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Review Article

Hippocampal adult neurogenesis: Does the immune system matter?

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ABSTRACT

Adult hippocampal neurogenesis involves proliferation, survival, differentiation and integration of newborn neurons into pre-existing neuronal networks. Although its functional significance in the central nervous system (CNS) has not comprehensively elucidated, adult neurogenesis has been attributed a role in cognition, learning and memory. There is a growing body of evidence that CNS resident as well as peripheral immune cells participate in regulating hippocampal adult neurogenesis. Microglial cells are closely associated with neural stem/progenitor cell (NSPC) in the neurogenic niche engaged in a bidirectional communication with neurons, which may be important for adult neurogenesis. Microglial and neuronal crosstalk is mediated in part by CX3CL1/CX3CR1 signaling and a disruption in this pathway has been associated with impaired neurogenesis. It has been also reported that microglial neuroprotective or neurotoxic effects in adult neurogenesis occur in a context-dependent manner. Apart from microglia other brain resident and peripheral immune cells including pericytes, perivascular macrophages, mast cells and T-cells also modulate this phenomenon. It is worth mentioning that under some physiological circumstances such as normal aging there is a significant decrease in hippocampal neurogenesis. A role for innate and adaptive immune system in adult neurogenesis has been also reported during aging. Here, we review the current evidence regarding neuro-immune interactions in the regulation of neurogenesis under distinct conditions, including aging.

Contents

Abbreviations: BAI1, brain-specific angiogenesis inhibitor 1; BDNF, brain derived neurotrophic factor; BRDU, bromodeoxyuridine; C3, complement component 3; CCL11, eotaxin; Cq1, complement component 1; CR3, complement receptor 3; CSF-1R, colony stimulating factor-1 receptor; CX3CL1, fracktalkine; DCX, doublecortin; DG, dentate gyrus; GITR, glucocorticoid-induced tumor necrosis factor (TNF) receptor; HUCB, human umbilical cord blood; IFN-γ, interferon gamma; IGF-1, insulin growth factor 1; IL-1, interleukin 1; IL-4, interleukin 4; IL-6, interleukin 6; IL-34, interleukin 34; LTC4, leukotriene C4; MAPK, mitogen activated protein kinase; MHC-II, class-II major histocompatibility complex; NBs, neuroblasts; NLR, nucleotide binding oligomerisation domain (NOD)-like receptors; NSPC, neural stem/progenitor cells; PI3κ, phosphatidylinositol-3-kinase; PRR, pattern recognition receptors; PS1, presenilin 1; PSA-NCAM, polysialylated neuronal cell adhesion molecule; ROS, reactive oxygen species; SGZ, subgranular zone; SOX2, sex determining region Y-box 2; TIM-4, T cell immunoglobulin mucin 4; TIMP-1, metallopeptidase inhibitor 1; TGF-β, transforming growth factor beta; TLR, toll-like receptors; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide; VPAC1, vasoactive intestinal polypeptide receptor 1.

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1. Introduction

Microglia are central nervous system (CNS) resident myeloid cells and have traditionally been recognized as innate immune cells mediating brain inflammatory responses under pathological conditions [100,103]. For instance, microglial cells, by expressing the so-called pattern-recognition receptors, are able to quickly recognize molecules associated with pathogens or cellular damage, promoting a brain inflammatory state. Accordingly, activation of microglia has been associated with neurodegenerative diseases such as Alzheimer's disease as well as cognitive and behavioral changes following infections like bacterial meningitis and sepsis (for review see [152]).

In recent years, however, a great body of evidence has supported several roles for microglia in the physiology of the CNS, including surveillance, debris and apoptotic cells phagocytosis, synaptic plasticity and neurogenesis [6,90,119,150]. It is worth mentioning that the role played by microglia in the maintenance of CNS functioning depends on a dynamic crosstalk between these cells and neurons. For instance, the chemokine Fractalkine (CX3CL1), highly expressed in neurons, when binding in its receptor CX3CR1, expressed in high levels on microglia, can suppress microglia activation keeping these cells in a surveillant/ramified state [102,124]. Fractalkine signaling could also be involved in adult neurogenesis mediating neuron-microglia crosstalk in the neurogenic niche [6,107].

Adult neurogenesis is a complex process that involves the proliferation of neural stem and progenitor cells and their subsequent differentiation, migration, functional integration into pre-existing circuitry along with a gradual increase of neuronal connectivity as well as changes in physiological neuronal properties. In adult mammalian brain, this phenomenon occurs in the subventricular zone, which gives rise to olfactory bulb interneurons, and in the dentate gyrus (DG) of the hippocampal formation, originating granule cells [26,54]. Apart from microglia role in adult neurogenesis, peripheral immune cells such as $CD4^+$ and $CD8^+$ T cells as well as circulating inflammatory mediators seem to influence this phenomenon. For instance, the controlled activity of T cells directed to autoantigens in the CNS is needed for post-injury neuronal survival and functional recovery. Activated T cells modulate the behavior of microglia making their phenotype supportive of neural cell survival and renewal [16,151]. A decrease in neurogenesis was reported in transgenic and knockout mice lacking T cells, while it could be restored by T cells repopulation, supporting a role for adaptive immune system in adult neurogenesis [151]. Impairment in neurogenesis has also been associated with aging [6,132]. In this scenario, a major role for the chemokine Eotaxin (CCL11) has been proposed in the age-related decline of hippocampal neurogenesis [132].

In the current review, we aim to discuss the role of microglia and of peripheral immune mediators in adult neurogenesis as well as how the immune system influences this phenomenon during aging.

2. Microglia definition and ontogeny

Microglia are recognized as CNS resident myeloid cells [103], broadly distributed in the brain and in the spinal cord accounting for 5–20% of glial cells in the CNS parenchyma [65,96]. The ontogeny of these cells is not completely understood and has become a longstanding subject of research.

In the late nineteenth century (1899), Franz Nissl was among one of the first to describe reactive glial elements with similar functions to macrophages such as migratory, phagocytic and proliferative potential, describing them as rod cells ("Stabchenzellen"). The origin and nature of these rod cells become an issue of debate among the researchers of that period. In this context, W. Ford Robertson in 1900 upheld the concept of "mesoglia" to determine mesoderm-derived phagocytic components of the CNS with distinct origins from those of neuron or neuroglia (astrocytes and oligodendrocytes). Pio Del Rio-Hortega, a former student of Ramon y Cajal, later identified the "mesoglia" reported by Robertson as cells mainly derived from oligodendroglia lineage. Using silver staining techniques, Del Rio-Hortega (1919) further refined the "third element" concept, previously postulated by Ramon y Cajal (1913), distinguishing these cells from other CNS components (neurons and neuroglia) based on its origin, morphological and functional characteristics. A major population lacking phagocytic activity was identified as oligodendroglia and a minor population of ramified cells as the true "third element" of the CNS. Del Rio-Hortega introduced the term "microglial cell" to describe the "third element" of the CNS, with migratory and phagocytic properties, and considered a mesodermal origin for these cells rather than the neurectodermal origin described for oligodendroglia (for historic review see [106]). The hypothesis of a neuroectodermal origin similar to the other glial cells was also supported at that time and remained as a subject of studies in the later twentieth century [30,57]. Moreover, other theories regarding microglia origin have been raised, including pericytes and lateral ventricles subependymal cells origin [8,67].

Over the past two decades, advances in immunology, imaging and genetics field have opened the road to the hypothesis of microglia embryonic ontogeny. The myeloid origin of microglia is now well recognized. For instance, mice lacking the transcriptional factor PU.1, exclusively expressed in hematopoietic cells, present abnormalities in myeloid lineages including absence of microglia in the CNS as well as systemic B and T cells [77]. However, the precise nature of microglial progenitors remain to be addressed [36]. It has been reported in a fate mapping study, that adult radiation resistant microglia derive from primitive myeloid progenitors that arise before embryonic day 8 (E8), and are maintained throughout life by local precursors that colonize the brain before birth [35]. Indeed, hematopoietic progenitors first appear in the extra-embryonic yolk sac leading to the production of primitive hematopoiesis between days E7 and E9. Previous studies revealed the yolk sac cells as the predominant source of microglia by inducing Cre recombinase activity in the Runx locus or in the colony stimulating factor 1 receptor (CsfR-1) locus via injections of tamoxifen into pregnant mice between E7.0 and E8.5 [35,112]. Moreover, cells expressing the Fractalkine receptor (CX3CR1), a marker of early myeloid progenitors and microglia, were visualized in the yolk sac and neuroectoderm at embryonic day E 9.0, supporting the contribution of the yolk sac as a source of microglial precursors [80]. Confocal and three-dimensional images from mice expressing the green fluorescent protein (GFP) for CX3CRI ($Cx3cr1^{gfp/+}$ knockin mice) revealed that microglia at E10.5 were present in both the cephalic mesenchyme and the neuroepithelium [35,80]. Moreover, DNA analysis and *in vivo* live