Brain, Behavior, and Immunity 65 (2017) 68–89

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

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

Named Series: BBI and the Microbiome

Immunoregulatory effect of mast cells influenced by microbes in neurodegenerative diseases

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ARTICLE INFO

Article history:
Received 20 February 2017
Received in revised form 17 May 2017
Accepted 30 June 2017
Available online 1 July 2017

Keywords:
Alzheimer's disease
Amyotrophic Lateral Sclerosis
Blood-Brain Barrier
Epilepsy
Mast cell
Microbiota
Multiple Sclerosis
Neurodegeneration
Neuroinflammation
Parkinson's disease

ABSTRACT

When related to central nervous system (CNS) health and disease, brain mast cells (MCs) can be a source of either beneficial or deleterious signals acting on neural cells. We review the current state of knowledge about molecular interactions between MCs and glia in neurodegenerative diseases such as Multiple Sclerosis, Alzheimer's disease, Amyotrophic Lateral Sclerosis, Parkinson's disease, Epilepsy. We also discuss the influence on MC actions evoked by the host microbiota, which has a profound effect on the host immune system, inducing important consequences in neurodegenerative disorders. Gut dysbiosis, reduced intestinal motility and increased intestinal permeability, that allow bacterial products to circulate and pass through the blood-brain barrier, are associated with neurodegenerative disease. There are differences between the microbiota of neurologic patients and healthy controls. Distinguishing between cause and effect is a challenging task, and the molecular mechanisms whereby remote gut microbiota can alter the brain have not been fully elucidated. Nevertheless, modulation of the microbiota and MC activation have been shown to promote neuroprotection. We review this new information contributing to a greater understanding of MC-microbiota-neural cells interactions modulating the brain, behavior and neurodegenerative processes.

1. Introduction

Mast cells (MCs) originate from progenitor cells in the bone marrow, which move through the circulation and become mature MCs after homing to different organs under the influence of the local microenvironment (Kitamura and Ito, 2005). MCs are located at host/environment interfaces like skin, airways, and gastrointestinal (GI) and urogenital tracts, populate connective tissues in association with blood and lymphatic vessels and nerves, and are absent in avascular tissues, such as mineralized bone, cartilage, and cornea (da Silva et al., 2014).

It is believed that the role of MCs in physiologic and pathological processes extends far beyond the allergy processes: they are involved in wound healing, in chronic inflammation, tumor growth, and angiogenesis, and may be considered a component of the immune system (Bachelet et al., 2006).

MCs release a broad array of preformed mediators and signaling molecules in the surrounding microenvironment affecting the functional profile of different resident tissue cells, including fibroblasts, smooth muscle cells, endothelial cells, epithelial cells and nerve fibers. They synthesize and release both serine- and metalloproteinases (MMPs), which cause extracellular matrix degradation and tissue remodeling. Moreover, MCs synthesize several pro-angiogenic molecules (Ribatti, 2013).

Correlated with this vast heterogeneity among cell types, distribution, and anatomical localizations, the physiological role of MCs may be different in different tissues. Despite the broad spectrum of knowledge concerning the role of MCs in different pathological conditions, their role in neurodegenerative diseases has not been sufficiently investigated.

MCs are numerous within tissues exposed to the external environment but are scarce in the healthy human Central Nervous System (CNS), being present mainly in the meningeal layers and secondarily within nervous tissue, where they are associated to the abluminal side of blood-brain barrier (BBB)-provided microvessels contributing the neurovascular unit (NVU). Nevertheless, their exact role remains indistinct (Dimitriadou et al., 1987; Dines and Powell, 1997; Khalil et al., 2007; Silver et al., 1996). In addition, MCs lie preferentially at perivascular locations in other examined mammal brains (Florenzano and Bentivoglio, 2000; Ibrahim, 1974; Manning et al., 1994; Olsson, 1968; Silverman et al., 2000) and are concentrated in the thalamus (Asarian et al., 2002; Florenzano and Bentivoglio, 2000), neurohypophisis

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http://dx.doi.org/10.1016/j.bbi.2017.06.017
0889-1591/

(Campbell and Kiernan, 1966), hypothalamus, especially the median eminence (Pollard et al., 1976).

Brain MCs are active and capable of phagocytosis, antigen presentation and production and release of pro-inflammatory mediators, and thus potentially become aggressive players in sustaining the inflammatory network of the CNS. MCs with their degranulation have been found to boost neuronal excitotoxicity (Patkai et al., 2001) and augment the effects of numerous vasoactive, neuroactive, and immunoactive cellular and molecular responses to injury (Hendrix et al., 2006; Taiwo et al., 2005). A great variability in number and distribution of brain MCs has been reported by several investigators, and often coincides with an increased susceptibility to the induction of demyelinating diseases such as Experimental Autoimmune Encephalomyelitis (EAE) (Bebo et al., 1996; Goldschmidt et al., 1984; Johnson et al., 1991).

Several studies have found an increase in the MC number or activity associated with a variety of neurological disorders, including Wallerian degeneration (MacDonald et al., 1981), galactose neuropathy (Powell et al., 1981), Guillain–Barré syndrome (Finol et al., 1991), Alzheimer's disease (AD) (Nelson et al., 1993), and multiple sclerosis (MS) (Dines and Powell, 1997). In addition, in patients with migraines or cluster headaches, increased serum histamine levels have been revealed that suggest MC degranulation (Alstadhaug, 2014). Primary MC disease (systemic mastocytosis or MC activation syndrome-MCAS) is associated with symptoms of "brain fog": loss of attention, focus, short-term memory, multitasking ability, and the development of depression (Jennings et al., 2014; Moura et al., 2012; Rogers et al., 1986), underlining the connection between the innate immune system and the CNS.

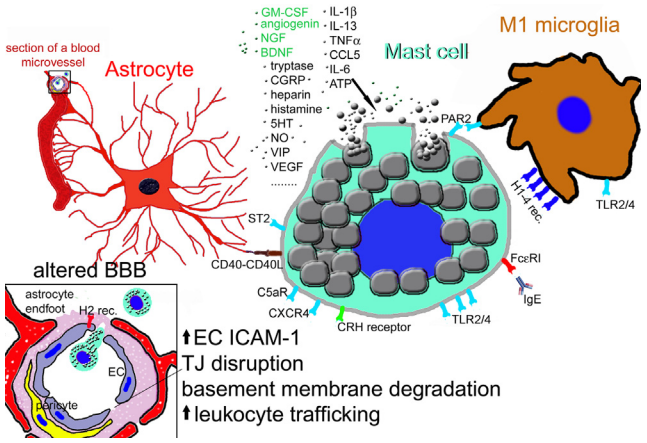

Fig. 1. Schematic depiction of multiple mast cell interactions with glia and neurovascular unit. The list in the upper part of the Figure shows potential beneficial (green) and harmful (black) molecules released by degranulation/de novo synthesis after mast cell activation. Several transmembrane receptors trigger mast cell activation or cell-cell communication with astrocytes and microglia. Activated mast cells also respond by an overexpression of those ligands that promote communication with other immune cells and responses to inflammatory molecules. Mast cells can pass through the CNS microvessels and disrupt blood-brain barrier (BBB) integrity by releasing of heparin, histamine, serotonin (5HT), nitric oxide (NO), vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), vascular endothelial growth factor (VEGF), IL-1β, IL-6, and TNFα. TNFα induces an over-expression of intercellular adhesion molecule-1 (ICAM-1) by endothelial cells (EC) and disrupts EC tight junctions (TJ). Histamine increases the EC transcellular transport, chymase and tryptase activate matrix metalloproteinases, degrading the basement membrane of the microvessel. The net effect of mast cell activation is an increased leukocyte trafficking through an altered BBB. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Molecular interactions between mast cells and glia during neurodegenerative disorders

Neurodegenerative disorders such as AD, amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and frontotemporal lobar dementia are among the most alarming health problems in developed countries, with their aging populations (Shah et al., 2016). Accumulating evidence suggests that degeneration of neurons occurs together with a cascade of reactions that is collectively termed neuroinflammation (Dauer and Przedborski, 2003; Gonzalez-Scarano and Baltuch, 1999; Ransohoff, 2016). The initiation and propagation of neuroinflammation appear to rely on the interactions between glia, immune cells and neurons. Signaling between the nervous and immune system is integrated because, at least in part, they share common ligands and receptors. Activation of both the systemic innate and adaptative immune systems play a key role in the pathogenesis of neurodegenerative disorders (Calvo et al., 2010; De Virgilio et al., 2016; Minter et al., 2016b). MCs are recently emerging as important regulators of innate and adaptative immune responses capable of a faster response to CNS injury than glia (Jin et al., 2009). Degranulation/release of mediators is very rapid and, leaving CNS MC intact, these cells remain able to deliver their cargo several consecutive times for bifunctional interactions with CNS cells (Conti and Shaik-Dasthagirisaheb, 2015; Skaper et al., 2014). CNS-resident MCs do not only promote a deleterious effect on brain functions but also beneficially contribute to cognition and emotion (Dong et al., 2014b).

2.1. MCs and microglia

Microglia perform immune surveillance in the CNS. A dysregulated interaction between CNS MCs and microglia can promote the neuroinflammation that develops during neurodegenerative disorders (Skaper et al., 2014) (Fig. 1).

Human clinical data show that microglia-mediated neuroinflammation activated by histamine is recognized to play a role in chronic neurodegeneration (Passani and Ballerini, 2012; Rocha et al., 2014) and is also involved in compromised healthy brain aging (Rosano et al., 2012; Zhang et al., 2013). CNS MCs and microglia express the receptor for a protein of the complement system, C5a, that is released during neuroinflammatory processes that induce neurodegeneration (Gasque et al., 1997; Griffin et al., 2007; Soruri et al., 2008).

Several molecular interactions between MCs and microglia have been described in vitro (Skaper et al., 2012). Histamine is a vasoactive amine released by MCs and murine microglia (Katoh et al., 2001), that promotes BBB permeability to cells and proteins, acts as a signaling molecule for CNS inflammation and as a neurotransmitter used by tuberomammillary neurons to influence cerebral cortex neurons (Umehara et al., 2012). Histamine receptors (H1-H4 receptor types) are expressed by microglia (Haas et al., 2008; Strakhova et al., 2009). Histamine infusion in rat substantia nigra provoked acute inflammation with microglia activation and loss of astrocytes and neurons (Vizuete et al., 2000). Histamine-related microglia activation has been investigated at the molecular level, revealing an increased inositol-3-phosphate-dependent Ca^{++} release from the endoplasmic reticulum that promotes motility, the expression of iNOS and release of IL-1β and tumor necrosis factor α (TNFα) (Ferreira et al., 2012; Pannell et al., 2014; Rocha et al., 2014; Seifert et al., 2011). These effects are mediated by activation of the H4 receptor together with α5β1 integrin that turn on p-38 and AKT intracellular signaling pathways (Dong et al., 2014a; Ferreira et al., 2012). In addition, a subpopulation of adenosine triphosphate (ATP)-responding microglia cells becomes more sensitive to ATP pro-inflammatory activation in the presence of histamine (Kettenmann et al., 2011; Pannell et al., 2014; Pinheiro