Journal of Neuroimmunology 274 (2014) 1–13

Contents lists available at ScienceDirect

Journal of Neuroimmunology

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

Review article

Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases

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ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form 27 June 2014
Accepted 16 July 2014

Keywords:
Neuroinflammation
Neurodegenerative disorders
Microglia
T-cells
Neo-antigens
Blood–brain barrier

ABSTRACT

Neuroinflammation constitutes a fundamental process involved in the progression of several neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and multiple sclerosis. Microglial cells play a central role in neuroinflammation, promoting neuroprotective or neurotoxic microenvironments, thus controlling neuronal fate. Acquisition of different microglial functions is regulated by intercellular interactions with neurons, astrocytes, the blood–brain barrier, and T-cells infiltrating the central nervous system. In this study, an overview of the regulation of microglial function mediated by different intercellular communications is summarised and discussed. Afterward, we focus in T-cell-mediated regulation of neuroinflammation involved in neurodegenerative disorders.

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Abbreviations: α-syn, α-synuclein; Aβ, β-amyloid peptide; AD, Alzheimer's disease; ALCAM, activated leukocyte cell adhesion molecule; ALS, amyotrophic lateral sclerosis; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; APCs, antigen-presenting cells; BBB, blood–brain barrier; CCL*n*, C–C chemokine ligand *n*; CCR*n*, C–C chemokine receptor *n*; CD*n*, cluster of differentiation *n*; CNS, central nervous system; CSF, cerebrospinal fluid; CTLA4, cytotoxic T-lymphocyte antigen 4; CXCL*n*, C–X–C chemokine ligand *n*; CXCR*n*, C–X–C chemokine receptor *n*; DCs, dendritic cells; GATA3, GATA binding protein 3; GFAP, Glial Fibrillary Acidic Protein; GM-CSF, granulocyte macrophage-colony stimulating factor; HLA, human leukocyte antigen; HMGB1, high mobility group box 1; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon γ; IL-*n*, interleukin *n*; iNOS, inducible Nitric Oxide Synthase; LFA-1, lymphocyte function-associated antigen 1; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; MHC, Major Histocompatibility Complex; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; mSOD1, mutant SOD1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NMDA, N-methyl-D-aspartate; NO, nitric oxide; PD, Parkinson's disease; P2Y6, purine-receptor 6; RNS, reactive nitrogen species; ROS, reactive oxygen species; SN*pc*, *substantia nigra pars compacta*; SOD1, superoxide dismutase 1; TCR, T-cell receptor; Th*n*, T helper *n*; TLRs, Toll like receptors; TLR*n*, Toll like receptor *n*; TGF-β, transforming growth factor β; TNF-α, tumour necrosis factor α; TNFR1, TNF-α receptor 1; VCAM-1, vascular cell adhesion molecule 1.

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http://dx.doi.org/10.1016/j.jneuroim.2014.07.012
0165-5728/

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1. Introduction

The immune system plays a fundamental role in the regulation of inflammation, a process that may be beneficial in promoting protection against pathogens and tumours and reparation of damaged tissues, but also can be detrimental when it is induced chronically (Takeuchi and Akira, 2010). Neuroinflammation, the inflammation of the central nervous system (CNS), is recognised as a prominent hallmark of many different pathological conditions (Glass et al., 2010). In this regard, several lines of evidence strongly suggest that neuroinflammation is a pivotal process involved in the progression of neuronal degeneration, a common feature observed in several neurodegenerative disorders (Glass et al., 2010; Lucin and Wyss-Coray, 2009).

A common feature in the physiopathology of most neurodegenerative disorders is the presence of protein aggregates in the CNS (Lucin and Wyss-Coray, 2009). Several lines of evidence have shown that these protein aggregates associated with neurodegenerative diseases are recognised by danger-signal sensors called Toll-like receptors (TLRs) expressed in microglial cells, promoting thus their activation. Importantly, depending on the integration of regulatory signals, microglial cells may undergo two different kinds of activation, acquiring a neurotoxic phenotype or a neuroprotective phenotype, which have been called M1-like and M2-like phenotypes respectively by their analogy with phenotypes in peripheral macrophages. Whereas M1-like microglia generate a detrimental microenvironment for neurons by producing inflammatory cytokines and reactive oxygen species (ROS), M2-like microglia secrete neurotrophic factors and anti-inflammatory mediators, thus inducing a supportive microenvironment for neurons (Kettenmann et al., 2011).

Microglial activation, which plays a central role in neuroinflammation and consequent neurodegeneration, may be regulated by several intercellular interactions involving cell-surface molecules and soluble mediators, such as cytokines, ROS and neurotransmitters. Intercellular interactions which regulate microglial activation involve cross-talks of microglia with neurons, with the blood–brain barrier (BBB), with astrocytes and with T-cells which infiltrate the CNS parenchyma. Of note, emerging evidence has shown a fundamental role of T-cells in the regulation of neuroinflammation associated with neurodegenerative disorders and thereby in neuronal fate. An overview of the different interactions regulating microglial function is summarised and discussed in this review. Afterward, we focus in the discussion of the current evidence about T-cell-mediated regulation of neuroinflammation and consequent neurodegeneration involved in neurodegenerative disorders. Finally, we analyse the current data suggesting that the aggregation and covalent modifications of CNS constituents result in the generation of neo-antigens for T-cells, thus giving rise to the hypothesis that autoimmune response against CNS antigens constitutes a major component in the physiopathology of neurodegenerative disorders.

2. Overview of microglial function

Neuroinflammation corresponds to inflammatory processes occurring in the CNS, which is observed in several pathological conditions such as stroke, infections, and neurodegenerative disorders (Glass et al., 2010). This process is characterised by the activation of microglial cells, consequent changes in the permeability of the BBB followed by the infiltration of peripheral immune cells into the CNS parenchyma, secretion of inflammatory cytokines and finally, neuronal damage and death. The current data have indicated that this process involves several cellular types, including microglia, astrocytes, neurons, endothelial cells and cells of the adaptive immune system, such as T-cells (Glass et al., 2010; Goverman, 2009; Lucin and Wyss-Coray, 2009). Because of their central role in neuroinflammation, microglial cells have attracted the attention of several studies addressing cellular and molecular mechanisms involved in neurodegenerative disorders. In this regard, microglial activation seems to be a highly regulated biological process which is not yet fully understood. Despite microglial cells behaving similarly to peripheral macrophages, they also show some important differences. For instance, the disruption of the BBB is sensed by microglia, which become activated by serum proteins (Ransohoff and Perry, 2009). Another important difference is that unlike macrophages, which are constantly replaced by new myeloid progenitors, microglial cells are not continuously recycled in the brain; nevertheless they proliferate upon activation (Kettenmann et al., 2011; Ransohoff and Perry, 2009). In the healthy brain, microglial cells display a "homeostatic" phenotype, which continually monitor the surrounding environment (Nimmerjahn et al., 2005). In this regard, they express surface molecules and secrete soluble factors which influence astrocytes and neuron function (Kettenmann et al., 2011), promote the clearance of cellular debris and aggregated proteins (S. Lee et al., 2010) and play an active role in synaptic pruning (Paolicelli et al., 2011) — all activities which support brain homeostasis. However, when exposed to infections or injuries, microglial cells exhibit responses similar of that of peripheral macrophages. In this regard, in response to lipopolysaccharide (LPS), TNF-α and/or IFN-γ, macrophages become classically activated and acquire an M1 phenotype, which express several pro-inflammatory cytokines and enzymes that promote a sustained tissue inflammation. In contrast, "alternative activation" in response to IL-4, IL-13, glucocorticoids, TGF-β and/or IL-10, macrophages differentiate into the anti-inflammatory M2 phenotype, which is associated with the resolution of inflammation and tissue reparation (Shechter et al., 2013; Sica and Mantovani, 2012). Similarly, in response to CNS injury or infection, homeostatic microglial cells exposed to LPS and IFN-γ become activated and undergo phenotypic changes acquiring M1-like features, including amoeboid shape, production of high amounts of pro-inflammatory cytokines, high mobility, strong phagocytic capacity and up-regulation of some molecular markers such as CD86, inducible Nitric Oxide Synthase (iNOS) and CD16/32 (Bedi et al., 2013; Burguillos et al., 2011; Ransohoff and Perry, 2009). In contrast, in response to anti-inflammatory cytokines, such as IL-4 and IL-10, microglial cells acquire an M2-like phenotype characterised by thin cell bodies, branched processes, and up-regulation of specific molecular markers, for instance macrophage mannose receptor 1 (CD206) and Arginase-1 (Nimmerjahn et al., 2005; Ransohoff and Perry, 2009). Thus, normally, after a CNS injury or infection, there is an initial inflammatory response mediated by M1-like microglia. This early activation plays a beneficial role, involving microbicide activity against most microorganisms and phagocytic activity necessary for the clearance of cellular debris, which is required for subsequent reparation of lesions. After early activation, M1-like microglia can acquire two different fates in the recovery phase. The beneficial fate is when, during late stages, M2-like microglia participate in attenuating inflammation induced by M1-like microglia and, concomitantly, produce neurotrophic factors, thus promoting tissue reparation (Shechter et al., 2013). The second option, the detrimental fate, is when M1-microglia undergo uncontrolled activation or over-activation, thus triggering chronic inflammation which results in the production of neurotoxic factors and leads to neuronal loss over time (Burguillos et al., 2011). In this case, microglial cells become a prominent source of inflammatory mediators such as TNF-α, IL-6, IL-1β, IL-1α, nitric oxide (NO), hydrogen peroxide, superoxide anion, chemokines such as RANTES and MCP-1, proteolytic enzymes