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Invited review

How dependent is synaptic plasticity on microglial phenotype?

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ABSTRACT

Microglia are particularly plastic cells which can be shifted from their resting state by numerous factors and adopt distinct phenotypes. The cells are multifunctional, though their main role is probably maintenance of homoeostasis. Resting cells are responsible for surveillance, whereas activation induces the cells to adopt neuroprotective or neurodetrimental roles, which are anti-inflammatory or pro-inflammatory respectively. The evidence indicates that activated cells with a pro-inflammatory phenotype predominate in neurodegenerative diseases and models of neurodegeneration and that this may significantly contribute to the deteriorating neuronal function. This question is considered in this review, in particular in the context of animal models of Alzheimer's disease (AD).

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1. Introduction

The idea that microglia are 'the macrophages of the brain', although inaccurate, is useful when considering their phenotypes since there is a great deal more understanding of the biology of macrophages. While macrophages and microglia are cells of the myeloid lineage, microglia are derived from primitive macrophages in the yolk sac that migrate to the central nervous system (CNS) early in development (Ginhoux et al., 2010). Therefore, a fundamental difference between the cells is that they encounter entirely diverse stimuli throughout life; for example, microglia are juxtaposed with cells that are electrically active, while macrophages are exposed to a wide variety of pathogens that, in the main, do not pass the blood brain barrier and therefore are generally not encountered by microglia.

Microglia, as sentinel cells in the brain, react to any stimulus that poses a potential threat to the brain. Indeed activation of glia, especially microglia, is fundamentally responsible for the inflammatory changes that characterize the brain following exposure to any insult. For example, ischaemia, injury and infection are associated with rapid microglial activation and inflammatory changes, but these are designed to combat the effect of the insult and ultimately return the tissue to homoeostasis. This acute reaction is therefore considered to be protective. In contrast, persistent microglial activation with the associated increase in expression of inflammatory cytokines and chemokines, accompanied by recruitment of peripheral cells into the brain, characterizes chronic neuroinflammation (Lynch, 2009, 2010). It has been known for many years that neuroinflammatory changes are a characteristic of, and persist in, the brain of aged individuals and a great deal of data suggests that neuroinflammation is one of the common features of several neurodegenerative diseases (Akiyama et al., 2000; Lynch, 2013). As reviewed by several authors, microglial activation has been described in Alzheimer's disease (AD) (Fuller et al., 2009; Heneka and O'Banion, 2007; McGeer and McGeer, 2003), Parkinson's disease (PD) (Long-Smith et al., 2009; McGeer and McGeer, 2008; Ouchi et al., 2009) and indeed there is epidemiological evidence indicating that anti-inflammatory agents reduce the risk of AD (Launer, 2003; Rich et al., 1995; Vlad et al., 2008) and PD (Chen et al., 2005; Esposito et al., 2007).

It has become increasingly clear that to categorize microglia as resting or activated is simplistic, since the cells express a diverse array of receptors and therefore respond to an equally diverse array of ligands. Current evidence indicates that, like macrophages, microglia react differently to various stimuli. It is also simplistic to consider that microglia are a homogenous population of cells and emerging evidence indicates that there are probably regional differences. Microglia are unevenly distributed in the brain; in the mouse brain, microglial numbers are greater in grey matter than in white matter (Lawson et al., 1990), but the opposite has been reported in human brain (Mittelbronn et al., 2001). With respect to anatomical areas, overall microglial numbers are amongst the lowest in cerebellum of both mouse and human brain and highest in hippocampus of the mouse and medulla oblongata of the human (Lawson et al., 1990; Mittelbronn et al., 2001). Interestingly, phenotypic differences have been observed in unstimulated

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microglial cultures prepared from different brain regions, with higher mRNA expression of tumour necrosis factor alpha (TNFα), Fc gamma receptor and CD4 in microglia from hippocampus than other regions studied, including cortex and cerebellum (Ren et al., 1999). This, and other findings, raise the possibility that resting state microglia are a heterogeneous population with subgroups of microglia assigned specific 'house-keeping' functions, as so eloquently discussed in a recent review (Hanisch, 2013). The heterogeneity of microglia becomes more evident when cells shift from their resting state; for example, age-related changes in expression of different markers of microglial activation were found to be region-specific with the most profound changes in CD11b, CD68 and F4/80 observed in the cerebellum (Hart et al., 2012).

2. Microglial activation

2.1. Resting microglia

The primary role of microglia under resting conditions is maintenance of homoeostasis, neuroprotection and neurorepair, and repair, at least, is probably dependent on release of growth factors such as brain-derived neurotrophic factor (BDNF) and transforming growth factor (TGF)β (Morgan et al., 2004). Time-lapse transcranial imaging of resting microglia showed that protrusion and retraction of processes is transient and occurs with high turnover. These processes make contact with astrocytes, neurons and blood vessels and sample the parenchyma every few hours. Tissue insult results in rapid recruitment of adjacent microglia and the appearance of spherical protrusions on their retracted processes, which is indicative of phagocytosis (Nimmerjahn et al., 2005). Interestingly, microglial interaction with presynaptic terminals and dendritic spines is dependent on neuronal activity (Wake et al., 2009).

2.1.1. What factors contribute to the maintenance of microglia in a resting state?

Resting microglia constitutively express surface receptors including complement receptors, Fc and CD4, and also CD200 and fractalkine receptors (CX3CR1) which are described as 'off signals' by Biber et al. in their review; these receptors engage with their respective ligands and help to maintain microglia in a quiescent state (Biber et al., 2007). Whereas CD200 is widely distributed, CD200 receptor (CD200R) expression is confined to cells of the myeloid lineage; consequently co-culturing of neurons with microglia decreases lipopolysaccharide (LPS)- or amyloid-β (Aβ)-induced microglial activation and this is dependent on interaction of CD200 with its receptor (Lyons et al., 2007a, 2009b). The largely complementary expression of fractalkine on neurons and its receptor on microglia (Harrison et al., 1998) suggests an interaction similar to that described for CD200-CD200R, and evidence to support this has been reported (Cardona et al., 2006; Lyons et al., 2009a). CD45 and signal regulatory protein (SIRP)1α, which are expressed predominantly on microglia, interact with neuronally expressed CD22 and CD47 respectively (Biber et al., 2007; Mott et al., 2004). These interactions appear to function as 'off' signals as do secreted CD22 and fractalkine (Biber et al., 2007), neurotrophins and anti-inflammatory cytokines such as interleukin (IL)-10 and IL-4 (Biber et al., 2007; Lyons et al., 2007b). These factors attenuate changes induced in microglia by stimuli that include interferon-γ (IFNγ), LPS and Aβ (Clarke et al., 2008; Lyons et al., 2007b) and, interestingly, age-related decreases in expression of several of these 'off' signals have been reported (Lyons et al., 2009a; Moore et al., 2007; Nolan et al., 2005).

2.2. The shift of microglia from their non-resting state and markers of activation

Activated microglia typically upregulate expression of cell surface markers such as major histocompatibility complex (MHC) II and co-stimulatory molecules including CD80 and CD86 (Bhatia et al., 2006; Greenwald et al., 2005; Wolf et al., 2001), which enable microglia to interact with T cells and function as antigen presenting cells (APC). In addition, CD40 and CD11b, which are constitutively expressed on microglia, are upregulated upon activation (Nguyen and Benveniste, 2000; Qin et al., 2005; Streit et al., 1999; Tan et al., 2002); these contribute to activation and restimulation of T cells (Benveniste et al., 2004), production of inflammatory cytokines (Chen et al., 2006), cell motility, cell-mediated cytotoxicity and chemotaxis (Nagai et al., 2005; Solovjov et al., 2005; Weber et al., 1997), whereas upregulation of intercellular adhesion molecule (ICAM)-1 correlates with blood brain barrier permeability and leucocyte infiltration (Corti et al., 2004; Zameer and Hoffman, 2003). It has been repeatedly shown that increased expression of these markers of microglial activation is associated with impaired neuronal/synaptic function and therefore with deficits in different types of learning and memory and in the archetypal form of synaptic plasticity, long-term potentiation (LTP); for example, this relationship has been reported following treatment of animals with LPS or Aβ and in aged animals (Clarke et al., 2008; Cowley et al., 2012; Lynch et al., 2007; Lynch, 2010).

2.2.1. Microglia adopt different phenotypes in response to different stimuli

It has been known for a few decades that macrophages adopt different activation states, identified by upregulation of specific markers, in response to diverse signals and this has been comprehensively reviewed (Gordon, 2003; Mosser, 2003). The activation states are broadly described as the classically-activated, or M1, phenotype and the alternatively-activated, or M2, phenotype. Typically the Th1 cell-derived cytokine IFNγ induces the M1 phenotype, which is identified by increased mRNA expression of TNFα and inducible nitric oxide synthase (iNOS). The term alternative activation (M2a phenotype) was first used to describe a macrophage which adopted a phenotype distinct from that induced by IFNγ and LPS (Stein et al., 1992). These cells were not capable of producing nitric oxide (NO) and so were not cytotoxic and, although MHCII expression was increased, the cells were not efficient APC and prevented proliferation of T cells (Mosser, 2003). This phenotype is induced by the Th2 cell-derived cytokines, IL-4, IL-5 and IL-13 and is identified by increased mRNA expression of arginase 1, mannose receptor, chitinase 3-like 3 and found in inflammatory zone (FIZZ)-1. Two further M2 phenotypes have been described; the acquired deactivated (M2c) phenotype is induced by the immunosuppressive cytokines, IL-10 and TGFβ, and is associated with upregulation of anti-inflammatory cytokines and downregulation of factors that contribute to APC function such as MHCII, whereas the immunoregulatory M2b phenotype is induced by a number of factors including immune complexes (Gordon, 2003). A recent comprehensive study revealed that, broadly, these phenotypes could be identified in cultured microglia (Chhor et al., 2013). Table 1 summarizes the characteristics of M1 and M2 phenotypes.

A significant issue relates to the nature of the stimuli that might trigger classical and alternative activation states in microglia *in vivo* since resident cells in the brain produce limited IFNγ and IL-4. One possibility is that infiltrating cells are responsible for production of these cytokines and, consequently, for triggering polarization of microglia into classically- and alternatively-activated phenotypes. Increased expression of markers of M1 microglia have been