The roles and findings of microglia in brain homeostasis

As funções e descobertas da microglia na homeostase cerebral

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ABSTRACT
Microglia participate in neurological homeostasis, as a mediator of neurogenesis and synaptic modulation events, programmed cell death, neuronal stabilization and remodeling. The recent discoveries, have shown that the failure to suppress these events,
or the hyperactivation of the microglia population, implies the appearance of a series of pathological injuries to the Central Nervous System.

Keywords: roles of microglia, cerebral homeostasis, neuroimmunology findings, neurodiseases and microglia, multifunctions and perspectives.

RESUMO
A micróglia participa da homeostase neurológica, como mediadora da neurogênese e dos eventos de modulação sináptica, morte celular programada, estabilização e remodelação neuronal. As descobertas recentes mostraram que a falha na supressão desses eventos ou a hiperativação da população de micróglia implica o surgimento de uma série de lesões patológicas no Sistema Nervoso Central.

Palavras-chave: papéis da microglia, homeostase cerebral, achados neuroimunológicos, doenças neurológicas e microglia, multifunções e perspetivas.

1 INTRODUCTION
Microglia are phagocytic mononuclear cells of the myeloid lineage, which reside solely in the Central Nervous System (CNS). Its function as the first line of innate defense and participation in the adaptive immune system is already widely known and, since its definition by Pio Del Rio-Hortega in 1932, such knowledge has been deepened.\(^1\)-\(^3\)

In embryogenesis, it can be found in the mesenchyme of the conceptus between three to four and a half weeks, migrating to the nervous parenchyma through the hematogenous route - before the complete formation of the cerebral vasculature and the blood-brain barrier - at approximately 5 weeks of gestation through the leptomeninges, choroid plexus and ventricular zones. There, the microglia proliferate and initiate an important communication via interleukins IL-1β and IL-6 with incipient neurons and oligodendrocytes, reinforcing the maturation of these cells. Throughout life, these chemical and contact-dependent signals will play a key role in maintaining brain homeostasis and combating injuries and infections.\(^4\)-\(^6\)

Microglia have transcriptional factors distinct from other mesenchymal-derived cells, and can assume different functions at specific anatomical sites in the CNS. Recently found microglia-specific genes are olfactomedin-like protein 3 (Olfml3) and sialic acid binding Ig-like lectin H (Siglech), associated with immune development and differentiation, respectively. Furthermore, Sall1, Spi1, Mafb and Mef2c are transcriptional factors that tightly regulate microglial bases. The change of environment, however, seems to have an important effect on the epigenetic regulation of microglia. In a study evaluating the behavior of this immune cell in the retina of mice, O’Koren et al
(2019), realized that this variant was less dependent on IL-34, with an upregulation of injury-responsive genes. This variance allowed better protection of the retinal pigment epithelium.  

The balance between the external and internal environment (temperature control, amount of acids, bases, ions and water, defensive mechanisms against invading microorganisms) and intrinsic cellular and tissue processes (DNA repair, protein synthesis, response mechanisms to stress and tissue maintenance), is a mutual undertaking of all parts of the body, in which microglia have gained increasing prominence.

However, and due to its multitasking characteristic, microglial dysregulation has been implicated in neurodegenerative diseases such as Alzheimer's, Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) and Parkinson's Disease (PD). Genetic alterations still at the neurodevelopmental stage can trigger a pro-inflammatory phenotype in young microglia, thereby inducing the expression of pro-inflammatory cell surface markers such as galectin 3 (LGALS3), receptor tyrosine protein kinase UFO (AXL), CLEC7A, class II molecules of the major histocompatibility complex (MHC) and CXC-chemokine receptor 4 (CXCR4), leading to a possible relationship with disorders of this phase, such as Autism Spectrum Disorder (ASD) and schizophrenia.

2 THE DYNAMICS OF CEREBRAL HOMEOSTASIS

The individual's relationship with the environment determines neural circuits, which characterize the organism's neural plasticity. The brain is responsible for monitoring changes that occur in the body and in the plasmatic levels of the main existing hormones and nutrients. Neurons and glial cells form the neuronal network of the nervous system that can coordinate adaptations in food intake and energy expenditure according to changing metabolic conditions. Glial cells are considered very important because they participate in the development of the extracellular environment of neurons, thus contributing to cerebral homeostasis.

The blood-brain barrier (BBB) prevents toxic components, blood cells and microorganisms from entering the brain, as well as controlling the transit of molecules that enter and leave the CNS, maintaining control of the chemical composition of the neuronal environment, which is necessary for proper functioning. In pathological
situations, BBB dysfunction leads to infiltration of harmful components into the CNS, cell invasion and unregulated transport of molecules. 29

In addition, cerebrospinal fluid directly influences the metabolic homeostasis of the CNS by maintaining the balance of the electrolyte environment and serving as a means of supplying nutrients to neurons and glial cells. It also works as a lymphatic system, removing waste substances from cellular metabolism and transporting neurotransmitters, hormones and other products throughout the CNS. 30

3 FUNCTIONAL CHARACTERISTICS OF MICROGLIA

The functional characteristics of microglia have been increasingly recognized, for example: refinement of synaptic networks, promotion of developmental apoptosis along with removal of apoptotic cells, positioning of neurons within the developing cortex and need for secretion of growth factors to neuronal survival. 7-10 Furthermore, as a primary source of pro-inflammatory cytokines, microglia are essential mediators of neuroinflammation and can induce or modulate a broad spectrum of cellular responses. Alterations in microglia functionality are implicated in brain development and aging, as well as in neurodegeneration. 23,27 Recent observations on microglial ontogeny combined with extensive gene expression profiling and new tools to study microglial biology have allowed us to characterize the spectrum of microglial phenotypes during development, homeostasis and disease. 7, 23, 30

With that, it was noted that under usual circumstances it shows an immunophenotyping with reduced levels of expression and functionality 24, 27. However, as responsible for the primary defense of the central nervous system (CNS) it has a high sensitivity to detect even the most succinct changes that may occur in the CNS and is constantly monitoring it through its long extensions that extend to the locations around it, in the same way, it maintains contact with the other cells of the CNS 24, 26. In addition, it can quickly turn into its activated form, in which, through a change in its morphology, with retraction of its extensions, it acquires the configuration of macrophages and begins to act in the face of damage and repair needs of nervous tissue 24, 25, 26, 27.

Thus, through its phagocytic capacity, it promotes the elimination of cellular residues from apoptosis that occur during the period in which the central nervous system is developing, in addition to the removal of pathogenic microorganisms that can invade the central nervous system, debris and cells. dead. 24 And when faced with an injury, it moves to the injured site, proliferates and expresses numerous antigens (MHC II) located
on its surface, thus characterizing itself as an antigen-presenting cell. In addition, it produces and releases cytokines, such as interleukin IL-6, IL-1β and tumor necrosis factor (TNF), recruiting more cells of the immune system and generating a pro-inflammatory reaction that aims to fight pathogens, repair and minimize CNS damage.

Demyelinating diseases, such as multiple sclerosis, cerebral infarctions, chagasic and HIV encephalitis, Krabbe's disease and parenchymal neurosyphilis, are some examples of injuries that will have a direct effect on microglia in their activated form, with the aim of promoting protection, restoration and limitation of damage to CNS.

### 4 MICROGLIA AND HOMEOSTASIS

Although the totality of microglia functions is still unclear, it is known that they represent the main immune cells to be recruited in specific situations, such as infections and direct injuries that induce an immediate immune response. However, its role extends beyond innate immunity, interfering in the etiology and course of neurodegenerative and/or demyelinating disorders, such as Multiple Sclerosis, Amyotrophic Lateral Sclerosis and Alzheimer's Disease, in addition to neurodevelopmental disorders (ASD), psychiatric disorders and neoplasms.

In 2012, it was verified for the first time that microglia activation could be controlled in synaptic modulation, from the signaling of fractalkine receptors - CX3CR1 expressed in cells. It is known that individuals with mutation in CX3CR1 have a low number of active microglia cells, suggesting that these receptors are involved in immune modulation.

Microglia play an important role in cleaning connections, by eliminating synapses that depend on their activation. Inactivation by the mutated CX3CR1 results in a greater accumulation of immature synapses, loss of connectivity in specific areas such as the hippocampus, and mimicry of autistic behaviors.

Changes in behavior, due to a mismatch in the synaptic regulation pathways, interfere with continued social learning, which extends into adulthood in patients with Autism Spectrum Disorder. Learning processes are also modulated by microglia, and should be understood as a result of homeostasis between neurogenesis and neuroapoptosis, reflecting in the acquisition of cellular memory.

Another way to regulate microglial activation is through the complement 3 system, also known as CD11b. In 2019, another study showed a blockade in neural pruning of mice with C3-, C1q-, C3R and CX3CR1 deficiency. Furthermore, it was
shown that disturbances in the production of ADAM10, a substance modulated in the cortex whose substrate is CX3CR1 (or CX3CL1), culminated in defects in synaptic clearance and neuron engulfment.  

The ADAM10 substance has recently been correlated to the late-onset Alzheimer's Disease loci, such that the performance of microglia is linked to the loss of multiple cognitive functions. Cognitive decline occurs primarily through the breakdown of microtubule-associated protein Tau (MAPT), which should be neutralized by microglia. However, the role of microglia proved to be limited and unable to completely prevent Tau seeding.  

Thus, even with its ability to absorb and decompose part of the protein, the remainder not neutralized by microglia would be sufficient for the spread of the pathology. In the presence of large amounts of pro-inflammatory interleukins and pro-apoptosis agents, such as IL1β and TNFα, the Tau protein persisted, even with active microglia.  

It is worth noting that the production of pro-inflammatory cytokines suppresses neurogenesis, and the inflammation process is directly regulated by the presence of microglia. This occurs from the induction of gene transcription of β2-microglobulin, H2- and D1, with subsequent stimulation of the complement system – which controls the population of active microglia, and in sequence, a broad inflammatory response appears, with production of COX-2 and CX3C.  

The presence of pro-inflammatory states (for example, due to genetic vulnerability and prenatal infections) interferes with brain homestasis and mental health. In the case of disorders such as Schizophrenia, through pro-inflammation, microglia enter a chronically active and more excitable state, thus the immune system participates in the origin and course of this disorder. 

Microglia mediate both the process of recognition and activation of the pro-inflammatory response, and antagonistically, induce a regulatory and neurogenic repair anti-inflammatory response. This interferes with the support and differentiation of oligodendrocyte progenitor cells, supporting their survival, while acting together in the induction of phagocytosis of precursor cells and regulation of the inflammatory response.  

In addition to their role in phagocytosing newborn cells that undergo apoptosis during adult hippocampal neurogenesis, microglia play an important role in maintaining neurogenesis. In one study, the interruption of neurogenesis was evidenced in mice
deficient for the P2Y12 and MerTK / Axl phagocytosis pathways. On the other hand, MerTK-induced down-regulation transiently enhances neurogenesis, suggesting that phagocytosis performed by microglia maintains a long-term negative feedback mechanism to maintain adult hippocampal neurogenesis. Therefore, it can be assumed that the effects of degradation of cell debris can promote regeneration in development, aging and in the presence of neurodegenerative diseases.  

It is noteworthy that microglia undergo changes with aging, although other cells decrease over time, microglia tend to divide slowly and remain constant over the years, but tend to undergo changes such as a decrease in responsiveness to injuries. On the other hand, although the expression of the M1 marker is reduced with time, the expression of M2 is performed in a positive way, which contributes to the repair, regeneration and protection of the CNS in old age against neurodegenerative diseases.  

The microglia are involved in homeostasis of other systems as well, through bodily neuroimmune factors, such as cutaneous inflammation. For example, the formation of urticarial plaques in chronic or idiopathic urticaria, and presentations such as pruritus and angioedema, are related to mechanisms of neuroinflammation, neurotransmission and neurogenesis. Therefore, imbalances in cerebral immune homeostasis have a direct influence on dermatological manifestations, just as chronic skin diseases contribute to neuropsychiatric disorders.  

5 FINAL CONSIDERATIONS

Microglia play a participatory role as mediators and witnesses of the multiple events addressed - neurogenesis, synaptic modulation, programmed death (apoptosis), neuronal stabilization and remodeling. They are the main immune cells of mesodermal origin to be recruited in situations such as infections, injuries, neoplastic activities or neurodegenerative diseases.  

Current research on their multifunctions allows the affirmation of a safe intersection between neuroscience and immunology. Microglia cells are shown to be able to participate directly in the network of interventional interactions in the organism's homeostasis. Thus, it is possible to infer that non-suppression of microglia activation, super activation, or any dysfunctions in this immune apparatus imply the onset of CNS injuries and pathologies.
REFERENCES


