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Review

Differential roles of M1 and M2 microglia in Parkinson's disease: a critical narrative review

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Abstract: Parkinson's disease (PD) is marked by the selective loss of dopaminergic neurons, leading to debilitating motor and non-motor symptoms. Central to PD pathogenesis is the intricate involvement of microglia, the resident immune cells of the brain. This narrative review delves into the distinct functions of M1 and M2 microglia in the context of PD. M1 microglia exhibit pro-inflammatory characteristics, releasing cytotoxic factors that exacerbate neuronal damage. In contrast, M2 microglia contribute to neuroprotection by secreting anti-inflammatory cytokines and participating in the clearance of cellular debris. The dynamic interplay between these microglial phenotypes is explored, providing insights into their roles in disease progression. Emerging therapeutic strategies aimed at modulating microglial polarization are discussed, emphasizing their potential in PD intervention. By unraveling the nuanced contributions of M1 and M2 microglia in PD, this review not only advances our understanding of neuroinflammatory mechanisms but also underscores the importance of targeted interventions to alleviate disease-associated pathology and preserve neuronal integrity in Parkinson's disease.

Keywords: Parkinson disease; Microglia; Neurodegenerative disease.

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1. Introduction

Parkinson's disease (PD) is determined by the impairment of the dopaminergic system in the pars compacta of the substantia nigra. As a result, the dopaminergic neurotransmitter is nullified, causing motor symptoms such as bradykinesia, resting tremors and postural instability [1]. The pathogenesis of PD involves neural inflammation that leads to CNS degeneration. This process occurs through pro-inflammatory cytokines, microglial activation, immune responses to pathogens and neural damage [2]. In support of this, microglia perform the clearance of excess tissue and neuronal compounds, dynamic relationship with neurons, along with synaptic pruning and control of brain homeostasis [3].

In this sense, microglia are activated when presented with neural inflammation. Once activated, these cells divide into categories, including M1 and M2. Both act in the neuroinflammation process, but their functions are antagonistic. M1 (classical) causes neurotoxicity and inflammation, while M2 (alternative) causes neuroprotective and an-

ti-inflammatory action [4]. Therefore, oxidative stress and neuroinflammation are common foundations for the onset and progression of PD [5]. The actions of each microglia are carried out through the release of cytokines [6]. In addition, the polarization of these cells occurs through the expression of Toll-Like Receptors (TLR2 and TLR4) [7]. In the progression of PD, inflammatory microglia stimuli (cytokines) and excess alpha-synuclein develop the pro-inflammatory signaling cascade [3].

In summary, the modulation of M1/M2 polarization in neurodegenerative diseases has been the subject of many studies [4]. In addition, there is a strong relevance of microglial transcription in PD [3]. In this article, the roles of M1 and M2 in PD will be addressed. Including their functions in neuroinflammation, because of the response to the breakdown of homeostasis.

2. Material and methods

A narrative literature review was carried out in the Medline (PubMed) database, from 2011 to 2023, on Parkinson's disease and microglia polarization. In the Medline (PubMed) database, 96 articles were found using the Mesh descriptor "(Parkinson's disease) AND (microglia polarization)", of which 69 were included, after excluding articles that followed the first set of criteria - exclusion of articles not included in the 2018-2023 search period, as well as articles that were not originally in English. In addition, using the same database, 23 articles were found using the Mesh descriptor "(Parkinson's disease) AND (Microglia) AND (Neurodegeneration)".

3. Discussion

3.1. The Role of Microglia in Parkinson's Disease

The actions of each microglia are carried out through the release of cytokines. M1 releases interleukin-6 (IL-6), interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), while M2 releases IL-4 and IL-10 [6]. In the pathogenesis of PD, unusual processing of M1 and M2 may occur, leading to an imbalance of dopaminergic neurons [8]. The pro-inflammatory signaling cascade is triggered by the binding of TLR4 to complexes such as myeloid differentiation factor adapter protein 88 (MyD88), tumor necrosis factor receptor (rTNF), transforming growth factor β-activated kinase-1 complex (TAK1), nuclear factor kappa-B (NF-kB) and by mitogens (MAPK). The latter two are responsible for pro-inflammatory pathways [4, 9].

Another signaling pathway is TLR2, which is determined as a critical moderator of inflammation in the brain, since it is capable of recognizing protein clusters such as β-amyloid (Aβ) and α-synuclein, together with evidence of endogenous damage. Therefore, negative damage through the stimulation of TLR2 in the integrity of neuronal activity and activation of microglia is justified [10].

3.2. Gut-Brain Axis in Parkinson's Disease

Motor disorders and mild to severe cognitive impairments are common in PD patients, however, they can also develop intestinal symptoms. The enteric nervous system (ENS) and the CNS have a bidirectional communication, since α-synuclein has concentrations present in peripheral sites, supporting the "gut-brain axis" [11]. In addition, there is a correlation between the gut-brain and the branches of the parasympathetic and sympathetic autonomic nervous system (ANS), neuroendocrine and neuroimmunological signaling pathways. This communication occurs via visceral feedback from the intestinal pathway to the spinal cord (specifically thoracic and upper lumbar), as well as via the spinal sensory, vagal, and afferent nerves to the nucleus of the solitary tract [12].

Given this situation, the nerves mobilize polysynaptic accesses to the hypothalamus and limbic forebrain. Thus, there is a change in the vagal and spinal autonomic efflux to the viscera via the cortex and hypothalamus. Consequently, these structures, along with

hormones and molecules, also contribute to the bidirectional control of the brain-intestine axis [12]. In continuity, microbes are able to relate directly to the CNS through actions in the gastrointestinal (GI) tract, such as the translocation of metabolites or the release of serotonin in the lamina propria and endotoxins from the intestinal lumen associated with the main circulation. These actions occur in addition to indirect effects via the vagus nerve [14]. From this, the gut-brain axis provides a transmission route for malformed α-synuclein to regions beyond the CNS, which contributes to the pathogenesis of the initial symptoms of PD and later neurodegenerative symptoms.

3.3. Dysbiosis and Neuroinflammation in Parkinson's Disease

The human gastrointestinal tract is filled with a rich diversity of microbial communities. This community and its metabolites are responsible for regulating neuroinflammation, shaping neural development, barrier function and neurotransmitter activity. For example, Candida, Escherichia, Enterococcus and Streptococcus produce serotonin, while Lactobacillus produce GABA. Serratia and Bacillus both release dopamine. Due to the blood-brain barrier, these neurotransmitters do not reach the brain directly, but can influence its activity thanks to the gut-brain axis seen above [12].

The imbalance of this microbiome can trigger diseases associated with CNS neuroinflammation, such as PD. Pre-clinical and clinical studies have shown that infections, such as H. Pylori, psychological and physiological stress, together with the host's genetics cause intestinal dysfunction [13]. In addition to these factors, there is a relationship between the use of antibiotics and their effects on the composition of the intestinal microbiota. Recent studies have shown that this effect creates an imbalance in the immune homeostasis of the gastrointestinal system, which can influence dysbiosis and the development of neurodegenerative diseases such as PD [15].

Intestinal microbial dysbiosis or increased permeability of the intestinal wall leads to exposure of the intestinal neural plexus to toxins that can cause abnormal aggregation of α-synuclein [13]. Furthermore, it is important to note that α-synuclein is also present in the salivary glands, esophagus, and stomach, potentiating non-motor symptoms such as hypersalivation, gastroparesis and delayed gastric emptying [16]. Such dysbioses are relevant in PD, since they can be used as early biomarkers of the disease [17].

3.4. Therapeutic Strategies with a Focus on Microglia

With a view to therapeutic strategies for PD, the inhibition of microglia activation and the conversion of resting astrocytes to neurotoxic A1-reactive astrocytes shows promise for blocking the development of neurodegeneration. In addition, the use of NLRP3 inflammasome inhibitors, such as MCC950, have been shown to be effective in suppressing the activation of microglial inflammasomes, attenuating motor symptoms, nigrostriatal dopaminergic degeneration, and the accumulation of α-synuclein in different models of PD [1]. One example of an inhibitor is glibenclamide, which has been used in mice and has been shown to reduce the expression of NLRP3, interleukin 1-beta and activated caspase. In addition, treatment with glibenclamide reduced the pro-inflammatory microglial response. Therefore, evidencing a dopaminergic neuroprotective activity [18].

However, in addition to therapeutic strategies, there are situations that trigger PD. There are indications that a non-selective herbicide, paraquat, is one of the environmental factors that is widely used and has evidence in the development of PD, due to its toxicity. It was possible to conclude this from in vitro studies showing that paraquat activated BV2 microglia cells, increasing the expression and secretion of pro-inflammatory factors, interleukin 1β (IL-1β) and interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α). Such activity generated apoptotic effects on dopaminergic cells [19].

4. Conclusion

In view of this, the main purpose of this article is to clarify the different roles of microglia 1 and 2 in the pathogenesis of PD. Given this situation, current studies show the relationship between microglial polarization and the development of neuroinflammation in the progression of this disease. By recognizing the accumulation of α-synuclein in a non-functional conformation in peripheral nerve regions, studies have elucidated other mechanisms involved in the non-motor symptoms of PD, such as the digestive one. However, there is a need for further studies into the pathophysiology related to the symptoms of dysbiosis, with a view to early diagnosis of the disease.

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