REVIEW ARTICLE

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Microglia role as the regulator of cognitive function

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INTRODUCTION

Microglial cells are classified as the resident immune cells of the central nervous system (CNS), and they have been pointed out as key players in the development of neurodegenerative diseases[1]. These cells were discovered in the late eighties and early nineties, through studying the mouse brain, and showing that microglia are mononuclear cells distributed throughout the brain and spinal cord, accounting for over 20% of the glial cell population in the brain parenchyma[2]. The microglial cells are the only immune defense in the brain parenchyma.

These immune vigilants of infections contribute and regulate innate and adaptive responses, being involved in many different roles, such as the formation of synapses and connections, neuronal proliferation and differentiation, and the maintenance of brain homeostasis in health and disease[3]. Usually, microglia will protect the brain under inflammatory conditions by activating a strong immune response and supporting tissue repair and remodeling[4].

Microglial cells respond effectively to pathogens and brain trauma by promoting morphological changes. They respond to pathogens and injury by migrating to the site where the infection or injury occurred, changing its morphology, and destroying the pathogens to remove damaged cells and debris[5,6]. These glial cells secrete cytokines, chemokines, reactive oxygen species, and prostaglandins as part of the immune response[7,8]. On the contrary, microglia can regulate and increase the damage to the CNS when overstimulated, which generates a condition named by many authors as a reactive gliosis[9,10]. Therefore, microglia responses have been studied in many diverse types of infections, brain traumas, neurodegenerative diseases, and several other conditions[11-14].

However, the terms "reactive gliosis," "activated microglia," or "overactivated microglia" may not be the best choices to represent a range of several morphological, physiological, and sex-specific differences related to the multiple states of microglia, which vary not only from one condition or disease to another, but also from one specific brain region to another. Therefore, microglia have a key role in the defense and maintenance of CNS. Microglia have a remarkable therapeutic potential as a target in neurological disorders and brain injury. Here, we review what makes microglia so interesting to be studied as a possible therapeutic target in different conditions by starting to analyze its origins, passing through a few different conditions/diseases, and then discussing the potential future directions in research and clinic.

ORIGINS OF MICROGLIA

Virchow was the first to describe the neuroglia in 1856, which would be related to astrocytes and oligodendrocytes, while the first description of microglial cells came from Franz Nissl in the late 19th century by describing them as reactive glial elements with migratory potential, phagocytic activity, and the capacity of proliferating, which were named rod cells[15]. Santiago Ramon y Cajal defined these cells as the third element because they were neither neurons nor part of the neuroglia, which comprises astrocytes and oligodendrocytes, and Pio Del Rio-Hortega introduced the term microglial cell to differentiate them from the other glial cells and neurons[15]. Many hypotheses were tested until the establishment of the nature of microglia.

There is a growing body of evidence that suggests microglial cells are originated hematopoietically and able to reach the CNS through the bloodstream[16,17]. Initially, the evidence for a yolk sac microglial origin was mixed until Takahashi and Naito described the development of immature macrophages of the yolk sac at embryonic day 9 in mouse and rat tissues[18,19]. Thus, microglia are derived from yolk sac progenitors showing expression of the transcription factor RUNX1

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and CD117, a tyrosine kinase receptor, but these cells do not express CD45, a leukocyte marker protein[20]. Microglia emerge from the fetal yolk sac macrophages, whereas other tissue macrophages emerge from precursors produced later in development[21].

Migration and colonization of the brain by the microglial progenitors occur during fetal development before the blood-brain barrier (BBB) is completely formed, and microglia have the ability to self-renew throughout life when occurs the brain maturation and its confinement by the fully developed BBB[22]. However, human microglial cells appear near the mesenchymal tissue capillaries before their appearance in neural tissue in the fourth gestational week, and are present in the neural tissue around the fifth gestational week[23]. Nevertheless, it is important to mention that after bone marrow transplantation, and under other pro-inflammatory conditions, there might occur the recruitment of monocytes or other bone marrow-derived progenitors, which may supplement microglia to some extent[3].

REACTIVE GLIOSIS: A TERM TO BE REVIEWED

Reactive gliosis is classified as a change that occurs in the glial cells' morphology and activity due to damage in CNS, and seems to be the most important pro-inflammatory mechanism in the development of many neurodegenerative diseases, such as Alzheimer's disease and others[24,25]. Even during infectious conditions caused by virus like Zika, a higher phagocytic activity that contributes to changes in behavior can be seen in microglial cells[26]. Microglial activation is the expansion of microglia during microgliosis, the first step in the reactive gliosis, and results mainly from the existing resident microglia expansion, which might be harmful to neurons and will contribute to the development of a pro- and harmful inflammatory state[22].

A reactive gliosis consists of different stages where the primary response is the migration of macrophages and microglia to the specific site of the injury, followed by the recruitment of oligodendrocytes, which should contribute to remyelination, and, finally, there would be the enhancement of astrocyte expression, which leads to the formation of glial scars, completing, then, all steps of a reactive gliosis[9]. Thus, microglia act primarily as a neuroprotective mechanism, and when overactivated, according to the classic concepts mentioned above, they can be harmful to the CNS.

Besides being extensively used in research and review papers[27,28], the term reactive gliosis starts facing a new concept about microglial morphology, and the fact is that this term may disappear soon. The reason for this is that recent and impeccable studies have shown that microglia cannot be classified as simple as "resting" or "activated" microglia due to the fact that these cells can present multiple different states, morphology, and physiological function, and assume different characteristics that might change according to the brain area, sex, species, and several other factors[29,30].

A recently published article analyzed microglial cells in multiple periods (p7, p15, p22, and adult), diverse brain regions (cerebellum, primary somatosensory cortex, substantia nigra, cochlear nucleus, dentate gyrus, and frontal cortex), and in several conditions (healthy, Alzheimer's disease, and ovactomerized) in mice[29]. The authors have shown that different brain regions present a well-differentiated microglial morphology in adult mice; besides microglial developmental trajectories are similar between brain regions, in neonates (p7) and weaning (p22), they present higher similarities to adult morphology; frontal cortex and dentate gyrus of the hippocampus are definitely the brain regions where we can identify the biggest changes in microglia; and that there is not only a specificity regarding the morphology according to the brain region, but there is a sexual dysmorphism, which affects the production of estrogen during puberty with consequences in adult life. All these results together shed light on reviewing the term reactive gliosis and re-evaluating microglial mechanisms according to this vast pool of possible phenotypes (Figure 1).

A simplistic view such as microglia is "resting" or "activated" is no longer the best way of referring to the multiple phenotypes seen in microglia morphology and function in different brain regions, across several different conditions, and when looking at sex-specific differences too.

MICROGLIA IN ALZHEIMER'S DISEASE AND RELATED CONDITIONS

A more specific and sensitive discussion about microglia biomarkers in Alzheimer's disease has emerged[31]. It is known that Alzheimer's disease is the most common neurodegenerative disease and type of dementia, being determined clinically and in research by the excessive aggregation of extracellular amyloid-beta (Aβ) peptide and by the presence of neurofibrillary tangles, which are formed due to the hyperphosphorylation of the Tau protein, and these two main features would contribute to a progressive cognitive decline with the development of memory loss in more advanced stages of the disease[32,33]. Genetic causes of Alzheimer's disease correspond to 5% of

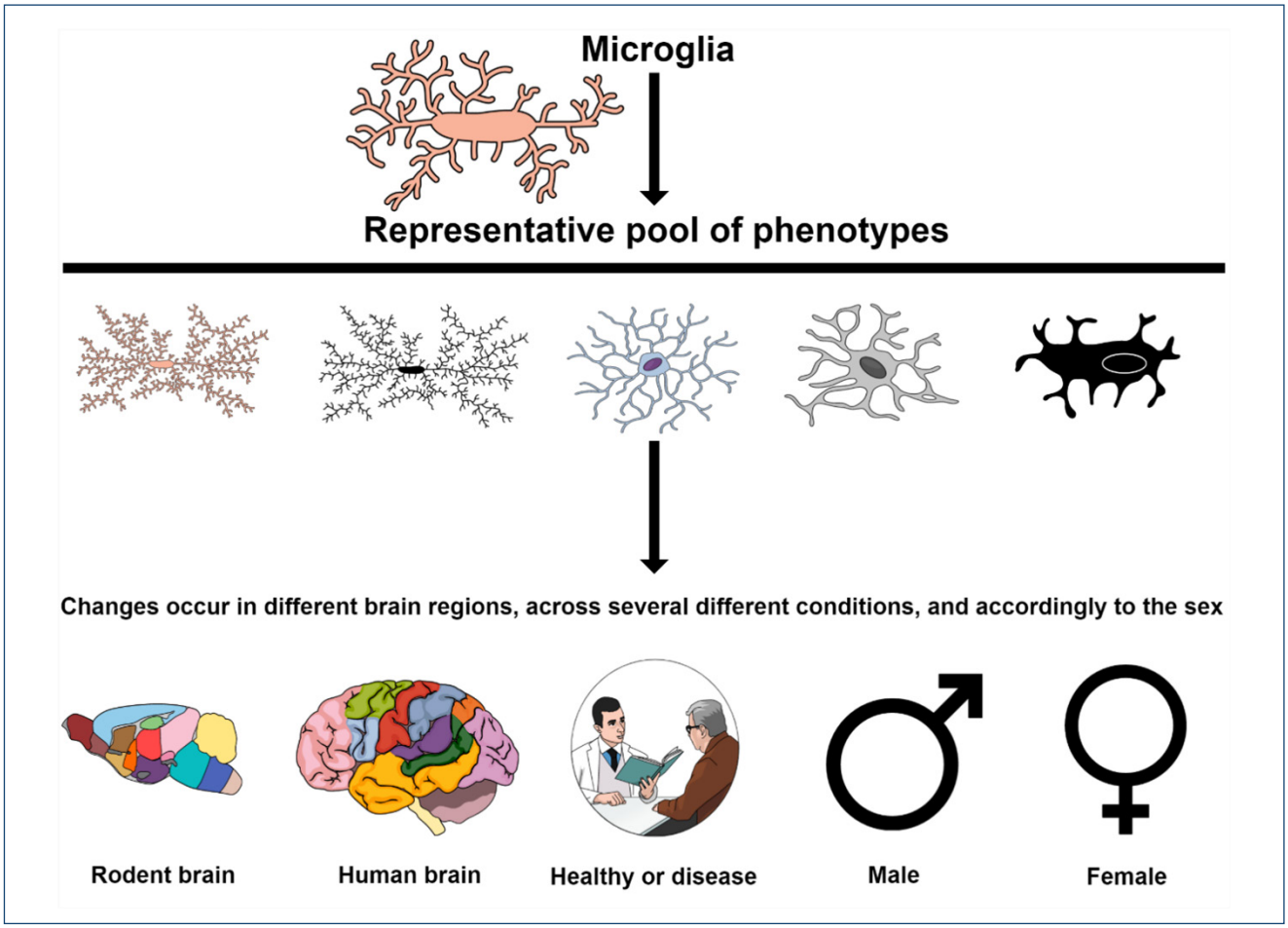

Figure 1. Representative pool of microglial phenotypes. Microglial cells present a vast pool of phenotypes that might change according to the species, brain region, condition, and sex.

the total cases, while the vast majority of the cases are related to the sporadic form of it. However, there is a common feature present in all types of dementia, that is, the presence of inflammation mediated by excessive activation of microglia and astrocytes[34].

This cognitive decline and memory loss mediated by brain inflammation is seen not only in Alzheimer's disease, but also in Alzheimer's-like pathologies, such as when there is excessive contact with air pollution[35], in type 2 diabetes mellitus[36], obesity[37,38], or even in the offspring born from gestational diabetes[39,40], among others. The fact is that a pro-inflammatory brain state is always present in cognitive impairment, with memory loss being the only common thing between all types of dementia and Alzheimer's-related pathologies. Thus, investigating the potential therapeutics of microglial interventions is essential.

CONCLUSION

Microglia are crucial for modulating cognition, memory, behavior, gene expression, oxidative stress, and inflammation. The vast pool of phenotypes exhibited by microglia brings new insights in finding specific pools of microglia that could be targeted into specific neurodegenerative diseases.

AUTHORS' CONTRIBUTIONS

RALDS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **RCC:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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