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Role of infiltrating monocytes/macrophages in acute and chronic neuroinflammation: Effects on cognition, learning and affective behaviour

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ABSTRACT

Peripheral macrophages have limited capacity to gain access to the brain parenchyma under normal physiological conditions. However, accumulating evidence indicates that significant trafficking to the central nervous systems occurs in response to injury or infection and is also apparent under chronic neuroinflammatory conditions. The role of infiltrating macrophages in neuronal function is unclear and confounded by the similarity in morphology and phenotype adopted by both activated macrophages and microglia. Furthermore, the ability of macrophages/microglia to adopt both pro- and anti-inflammatory activation states, along with the fact that these cells display heterogenous expression of molecules associated with both states, has made it difficult to discover their impact upon neuronal injury and cognitive processes. The ability of macrophages to exert a neuroprotective role is influenced by the microenvironment they encounter upon tissue invasion. Upon encountering an inflammatory microenvironment, macrophage polarisation is driven towards a pro-inflammatory (M1) phenotype, a state associated with reduced capacity for restorative processes such as the removal of debris, and enhanced production of pro-inflammatory mediators such as TNFα, IL-1β and NADPH oxidase. Prolonged production of these inflammatory mediators has been shown to affect neuronal function and health. Thus, macrophage polarisation may be dictated by the inflammatory queues these cells are exposed to upon migration and their subsequent impact on neuronal function may be determined by their ability to resolve the underlying inflammation.

1. Introduction

One of the most important characteristics of macrophages is their ability to adopt a variety of different activation states in response to the inflammatory environment they encounter. The protection afforded by the blood-brain barrier (BBB) prevents peripheral macrophages from gaining entry to the brain parenchyma under normal conditions. While microglia are the resident immune cells of the brain and serve a variety of functions designed to ensure optimal neuronal function, macrophages, under certain circumstances, may also gain access to the brain parenchyma. Much research has focussed on delineating the roles of both these cell types in brain function though the emphasis, in the case of macrophages, has centred on circumstances associated with injury, infection or damage to the blood-brain barrier given their 'limited' access. Whether both cell types carry out similar functions under the same circumstances is not clear and recent evidence has indicated that microglia may protect the injured brain while infiltrating macrophages may not (Girard et al., 2013; Yamasaki et al., 2014). However, ascribing specific roles to each of these cell types has been challenging due to the difficulty in discriminating between macrophages and microglia in the CNS. Though microglia are derived from extra-embryonic yolk sac progenitors and macrophages may be perivascular or monocyte-derived, the expression of many molecules on their cell surfaces is similar (Ginhoux et al., 2013). Additionally, in the injured CNS, activated microglia and monocyte-derived macrophages may adopt a similar amoeboid morphology, upregulate inflammatory surface molecules and secrete pro-inflammatory cytokines which further confounds the ability to discriminate between them. More recently, it has become apparent that while these cells are phenotypically similar, they may have distinct responses in times of injury or insult, and that these different responses may be more apparent due to the differing ageing process in these two cell types (Rawji et al., 2016). Activated microglia and macrophages are integral to neurological repair though they have been demonstrated to play both beneficial and detrimental roles in different pathological situations perhaps because of the impact of age on their cellular processes.

The process of polarisation has significant impact on the activity of macrophages and microglia. Macrophages express pattern recognition

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receptors (PRR), cytokine receptors and damage-associated molecule receptors that drive them towards a classically activated (M1) phenotype upon exposure to these ligands, at least in vitro. Adoption of the M1 state results in upregulated expression of cell surface proteins involved in antigen recognition, secretion of pro-inflammatory cytokines such as tumour necrosis factor-(TNF)α and the upregulated expression of NADPH oxidase and inducible nitric oxide synthase (iNOS). Alternative activation (M2) is adopted upon exposure to anti-inflammatory cytokines such as interleukin-4 (IL-4) and interleukin-13 (IL-13) and a number of subtypes exist. The M2 state of macrophages is typically associated with restorative processes and the resolution of inflammation (Biswas and Mantovani, 2010; Gordon and Taylor, 2005). Though it is accepted that microglia express many of the molecules associated with these states, their 'polarisation' is not so straight-forward. In fact, much research has indicated that microglia, in vivo, canonically express molecules of both polarised states and the use of M1/M2 terminology to characterise their state may not be appropriate (for review see Ransohoff, 2016).

With the identification of polarising states in macrophages, attempts to characterise these states in terms of function have been made, particularly in the context of phagocytosis as a necessary feature for the resolution of inflammation. A very recent report has indicated that phagocytosis is significantly reduced in LPS- or IFNγ-polarised macrophages, at least in the context of *E. coli* particles (Kapellos et al., 2016). However, it remains to be definitively demonstrated whether such is the case with misfolded proteins or cellular debris and consequently what the impact of macrophage polarisation may be following traumatic brain injury or in neurodegenerative disease such as Alzheimer's disease. The effect of macrophage infiltration on cognitive outcomes is not well understood – either in acute or chronic neuroinflammatory conditions. No doubt, the impact of macrophages on cognitive outcomes is influenced by the inflammatory environment driving macrophage activation. Though it is clear that macrophages do not adopt either M1 or M2 states exclusively, it may be possible to alter the balance towards one or the other state and therefore influence cognitive function.

As previously stated, macrophages gain access to the brain parenchyma only under specific conditions – for instance, where the BBB has been disrupted be it via trauma of some kind or as a result of the ageing process. Disruption of the BBB is generally apparent where pro-inflammatory cytokine secretion has been upregulated or in conditions of oxidative damage – both of which are capable of polarising macrophages towards the proinflammatory state. Given that the circumstances resulting in BBB disruption are likely to drive macrophage differentiation towards a pro-inflammatory phenotype it seems likely that cognitive processes would be negatively impacted. For instance, the neuroinflammatory environment experienced following traumatic brain injury (TBI) drives macrophages towards a pro-inflammatory phenotype (though not exclusively so) and much evidence has indicated that in this state macrophages may exacerbate neuroinflammation, directly impact upon resident microglia and impede restorative processes required to limit tissue damage (Kapellos et al., 2016; Kumar et al., 2015, 2016; Morganti et al., 2015).

It is difficult to define the time that determines the transition from acute to chronic neuroinflammation. For the purposes of this review, acute neuroinflammation, at least in the context of rodent models, will be defined as that associated with an acute injury and which persists from days to weeks but is ultimately resolved. Chronic neuroinflammation may be defined as that observed during normal ageing or in degenerative disease models where inflammation is evident during early middle-age and persists until death.

2. Acute neuroinflammation and the role of infiltrating macrophages

While it does not seem that macrophages play a significant role in molecular and cellular mechanisms responsible for learning and memory under normal physiological conditions, several rodent models have indicated their involvement in the restoration of brain function following brain injury/insult. TBI invokes a myriad of cellular and immune responses that induce the infiltration of immune cells into the CNS to limit the motor, cognitive and psychosocial disabilities that occur as a result of cellular damage. Early phases of TBI display enhanced microglial activation, the expression of pro-inflammatory (IL-1β, TNFα, IL-6) and anti-inflammatory (TGF-β, IL-10) cytokines in the brain parenchyma (for review see Lenzlinger et al., 2001). These early inflammatory changes are subsequently followed by hypoxia and oxidative stress which are known to induce immune cells and glia to produce pro-inflammatory cytokines (Lüth et al., 2001). Recently, the C-C chemokine receptor 2 (CCR2) has been identified as a potential therapeutic target for TBI since it is expressed on peripheral monocytes, facilitates their recruitment from bone marrow to sites of injury and it's deficiency has been demonstrated to improve cognitive outcome after TBI (Hsieh et al., 2014). Macrophage infiltration was reduced by 80–90% following controlled cortical impact in $Ccr2^{-/-}$ mice. Additionally, these mice performed significantly better than their wildtype counterparts in the hyperactivity aspect of the open field test (though not anxiety-related behaviour) and, while gross motor function was not improved 3 weeks after TBI, hyperactivity and deficits in spatial memory associated with TBI were attenuated by CCR2 deficiency. These changes were not attributed to altered levels of tissue loss or hippocampal volume however there did appear to be preserved neuronal density in CA regions adjacent to the lesion site. A confounding feature of investigating macrophage infiltration in the CNS is the difficulty in correctly discriminating between resident microglia and infiltrating macrophages. Morganti et al. (2015) utilised $CX3CR1^{GFP+}/CCR2^{RFP+}$ to delineate the role of peripheral monocytes in TBI and though concomitant expression of M1 and M2 molecules was observed, a correlation between macrophage accumulation and inflammatory gene expression was detected. Furthermore, antagonism of CCR2 reduced macrophage accumulation and abrogated hippocampal cognitive dysfunction (Morganti et al., 2015). These improvements were associated with reduced pro-inflammatory profile in hippocampal tissue and enhanced expression of molecules associated with the M2 state.

The identification of macrophages expressing M1 and M2-associated molecules simultaneously in the brain parenchyma following TBI has lead to many researchers investigating the therapeutic potential of M2 macrophages or of limiting adoption of the M1 state in improving cognitive outcomes. NADPH oxidase (NOX2) contributes to reactive-oxygen species (ROS) production which drives oxidative damage and it's expression is associated with the persistent M1 phenotype observed after cortical impact (Kumar et al., 2016). $NOX2^{-/-}$ mice appear to show reduced neurodegeneration and promotion of M2 activation while NOX2 inhibition reduced neuronal oxidative damage and M1 polarisation while enhancing the M2 state. In addition, NOX2 inhibition lead to the enhanced expression of M2-associated molecules, an attenuation of the TBI-induced decrease in neuronal density, a rescue of fine motor coordination as evidenced by improved performance in the beam walk task as well as improved performance in the Y maze. These data indicate that limiting the M1 profile of macrophages not only prevents the TBI-induced decrease in neuronal density but improves motor and cognitive outcomes.

While it is clear that M1/M2-mixed phenotypes accumulate within the brain following TBI, at least at a particular time, it is not clear what effect the surrounding inflammatory milieu has on them. A number of questions remain to be addressed to determine the therapeutic potential of macrophages in both chronic and acute inflammatory conditions. How are M2 macrophages recruited to inflammatory sites? Is the expression of M1-associated markers necessary for migration? Upon migration, how would M2 macrophages be prevented from switching to the M1 state given their surroundings? And finally, how do infiltrating macrophages impact upon resident glial cells?