Pharmacology & Therapeutics 139 (2013) 313–326

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

Associate Editor: C. Pope

Microglia during development and aging

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ARTICLE INFO

Keywords:
Microglia
P2X receptors
Aging
Development
Synapse stripping

ABSTRACT

Microglia are critical nervous system-specific cells influencing brain development, maintenance of the neural environment, response to injury, and repair. They contribute to neuronal proliferation and differentiation, pruning of dying neurons, synaptic remodeling and clearance of debris and aberrant proteins. Colonization of the brain occurs during gestation with an expansion following birth with localization stimulated by programmed neuronal death, synaptic pruning, and axonal degeneration. Changes in microglia phenotype relate to cellular processes including specific neurotransmitter, pattern recognition, or immune-related receptor activation. Upon activation, microglia cells have the capacity to release a number of substances, e.g., cytokines, chemokines, nitric oxide, and reactive oxygen species, which could be detrimental or beneficial to the surrounding cells. With aging, microglia shift their morphology and may display diminished capacity for normal functions related to migration, clearance, and the ability to shift from a pro-inflammatory to an anti-inflammatory state to regulate injury and repair. This shift in microglia potentially contributes to increased susceptibility and neurodegeneration as a function of age. In the current review, information is provided on the colonization of the brain by microglia, the expression of various pattern recognition receptors to regulate migration and phagocytosis, and the shift in related functions that occur in normal aging.

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1. Introduction

Microglia are resident cells of the brain involved in regulatory processes critical for development, maintenance of the neural environment, response to injury, and subsequent repair. These cells were included in the early mid-nineteenth century description of neuroglia by Virchow (1856). Later, they were classified as a third element in the central nervous system (CNS) morphologically distinct from neurons, astrocytes (Cajal, 1913), and oligodendrocytes (del Rio Hortega, 1932). Microglia sense pathological events in the CNS and serve as brain immune cells to orchestrate innate immune responses. They share phenotypic characteristics and innate immunological functions with other mononuclear phagocytes and express major histocompatibility complex (MHC) antigens, as well as T and B cell markers such

Abbreviations: ATP, adenosine triphosphate; AD, Alzheimer's disease; Aβ, amyloid beta; BBB, blood brain barrier; Cl^-, chloride; CD, cluster of differentiation; CR3, complement receptor 3; C1q, complement 1q; CNS, central nervous system; CX3CL1, fractalkine or neurotactin; CX3CR1, fractalkine receptor; GD, gestational day; IFN, interferon; MHC, major histocompatibility complex; MAPK, mitogen-activated protein kinase; PND, postnatal day; IL, interleukin; LPS, lipopolysaccharide; NO, nitric oxide; PRR, pattern recognition receptors; PI3K, phosphoinositide 3-kinase; K^+, potassium; P2, purinergic receptors; TREM-2, triggering receptor expressed on myeloid cells-2; TLR, toll-like receptors; TGFβ, transforming growth factor beta; TNF, tumor necrosis factor.

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0163-7258/$ – see front matter. Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.pharmthera.2013.04.013

as various cluster of differentiation (CD) proteins (Perry et al., 1985; Williams et al., 1994; McGeer & McGeer, 1995). However, they are distinct from other tissue macrophages due to their relative quiescent phenotype and tight regulation by the CNS microenvironment. They often provide the first line of defense against invading microbes and via interactions with neurons can be the first to detect critical changes in neuronal activity and health. In the mature brain, microglia are capable not only of actively monitoring but also of controlling the extracellular environment, walling off areas of the CNS from non-CNS tissue, and removing dead or damaged cells. Work by Schmid et al. (2009) suggested that the CNS environment contributes to differentiation of monocytes to a neural specific phenotype, separating microglia from mononuclear phagocytes while maintaining many similar features. This "nervous system specificity" is demonstrated in microglia in their functions associated with synaptic pruning (Bruce-Keller, 1999; Stevens et al., 2007; Paolicelli et al., 2011), phagocytosis of apoptotic neurons and reorganization of neuronal circuitry (Sierra et al., 2010; Tremblay et al., 2010), pruning of axonal collaterals (Gehrmann et al., 1995; Wake et al., 2009), facilitation of axonal sprouting (Nagamoto-Combs et al., 2010), and remyelination of central axons (Olah et al., 2012).

Much of the research on microglia is based upon functions within the adult brain; yet, data from developmental and aging studies suggest that the nature of these functions changes over the lifespan. During development, it is thought that microglia contribute to the formation of the final neural network by stimulating vascularization and assisting in pruning of excess neurons and synapses as well as facilitating cell differentiation. As sentinels in the adult brain, microglia maintain homeostasis and possibly contribute to the neural network by assisting in synaptic remodeling and plasticity (Svensson & Aldskogius, 1993; Moran & Graeber, 2004; Stevens et al., 2007; Trapp et al., 2007; Wake et al., 2009; Perry & O'Connor, 2010), as well as removing excess aberrant proteins and debris accumulating in the brain. With aging, multiple physiological changes occur that are associated with DNA damage, oxidative stress, and telomere shortening (Vijg & Campisi, 2008). Within the brain, this is accompanied by a decrease in synaptic structures (Jacobs et al., 1997; Duan et al., 2003; Hof & Morrison, 2004) and a deficit in synaptic plasticity. With aging, the ability of microglia to express pro-inflammatory cytokines tumor necrosis factor (TNF)α, TNFβ, interleukin (IL)-1α, IL-1β and IL-6, as well as cytokine receptors (Table 1) is thought to contribute to the mild chronic inflammatory condition that develops. This elevation in pro-inflammatory cytokines is accompanied by a decrease in anti-inflammatory cytokines, such as IL-10 (Ye & Johnson, 2001). These results suggest that aging is associated with an increase in microglia activation and a decreased regulatory status. It has been hypothesized that the active monitoring functions of microglia become compromised due to an onset of cell senescence that hinders the cell's ability to sense changes in their environment, and thereby limit performance of normal functions. In this case, one might expect that a loss of phagocytic ability of the cells would result in the accumulation of aberrant proteins, such as amyloid beta (Aβ), α synuclein, and apolipoprotein E (ApoE), that are known to be associated with neurodegenerative diseases. Senescence, or any mechanism that diminishes the function of microglia, could also have an impact on synaptic plasticity and associated cognitive function. Additionally, with aging, microglia may shift their functional phenotype such that they either express a higher level of proinflammatory factors creating an environment facilitating oxidative stress or thus, be neurotoxic to the neuronal or glial population. Such a shift could also occur in microglia that would inhibit the regulatory aspects or repair capabilities of microglia to downregulate inflammation and promote recovery and tissue remodeling.

Table 1
Cytokine receptors on microglia.

Receptor	Ligand	Expression
TNFR1	TNFα	Cell-death receptor
TNFR2	TNFα	Trophic receptor/2nd cell-death receptor
IFNγR	IFNγ	M1 phenotype
IFNAR type I IFN	IFNβ	Suppression of glutamate and super oxide
IL-1R1/IL-1R2	IL-1α; IL-1β	Induction of inflammatory mediators (IL-6)
IL-2Rα/β/γ(γ_c)	IL-2	Augment NO production, M2-like phenotype
IL-10R	IL-10	Induction of M2-like deactivation phenotype
IL-13R	IL-13	Induction of M2-like phenotype
IL-15R	IL-15	Reduced NO production, microglia survival
IL-18R (IL-1 related)	IL-18	Attenuation of induced IL-12

While characteristic features of microglia structure and function have been identified as they relate to brain development and as they change with aging, there are limited experimental data to fully demonstrate the altered function of microglia cells across the lifespan. However, based upon what we know about the general signaling of the cells for migration and phagocytosis, it could be hypothesized that microglia might change with regard to how they detect changes in the environment and how they respond to those changes, including the severity and duration and nature of the response. The wealth of data on the normal adult brain in response to injury provides a framework for asking critical questions to determine how the cells may function during development and change with aging and the impact of such changes. It is highly likely that a temporal gain or loss of function contributes to defining the nature and function microglia at different stages of the lifecycle. This includes their contribution to brain development and maintaining a healthy neural environment, and possibly the susceptibility of these cells to factors associated with aging. A thorough examination of the existing literature on the physiology of microglia is outside of the current review; rather, the present chapter will focus on data available for microglia during these two ends of the lifestage spectrum. This chapter attempts to set a framework for evaluating multiple aspects of microglia dynamic neural-specific cells as they may apply across the life span.

2. Microglia during brain development

Mononuclear phagocytes (macrophages, dendritic cells, monocytes) are hematopoietic cells belonging to the myeloid lineage (van Furth et al., 1979). A major breakthrough in the understanding of the origin of these cells came with the identification of a clonotypic bone marrow precursor by using adoptive transfer monocytes from CX3CR1 green fluorescent protein (GFP) reporter mouse (Varol et al., 2007). These cells are released into the peripheral circulation and transported from the bone marrow to eventually become tissue specific macrophages. The lack of unique expression of cell surface markers between mononuclear phagocytes that infiltrating the brain and activated resident microglia has hindered the ability to discriminate between the two and originally suggested a common origin. This led to the proposal that microglia were like mononuclear phagocytes and thus derived from the bone marrow and seeded to become tissue specific macrophages. This may still be the case for the few circulating blood progenitors penetrating the vascular wall in the neonatal and adult brain or those cells repopulating the mononuclear phagocytes associated with the CNS such as perivascular macrophages. Work by Priller et al. (2001) and others demonstrated GFP-expressing bone marrow cells in the brain several weeks after irradiation and bone marrow transplantation (Eglitis & Mezey, 1997; Massengale et al., 2005). When the head was shielded during irradiation or parabolic mice were examined, a much lower level of engraftment was observed, if at all (Matsumoto & Fujiwara, 1987; Ginhoux et al., 2010; Ajami et al., 2011). Work from Ginhoux et al. (2010) suggested that only approximately 10–20% of donor origin microglia were seen in the parenchyma of bone marrow chimeric mice 10–21 months after transplantation. This low level of engraftment was also observed in a busulfan/CX3CR1GFP+ chimeric mouse (Kierdorf et al., 2013). While parabiotic mice show a lower rate of chimerism, the