Chapter 4
Microglial Cells Function in the Central Nervous System: Beyond the Immune Function

Bilal El-Mansoury
https://orcid.org/0000-0002-2583-7515
Faculty of Sciences, Chouaib Doukkali University, Morocco

Ahmed Draoui
https://orcid.org/0000-0002-7700-059X
Faculty of Science Semlalia, Cadi Ayyad University, Morocco

Kamal Smimih
Faculty of Sciences and Techniques, Sultan Moulay Slimane University, Morocco

Samira Boulbaroud
Polydisciplinary Faculty, Sultan Moulay Slimane University, Morocco

Youssef Ait Hamdan
https://orcid.org/0009-0005-8616-8852
Higher Normal School, Cadi Ayyad University, Morocco

Arumugam Radhakrishnan Jayakumar
Miller School of Medicine, University of Miami, USA

ABSTRACT

Microglia are the resident macrophages of the central nervous system (CNS). These cells of mesodermal/mesenchymal origin migrate into all regions of the CNS. Recent studies indicate that even in the normal brain, microglia have highly motile processes by which they scan their territorial domains. By a large number of signaling pathways, they can communicate with macroglial cells (e.g. astrocytes) and neurons and with cells of the immune system. Under normal physiological conditions, microglia constantly monitor their microenvironment and survey neurons. Microglia have other functions including the participation in the formation of new blood vessels or angiogenesis, cognitive function, the regulation of synaptic plasticity, and neurogenesis and they play a crucial role in the CNS through communication with other brain cells. This chapter will provide an overview of the functions of microglial cells within the CNS.

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INTRODUCTION

The term "microglia" was introduced more than a century ago by Pio del Rio-Hortega in a published a paper in 1919. He distinguished between oligodendrocytes and microglia using an enhanced silver-staining technique (Matejuk & Ransohoff, 2020). For a very long time, it was believed that the main function of glial cells in the brain is to support and provide an ideal environment for the neurons. Neuroscientists have just lately concentrated on the distinct functions of these non-neuronal cells in maintaining brain homeostasis (Kettenmann & Verkhratsky, 2008). Therefore, it is evident that glial cells actively contribute to neuronal function and dysfunction rather of just filling "the space not occupied by neurons," as Virchow argued in the late nineteenth century (Peferoen et al., 2014a).

Microglial cells take their origin from yolk sac erythro-myeloid progenitors and colonize the developing brain before the blood-brain-barrier (BBB) closure (Ginhoux et al., 2010). After migrating as microglia progenitors to the developing CNS, these cells rapidly multiply and produce a reservoir of residual cells and have the capacity to renew themselves apart from the hematopoietic system. Microglia mature completely by the end of the second postnatal week and express adult gene signatures (Li & Barres, 2018).

It is well known that microglia play a crucial role in immune regulation of the CNS (Peferoen et al., 2014a). The role of microglia in the CNS's generation and maintenance of inflammatory responses has long been understood, but it is now obvious that they ensure other functions as well, especially in the healthy brain. Indeed, microglia, which were once thought to be "silent" in the healthy brain, have now been shown to play an active role in a number of physiological processes related to the brain, such as adult hippocampal neurogenesis, cognitive and behavioral function, biochemical homeostasis maintenance, neuronal circuit maturation during development, and experience-dependent remodeling of adult brain neuronal circuits. Furthermore, owing to their expression of a wide range of receptors and molecules on their cell surface, microglia can interact in bidirectional manner with the other brain cells including neurons, astrocytes, and oligodendrocytes. While microglia activation and the subsequent neuroinflammation has been recently observed in several conditions including Alzheimer disease (AD) (W. Chen et al., 2016), Parkinson disease (PD) (El-Mansoury et al., 2023), multiple sclerosis (MS) (El-Mansoury et al., 2023), Huntington disease (HD), amyotrophic lateral sclerosis (ALS) (W. Chen et al., 2016), and hepatic encephalopathy (HE) (B El-Mansoury et al., 2023), among others. This chapter will discuss the roles of microglial cells beyond immune function with focus on synaptic function, cognitive functions, angiogenesis and neurogenesis as well as their cross talk with the other CNS' cells including astrocytes, neurons, and oligodendrocytes.

THE DISCOVERY AND DEFINITION OF MICROGLIA

Microglial cells are well known by their role in regulating immune system function in the CNS (Peferoen et al., 2014a). In 1932, Pio del Rio-Hortega wrote a book chapter titled "Microglia" for the influential book Cytology and Cellular Pathology of the Nervous System, edited by Wilder Penfield. This chapter popularized the idea of microglia as a recognized cellular component of the CNS. Del Rio-Hortega made the following assertions: 1) during early development, microglia penetrate the developing brain. 2) The mesodermal origin of these invasive cells is indicated by their amoeboid shape. 3) They migrate throughout all parts of the brain using arteries and white matter tracts as guidance structures. 4) In the more developed brain, they change into a branching, ramified morphological pattern that is now referred