Pharmacology & Therapeutics 166 (2016) 40–55

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: P. Holzer

Microglia activation states and cannabinoid system: Therapeutic implications

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ARTICLE INFO

Available online 29 June 2016

Keywords:
Neuroinflammation
Microglia
Phenotypes
Cannabinoids
Neurodegeneration
Repair

ABSTRACT

Microglial cells are recognized as the brain's intrinsic immune cells, mediating actions that range from the protection against harmful conditions that modify CNS homeostasis, to the control of proliferation and differentiation of neurons and their synaptic pruning. To perform these functions, microglia adopts different activation states, the so-called phenotypes that depending on the local environment involve them in neuroinflammation, tissue repair and even the resolution of the inflammatory process. There is accumulating evidence indicating that cannabinoids (CBs) might serve as a promising tool to modify the outcome of inflammation, especially by influencing microglial activity. Microglia has a functional endocannabinoid (eCB) signaling system, composed of cannabinoid receptors and the complete machinery for the synthesis and degradation of eCBs. The expression of cannabinoid receptors – mainly CB2 – and the production of eCBs have been related to the activation profile of these cells and therefore, the microglial phenotype, emerging as one of the mechanisms by which microglia becomes alternatively activated. Here, we will discuss recent studies that provide new insights into the role of CBs and their endogenous counterparts in defining the profile of microglia activation. These actions make CBs a promising therapeutic tool to avoid the detrimental effects of inflammation and possibly paving the way to target microglia in order to generate a reparative milieu in neurodegenerative diseases.

1. Introduction

Microglia represents between 5–20% of total glial cells in rodents, depending on the specific central nervous system (CNS) region (Lawson et al., 1990), and they are the primary cells that respond to potentially harmful conditions that could lead to neuronal loss, like injury or infection. Thus, microglia is the central custodians acting under the protection of the blood–brain barrier (BBB: Daneman, 2012) and is activated in neuroinflammatory conditions to moderate any potential damage to the CNS and to favor tissue repair. Indeed, data has emerged to suggest that microglia can control proliferation and differentiation of neurons, as well as the formation of new synapses in the healthy CNS (Graeber, 2010; Hughes, 2012). This dual nature as a mononuclear phagocyte and a glial cell of the CNS expands the interest in microglial ontogeny, origin, development and function in health and disease.

1.1. The origin of microglia

Long before the introduction of the term "microglia" by del Río-Hortega early in the 20th century (del Río-Hortega, 1932), there had been much discussion about the nature and the origin of these cells. Two schools of thought developed at the same time supporting both the ectodermal or mesodermal origin of microglia. The neuroectodermal origin was suggested based on the supposition that a common progenitor existed for microglia, astrocytes and oligodendrocytes (Fujita & Kitamura, 1975; Kitamura et al., 1984), a theory for which further support gathered (Hao et al., 1991; Fedoroff et al., 1997). Pioneer bone marrow chimera experiments suggested the existence of radiation-resistant local precursors that are present in the

Abbreviations: 2-AG, 2-arachidonoylglycerol; Aβ, amyloid β; ABDH, α/β-hydrolase; AD, Alzheimer's disease; AEA, anandamide; Arg-1, arginase-1; BBB, blood brain barrier; BDNF, brain derived nerve factor; CB, cannabinoid; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; CD45, cluster of differentiation 45; CNS, central nervous system; CCL, CC chemokine ligand; CX3CR1, CX3C chemokine receptor 1; DAGL, diacylglycerol lipase; E, embryonic; EAE, experimental autoimmune encephalomyelitis; eCB, endocannabinoid; eCBSS, endocannabinoid signaling system; FAAH, fatty acid amide hydrolase; GPR, G-protein coupled receptor; IFNγ, interferon gamma; IGF-1, insulin growth factor-1; IL, interleukin; IL-1β, interleukin 1 beta; iNOS, inducible nitric oxide synthase; GPR55, G protein-coupled receptor 55; LPS, lipopolysaccharide; Mac, macrophage antigen; MAGL, monoacylglycerol lipase; MMP, matrix metalloproteinase; MS, multiple sclerosis; MPTP, 1-Methyl-4-phenyl-1,2,3,6,-tetrahydropropyridine; NO, nitric oxide; PD, Parkinson's disease; PPAR, peroxisome proliferator-activated receptor; SCI, spinal cord injury; SOCS, suppressor of cytokine signaling; TGF-β, transforming growth factor beta; TLR, Toll-like receptor; TMEV-IDD, Theiler's murine encephalomyelitis virus-induced demyelinating disease; TNFα, transforming growth factor alpha; YS, yolk sac.

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http://dx.doi.org/10.1016/j.pharmthera.2016.06.011
0163-7258/

CNS prior to birth, and showed that microglia is highly resistant to radiation in contrast to other blood leukocyte populations and cannot be replaced by donor cells (Lassmann et al., 1993; Priller et al., 2001). Indeed, recent studies suggest that brain irradiation per se results in the infiltration of bone marrow derived immune cells into the CNS (Moravan et al., 2016), including CCR2^{+} macrophages (Morganti et al., 2014).

The mesodermal origin was based on morphological evidence and phenotypic features that focused on the resemblance between microglia and macrophages. For example, microglia is recognized by antisera that interact with monocyte/macrophage antigens (Hume et al., 1983; Murabe & Sano, 1983), and both microglia and macrophages express markers like CD11b, the Fc receptor and F4/80 in mouse (Perry et al., 1985; Akiyama & McGeer, 1990). Pioneering studies were eventually able to establish the myeloid nature of microglia, since mice lacking the myeloid transcription factor Pu.1 were devoid of myeloid cells and microglia (McKercher et al., 1996). Further evidence supported this hypothesis (Herbomel et al., 2001; Beers et al., 2006; Schulz et al., 2012) and therefore microglia is classified as mononuclear phagocytes that include monocyte-derived cells, dendritic cells, peripheral and CNS-associated macrophages (Prinz et al., 2011; Gomez Perdiguero et al., 2013).

Fate-mapping studies provided evidence that under homeostatic conditions, microglia originates from hematopoietic stem cells in the yolk sac (YS) during early embryogenesis (Ginhoux et al., 2010; Schulz et al., 2012; Kierdorf et al., 2013). Although a population of maternally derived committed CD45 expressing macrophages has been found in the YS at E7.5, this population progressively declines and is no longer detected at E9. Thus, it is believed that these cells could have a restrictive protective effect against intrauterine infections in the embryo (Bertrand et al., 2005). In mice, primitive hematopoiesis initiates in the YS shortly after the onset of gastrulation at E7, and before the circulatory system becomes fully established between E8.5–E10 (reviewed in Ginhoux et al., 2013). Interestingly, c-kit^{+} cells that are negative for lineage markers of mature hematopoietic cell progenitors have been found in the early YS, and these cells can differentiate into CX3CR1 microglia and Ter119^{+} erythrocytes, suggesting a common progenitor in the YS for both lineages (Kierdorf et al., 2013). Microglia progenitors arise in the blood islands of the YS around E9 (Fig. 1), and they migrate through the embryo vascular system to the brain and

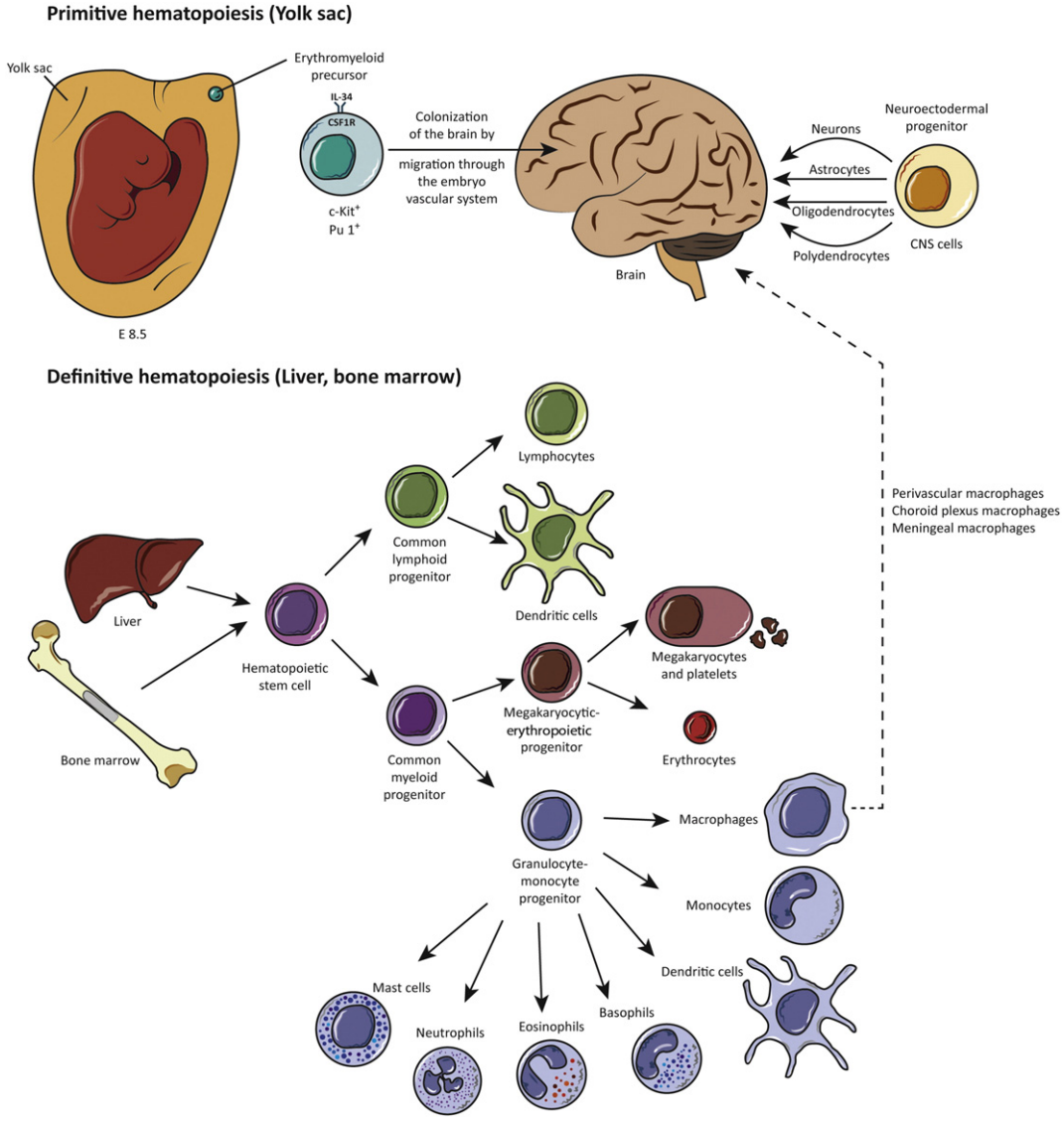

Fig. 1. Microglia derives from erythromyeloid precursors in the YS. Microglia progenitors, mainly regulated by CSF-1R and its ligand IL-34, are positive for c-kit gene and depend on the expression of the transcription factor Pu-1. They arise in the blood islands of the YS around E8.5 and migrate through the embryo vascular system to the brain and other tissues. Neurons, astrocytes, oligodendrocytes and polydendrocytes derive from neuroectodermal progenitors within the CNS. Definitive hematopoiesis is established from hematopoietic stem cells in the fetal liver and finally in the bone marrow, giving origin to both lymphoid and myeloid cells.