FEBS Letters 585 (2011) 3806–3812

journal homepage: www.FEBSLetters.org

Review

Innate immune responses in central nervous system inflammation

Bente Finsen, Trevor Owens *

Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark

ARTICLE INFO

Article history:
Received 20 April 2011
Revised 10 May 2011
Accepted 11 May 2011
Available online 27 May 2011

Edited by Richard Williams, Alexander Flügel and Wilhelm Just

Keywords:
T cell
Microglia
Astrocyte
Oligodendrocyte
Cytokine
Chemokine

ABSTRACT

In autoimmune diseases of the central nervous system (CNS), innate glial cell responses play a key role in determining the outcome of leukocyte infiltration. Access of leukocytes is controlled via complex interactions with glial components of the blood–brain barrier that include angiotensin II receptors on astrocytes and immunoregulatory mediators such as Type I interferons which regulate cellular traffic. Myeloid cells at the blood–brain barrier present antigen to T cells and influence cytokine effector function. Myelin-specific T cells interact with microglia and promote differentiation of oligodendrocyte precursor cells in response to axonal injury. These innate responses offer potential targets for immunomodulatory therapy.

1. Introduction

Inflammation in the central nervous system (CNS) is a defining feature of multiple sclerosis (MS) and is thought to play a role in neurodegenerative diseases such as Alzheimer's Disease. The innate signals that control CNS inflammation are of particular interest. Even in autoimmune disease where the response initiates outside the tissue or organ and the immune system may be perceived as an invader, the target tissue has capacity to respond and to participate by regulating the immune response. Glial cells, specifically microglia and astrocytes, can induce, regulate and are themselves regulated by inflammatory immune responses within the CNS. We here review central features of innate immunity and recent work from our labs that have identified novel pathways by which glial response can contribute to CNS inflammation and potentially influence regenerative responses in the CNS.

2. Multiple sclerosis spectrum diseases

Multiple sclerosis (MS) is an inflammatory demyelinating disease that predominantly affects young adult females [1]. MS has a very high prevalence in Europe, especially in northern countries. The etiology is believed to involve an infectious or other environmental trigger in genetically susceptible individuals [1]. MS typically presents as a relapsing-remitting disease, which is amenable to immune-targeted therapies, though varying between individuals and treatments, then progresses to secondary progressive MS, against which immune-directed therapies are ineffective [1]. The inflammatory pathology of MS suggests either a T cell + macrophage or antibody + complement attack on myelin and underlying axons [2]. The specificity of infiltrating T cells includes reactivity to myelin proteins. Both $CD4^+$ and $CD8^+$ T cells are implicated in MS [1,3].

Entry of T cells to the CNS involves a complex of interactions that can loosely be described as 'crossing the blood–brain barrier (BBB)'. This is described in greater detail elsewhere [4]. Aspects that are of particular relevance here include that following chemokine and adhesion molecule driven transmigration of T cells across the vascular endothelium and its associated basement membrane, these T cells interact with macrophages and dendritic cells (DCs) in the perivascular space, the fluid contents of which being ultimately contiguous with the subpial and subarachnoid compartments (discussed in [4]). The interaction with myeloid cells in perivascular

Abbreviations: AT1, angiotensin II receptor-1; CNS, central nervous system; DC, dendritic cell; EAE, experimental autoimmune encephalomyelitis; IFN, interferon; IFNAR, interferon receptor; IRF, interferon regulatory factor; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis

* Corresponding author. Address: Neurobiology, Institute of Molecular Medicine, University of Southern Denmark, J.B. Winsloewsvej 25, DK5000 Odense C, Denmark. Fax: +45 6550 3950.

E-mail address: towens@health.sdu.dk (T. Owens).

0014-5793/$36.00
doi:10.1016/j.febslet.2011.05.030

space can include T cell recognition of MHC-associated myelin antigenic peptides on DCs or macrophages. From this interim compartment T cells enter the CNS parenchyma via a chemokine and matrix metalloproteinase-dependent migration across the glia limitans, another basement membrane-associated structure that is primarily composed of astrocyte end-feet [4]. Astrocytes are a prominent source of many of the chemokines that regulate immune cell entry to the CNS and for this and their participation in the glia limitans they are recognized as key elements in controlling the integrity of the BBB. Astrocytes thus play a vital role in regulating CNS inflammation. This is exemplified by clinical consequences of experimental astrocyte loss or disabling in experimental autoimmune encephalomyelitis (EAE) [5,6].

The most widely-used animal model for MS is EAE, usually generated by immunization of mice with myelin proteins or peptides. In most models, EAE is induced by $CD4^+$ Th1 (interferon-gamma (IFNγ)-producing) or Th17 (IL-17 producing) T cells [3]. In C57BL/6 mice EAE can be induced by immunization with myelin oligodendrocyte glycoprotein (MOG) or a p35–55 peptide. T cells of other specificities are recruited to CNS infiltrates as disease progresses [3]. Antibodies against MOG and other myelin antigens can promote demyelination in MS and EAE [2,3].

Innate contributions to CNS inflammation in MS and EAE are well-recognized. In the absence of microglial response inflammation does not occur where as absence of reactive astrocytes exacerbates disease [5,7]. Interestingly the disparate effects of loss of these two glial cell types may both reflect participation in events at the BBB, a simplistic generalization being that reactive microglia facilitate whereas reactive astrocytes regulate leukocyte entry. Of particular interest are findings that suggest that reactive astrocytes may selectively influence macrophage versus T cell infiltration [6]. However, microglia have other pro-inflammatory roles and are implicated in both antigen presentation to T cells (see below) and release of pro-inflammatory mediators [8]. The latter activity can be induced by stimulation through innate receptors among which the Toll-like receptors (TLRs) have received much attention [9–12]. Ligands for such responses may include viruses, as are thought to be implicated in causation of MS, pathogen-derived products such as are contained in adjuvants in EAE, and endogenous ligands that have been proposed as a consequence of tissue damage or inflammation [12].

The first approved therapy for MS were drugs based on the cytokine IFNβ, and this remains a mainstay of clinical management, especially in relapsing-remitting MS. Efficacy varies between patients depending on factors that include generation of neutralizing antibodies and underlying cytokine status [1,3,13]. The predominant mechanism of action of IFNβ as an MS therapy is thought to be reduction of cell traffic to the CNS, and there may also be effects on regulatory cytokine production [1]. IFNβ and the multi-gene IFNα family comprise the Type I interferons (IFNI) which are implicated in Toll-like receptor-driven innate responses, notably to viral infection. The latter identifies a plausible link to MS etiology. The fact that IFNI are implicated in induction of inflammatory, e.g., antiviral immune responses, and are expressed in blood and CNS of MS patients [19], poses a conundrum for how IFNβ can be effective as a therapy against MS. One suggestion has been that whereas IFNα acts systemically to promote autoimmunity, IFNβ acts locally to suppress inflammation, possibly via regulation of tumor necrosis factor (see [19]). IFNI signal through a common IFNI receptor, IFNAR, a heterodimer of IFNAR1 and IFNAR2, which signals via Jak1/Tyk2 for STAT1/2 activation. Although differential signaling outcomes have been described for IFNα and IFNβ, there is considerable overlap [19]. Mice that lack IFNAR or IFNβ show exacerbated EAE and increased leukocyte infiltration to the CNS [14–16], and IFNAR expression by myeloid cells has been shown to be critical in this regulation [14]. Considering mechanism, it has been shown that whether IFNβ alleviates EAE depends on whether IFNγ and Th1 T cells are present, whereas in Th17 EAE as well as in relapsing-remitting MS with high IL-17 serum titers, IFNβ was ineffective [17]. Our own studies suggest that IFNI signaling modulated leukocyte infiltration in response to axonal lesion in which IFNγ is not easily detected (see below) [18]. Whether these or other cytokine-mediated effects contribute to control of leukocyte traffic, e.g., via regulation of adhesion interactions, another likely component of the mechanism of IFNβ effects in MS and EAE, and how and whether the induction of immune responses in the first place might be modulated by IFNβ in MS rheumatoid arthritis and other autoimmune diseases are reviewed elsewhere [19]. As discussed below, results from our studies point to a role for IFNI-induced glial chemokines.

3. Axonal lesion as a model for innate response in the CNS

Our general approach has been to use sterile axotomy as a trigger for innate glial response, and then compare findings to those in bona fide autoimmune situations, and in combinations of the two. This has allowed us to study mechanisms underlying immune-initiated glial responses in CNS demyelinating disease, by applying autoreactive T cells as additional triggers of glial response, such as in EAE (Fig. 1). Our research has shown a role for IFNI signaling in regulating innate glial response, as well as identifying signaling pathways for astrocytes that regulate immune access to the CNS. Our findings show roles for CNS glia in regulating endogenous innate cytokine and chemokine production, which in turn regulate immune cell entry.

3.1. Cellular sources of innate cytokines in the CNS

We have shown that microglia upregulate interferon response factor-7 (IRF7) in response to sterile axotomy and in EAE [18] (Salem, Khorooshi and Owens, unpublished). This implicates microglia as a source of IFNI, a point of intuitive acceptance that nonetheless remains to be rigorously demonstrated. Although IFNβ was detected by ELISA in the CNS of mice with EAE by Prinz et al. [14], it is more commonly detected via surrogate markers such as IRF7. This is true even in CNS virus infections, and reflects the biological potency of IFNI as an innate mediator [20]. The fact that interferon response factors are implicated both in actual response as well as feedforward induction of the cytokine itself means that interpretation of such findings must always be nuanced. All cells of the body are considered to have the capability to elicit an IFNI response, e.g., in innate receptor response to viral infection. However, we do not find that innate-responsive astrocytes express detectable IRF7 in response to axonal lesion (see below). Myeloid cells, especially DC, are favored candidate cell sources for the induction of immune regulatory cytokine levels [3,21].

We have shown that mice lacking IRF7 develop more severe EAE, with increased leukocyte infiltration to CNS (Salem, Khorooshi and Owens, unpublished). This is broadly consistent with the published work from Issazadeh, Fish, and Prinz and their colleagues [14–16] that shows that mice which lack either IFNβ or IFNAR show exacerbated EAE and enhanced leukocyte infiltration to the CNS in EAE. Our findings in the axonal lesion model generalize this observation to a non-autoimmune injury-induced innate response that may have regenerative consequences (see below). Thus endogenous or innate IFNI production is not only induced by pathogen-mimicking adjuvant-based immunization, but also in response to sterile injury in the CNS.

Prinz et al. used Cre-lox transgenic systems to show that myeloid cells were key responders to IFNI for regulation of EAE [14]. Taken together with results from adoptive transfers, which indicated