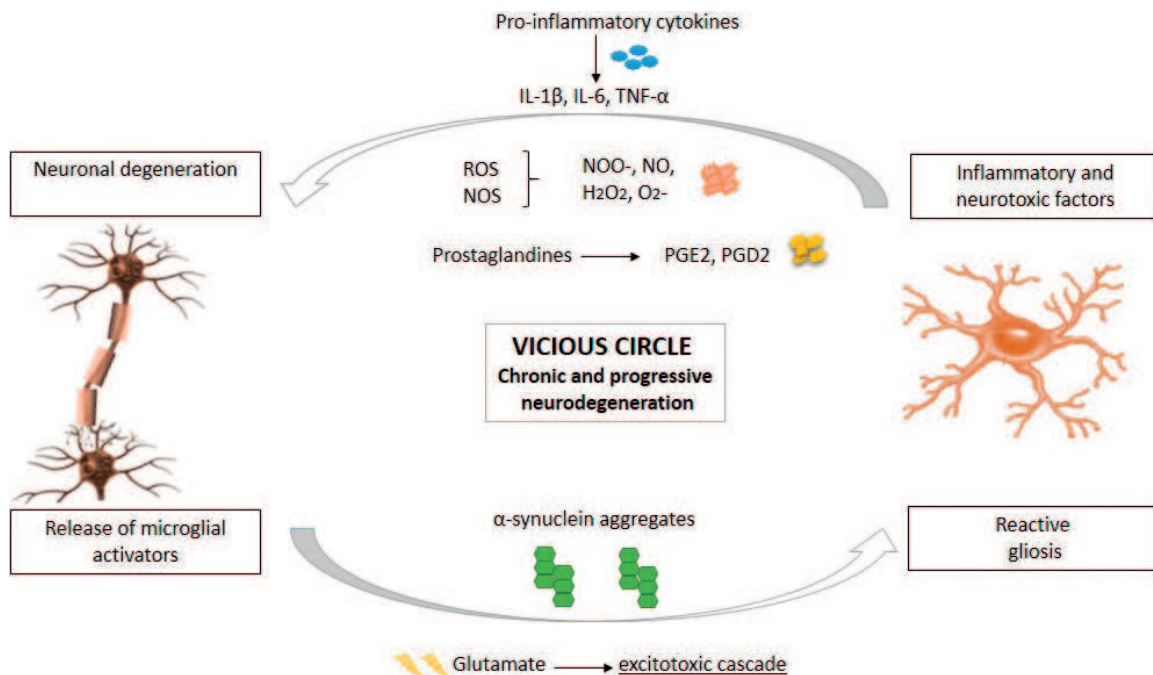


**Figure 6.** Microglia cells and PAMPs-DAMPs. The effect of PAMPs and DAMPs on neurodegeneration, its relation with toxic molecules, inflammation and tissue damage. PAMPs, pathogen associated molecular patterns; DAMPs, damage associated molecular patterns; MHC II, major complex histocompatibility II; RNS, reactive nitrogen species; ROS, reactive oxygen species; TLR, toll receptor 1 to 9; PD, Parkinson disease; IL-1 $\beta$ , interleukine-1 $\beta$ . Pathway builder online tool was used to draw the figure. The original image may be found at [www.QIAGEN.com/es/shop/genes-and-pathways](http://www.QIAGEN.com/es/shop/genes-and-pathways) in conjunction with any use of the IMAGES, either on the IMAGES themselves or in close proximity to the IMAGES, such that QIAGEN's right in the original IMAGES shall be conspicuous.

## 6. Lack of control in inflammation: the unresolved role of glial cells

The lack of control of the inflammatory cascade generates a vicious cycle that damages the neurons and is partially responsible of the progression of PD. Acute damage to the CNS can lead to neuronal degeneration. How does this initial damage to the neurons transform into a chronic and progressive neurodegeneration? It is postulated that damage to neurons triggers an uncontrolled signal in the glia to induce reactive gliosis, which further aggravates neuronal damage by releasing inflammatory and neurotoxic factors. Despite this, it remains unclear that it could boost inflammation in patients with Parkinson's disease—Parkinsonism. As a result of cellular damage, neurons consistently produce harmful compounds that are released into the extra-cellular medium that may be responsible for inducing the reactive gliosis. These compounds include membrane degradation products; processed, modified, or abnormally aggregated proteins; and altered or increased molecules such as the excitatory neurotransmitter glutamate which initiates the excitotoxicity cascade. These endogenous compounds activate the pattern of recognition receptors expressed in glial cells to activate an auto-amplifying inflammatory response. Therefore, the strict control of inflammation is lost, and, consequently, a vicious cycle is generated between the injured neurons and the uncontrolled inflammation (**Figure 7**).

One common pathway of these molecular and cellular events is the activation of microglial cells and astrocytes in specific regions of the brain. If protein aggregates cannot be removed, chronic activation of glial cells results in chronic neuroinflammation and oxidative stress [56].



**Figure 7.** Inflammation: a vicious cycle in Parkinson's disease. Chronic neuroinflammation is associated with the pathophysiology of Parkinson's disease. Neurotoxicity can generate a vicious cycle of cytotoxic and stimulatory factors that leads to microglial activation. Microglia enters in an overactive state in specific regions of the brain and release inflammatory and neurotoxic factors such as pro-inflammatory cytokines, reactive oxygen species (ROS) and reactive nitrogen species (NOS) that leads to gradual oxidative neurodegeneration of dopaminergic neurons and progressive neuronal loss over time.

Inflammation in PD causes a progressive degeneration of dopamine-secreting nigrostriatal neurons. Interestingly, chronic anti-inflammatory treatment with nonsteroidal anti-inflammatory drugs and/or dexamethasone significantly reduces the risk of developing PD [60].

7. Cytokines in Parkinson’s disease

Pro-inflammatory cytokines are low-molecular-weight mediators produced by both immunological and non-immunological cells, and they are key regulators of the innate and adaptive immune response [52]. In the brain, the main cytokines are TNF- $\alpha$ , IL-1 $\beta$ , IL-17, IL-6, transforming growth factor-beta (TGF- $\beta$ ), and the interferon-gamma family (IFN- $\gamma$ ) (Table 1). All of them act in a coordinated manner to modulate the inflammatory processes that affect the permeability of the blood-brain barrier [52, 61]. The IL-1 $\beta$  plays an important role in the development of acute neuronal lesions, since increased expression of IL-1 $\beta$  in the CNS is observed after brain damage [52, 60, 61]. Conversely, neuronal death is significantly reduced by IL-1 receptor antagonist [60].

Monocytes express TLR and produce pro-inflammatory cytokines (TNF, IL-1 $\beta$ , IL-6, and IL-12p70) and anti-inflammatory cytokines (IL-10) when TLR is triggered [56]. These cytokines seem to have a role in neuroinflammation in patients with PD. For example, increased levels of serum IL-6 and TNF receptor 1 have been found in patients with PD. It is known that monocytes are very sensitive to stimulation, and because of this whole-blood cell, cultures have been extensively used to evaluate their functions, especially regarding cytokine production. Due to a cross talk between immune cells in the CNS and the peripheral blood

Cytokine	Source	Function
Tumor necrosis factor-alpha (TNF- $\alpha$ )	Microglia, astrocytes, T lymphocytes	Endothelial cells activation, coagulation, inflammation, synthesis of acute phase proteins, endogenous pyrogen, apoptosis of many types of cells
Interleukin-1-beta (IL-1 $\beta$ )	Microglia, astrocytes, T lymphocytes	Endothelial cells activation, endogenous pyrogen, synthesis of acute phase proteins, neuronal death and damage
Interleukin-17 (IL-17)	Macrophages, endothelia, Epithelia, T lymphocytes	Induce and mediate pro-inflammatory responses, induces the production of other pro-inflammatory cytokines
Interleukin-6 (IL-6)	Microglia, astrocytes, Endothelial cells	Stimulatory of acute phase, increase proliferation of B lymphocytes
Interferon-gamma (IFN- $\gamma$ )	Macrophages, T lymphocytes	Activation of macrophages, Activates inducible nitric oxide synthase, promotes Th1 lymphocytes differentiation, antiviral effects
Interleukin-12 (IL-12)	Macrophages, dendritic cells	Increase differentiation of lymphocytes Th1, synthesis of IFN- $\gamma$ , increase cytotoxic activity

Table 1. Cytokine function in innate and adaptive immune response.



cells, the evaluation of the status of immune cell function in peripheral blood could unravel the participation of peripheral leukocytes in neuroinflammation. Thus, systemic immune alterations could be biomarkers of the level of neuroinflammation/neurodegeneration in PD, since DAMPs released during brain damage can modulate peripheral blood cell functions. Active astrocytes produce a variety of molecules (chemokines, eicosanoids, prostaglandins, and thromboxanes) [60] and nitric oxide. Therefore, astrocytes also play an important role in neurological disorders [62]. DJ-1, an abundant protein in the brain, is expressed primarily in astrocytes and has the following functions: transcriptional regulation, antioxidative stress reaction, chaperone, protease, and mitochondrial regulation, and its activity is regulated by its oxidative status. For example, the expression level of DJ-1 is increased under an oxidative stress condition, and excess oxidation of DJ-1, which renders DJ-1 inactive, has been observed in patients with sporadic PD [63].

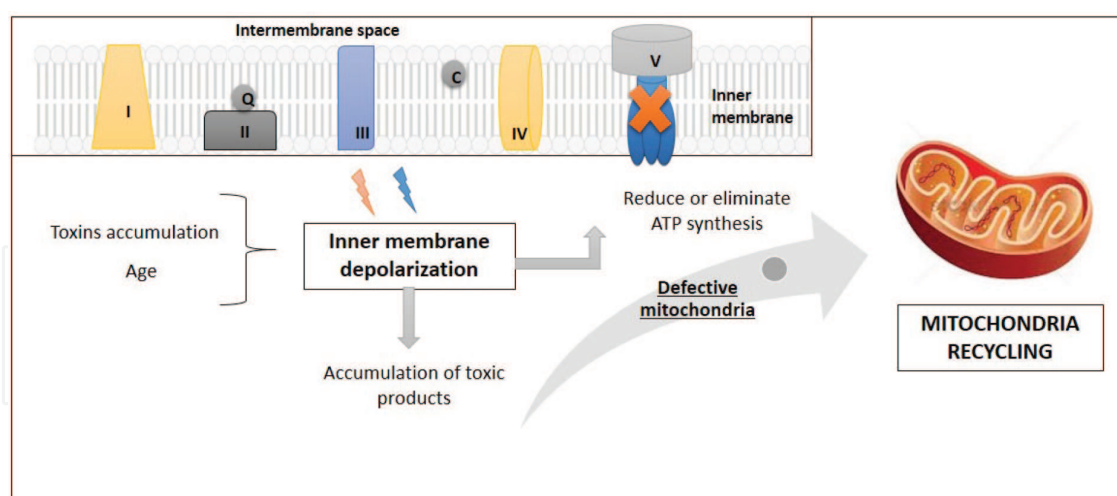
## 8. Role of mitochondria in Parkinson's disease

An oxidative stress sensor in the cells [64–75] is located within the mitochondria; therefore, the involvement of this organelle is crucial in the pathogenesis of PD. For instance, in sporadic forms of PD, the activity of the oxidative phosphorylation pathway, especially the complex I, is strongly reduced [72]. The 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and rotenone are two environmental toxins which have shown selective degeneration of the nigrostriatal pathway through the inhibition of complex I in the mitochondria [73]. Its acidic isoform accumulates after oxidative stress indicating that DJ-1 limits cellular toxicity [74].

On the other hand, leucine-rich repeat kinase 2 (LRRK2), a large multifunctional (286 kDa) protein which appears to be expressed in most of the brain regions, is very abundant in the outer membrane of the mitochondria [76]. The LRRK2 kinase domain belongs to the mitogen-activated protein kinase subfamily. It has multiple functions which include binding to substrates, protein phosphorylation, and regulation of protein-protein interactions. The mutations most frequently observed in the family study of Parkinson's disease within the Roc and kinase domains are the substitutions affecting the microarrays of high density of SNP's 40 codons R1441, G2019, and I2020. From epidemiological studies it has been deduced that the mitochondria are at the epicenter of the complex pathophysiological pathway of PD [77, 78]. An approximate 35% deficiency was found in the activity of complex I in the CNS [79], and this enzymatic defect was also identified in the platelet mitochondria of patients with PD [80–82]. Mitochondria are the energy powerhouse of the cells, producing through the oxidative phosphorylation system the adenosine triphosphate (ATP). The functions of mitochondria as energy producers lie in their ability to keep their inner membrane polarized. Such electrochemical potential difference is exploited by mitochondrial ATP synthase to produce ATP. When mitochondria age, or are affected by certain toxins, their inner membrane is depolarized and thus incapable of generating energy. Then, the cells eliminate these mitochondria (**Figure 8**).

Phosphatase and tensin homolog-induced putative kinase 1 (PINK1) protein is mutated in some forms of familial PD. It is usually located on the outer membrane of the mitochondria. Following





**Figure 8.** Mitochondrial cycle of renewal. Mitochondria is critical for cell survival due to their role in energy metabolism. Accumulation of toxins and aging leads to changes of the inner membrane permeability, causing depolarization, uncoupling of oxidative phosphorylation, release of intramitochondrial ions and metabolic intermediates. Mitochondria's are incapable of generating energy and they have to be eliminated and replaced by new ones.

depolarizing treatment, the cell responds by increasing the amount of PINK1 in the mitochondria. PINK1 seems to play an essential role in mitochondrial turnover because if cells do not produce PINK1, or produce mutated PINK1, they are unable to remove the depolarized mitochondria. Accumulated damaged mitochondria can generate or leak molecules such as ROS. It is also known that there is a relationship of PINK1 with parkin, a protein that has also been associated with PD. Parkin is a protein of the cytoplasm that is carried to the mitochondrial membrane when this organelle is depolarized. This protein is only recruited when there is non-damaged PINK1 within the mitochondria, which indicates that there is a link between PINK1 and parkin in the maintenance of healthy mitochondria. There is a cooperative work between PINK1 and parkin in the molecular tagging of the mitochondria that must be eliminated. In fact, it has been shown that mutated forms of parkin prevent the translocation of PINK1 protein to the mitochondria, which limits the initiation of autophagy, once again demonstrating the relationship of the tandem PINK1-parkin in the mitochondrial recycling [83]. That recycling could be done through macro-autophagy, a cellular catabolic process in which cytosolic components are degraded and take place in situations of nutrient shortage or toxic stress.

Experimental models offer an explanation capable of including many of the potential causes for the development of Parkinson's disease, including the mitochondrial failure, the presence of environmental toxins, the genetic load, and the processes of oxidative stress and inflammation associated with aging. These models offer possible therapeutic targets that can significantly improve the prognosis and treatment of PD.

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