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Cytokines in multiple sclerosis: from bench to bedside

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Abstract

Cytokines play an important role in the pathogenesis of inflammatory diseases including multiple sclerosis (MS). Experimental models have played a critical role in unraveling the roles of individual cytokines in this disease; however, these studies occasionally yield conflicting results, highlighting the complex role cytokines play in the disease process. Efforts to modulate cytokine function in MS have shown that effective treatments alter cytokine expression in the central nervous system (CNS) and in activated mononuclear cells, indicating that they are important therapeutic targets. In this review, we will summarize the current knowledge on the role of cytokine pathways in MS and what we learned from investigation of its animal model: experimental autoimmune encephalomyelitis (EAE).

Keywords: Multiple sclerosis; Experimental autoimmune encephalomyelitis; Neuroinflammation; T cell; Cytokines; Neuroprotection

Abbreviations: CNS, central nervous system; CNTF, cytokine ciliary neurotrophic factor; CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; Jak/STAT, Janus kinase and signal transducer and activator of transcription; MHC, major histocompatibility complex; MS, multiple sclerosis; OPC, oligodendrocyte progenitor cell; PBMC, peripheral blood mononuclear cell; RR, relapsing-remitting; RT-PCR, reverse transcriptase-polymerase chain reaction; SP, secondary progressive; TGF, transforming growth factor; Th, T helper; Th1, type 1 helper T; Th2, type 2 helper T; Th3, type 3 helper T; TNF, tumor necrosis factor; TNFR1, TNF alpha receptor 1; TNFR2, TNF alpha receptor 2.

Contents

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1. Introduction

Multiple sclerosis (MS) is the leading cause of neurological disability in young adults (Noseworthy et al., 2000). It is estimated that in the United States ~250,000 individuals suffer from MS. The disease has substantial personal, social, and economic costs. MS it is an immune-mediated demyelinating and neurodegenerative disease of the central nervous system (CNS) with lesions predominantly occurring in the CNS white matter. The majority of patients experience a relapsing-remitting (RR) form of disease with transient symptoms followed by a secondary progressive (SP) phase characterized by irreversible deficits and neurodegeneration.

Current therapies for MS primarily target the peripheral immune response but have limited efficacy and many side effects. Moreover, it is clear that these strategies alone are insufficient in preventing the chronic progressive disability that is the ultimate outcome of the disease. Therefore, novel therapies for MS should target the underlying mechanisms of chronic disability, and promote repair and regeneration in the CNS.

Cytokines are critical components of the immune inflammatory process and are implicated in oligodendrocyte cell death, axonal degeneration (Wujek et al., 2002; Bjartmar et al., 2003) and neuronal dysfunction, which are key features in MS pathology (Lucchinetti et al., 2000) and the substrate of irreversible deficits. Cerebrospinal fluid (CSF) from patients with aggressive MS carries soluble mediators that have been shown to induce axonal damage and apoptosis of neurons in vitro (Alcazar et al., 2000). Therefore, understanding the mechanisms of cytokine-mediated damage is necessary to design therapies that promote oligodendrocyte and axon survival and prevent irreversible chronic disability in MS.

Experimental autoimmune encephalomyelitis (EAE) is an animal model that mimics many aspects of MS. It is induced by subcutaneous injection of myelin proteins or CNS homogenate into a variety of animals, particularly mice and rats, and widely used to study the mechanisms of disease and therapeutic approaches to MS. We will review the role of cytokine pathways in the periphery and in the CNS in MS and will draw parallels from the animal model of MS, EAE.

2. Cytokines signaling pathways in multiple sclerosis

Differential cytokine signaling may underlie, at least in part, the genetic susceptibility in MS. Concordance of MS is 30% among monozygotic (identical) twins a 10-fold increase compared to dizygotic (fraternal) twins or first-degree relatives and is slightly higher in monozygotic than in dizygotic twins. In addition, MS is 20-fold more frequent among relatives of probands than in the general population (Ebers et al., 1996). The results of genetic studies to date suggest that MS risk depends on independent or epistatic effects of several genes with small individual effects rather than a few genes of major biologic importance, consistent with a polygenic disease (Ebers et al., 1996). One of the susceptibility genes is the major histocompatibility complex (MHC): HLA-DRB1*1501-DQB1*0602, also known as DR2 (Dyment et al., 2004), is associated with increased risk of MS with a further increased disease risk in homozygotes (Ligers et al., 2001). However, it is unclear how MHC class II gene polymorphisms modify susceptibility to the disease. Another possibility that is relevant to our discussion, is that various MHC class II genes dictate a differential cytokine expression and regulation as has been reported in other autoimmune disorders (Morahan et al., 2001). A second possibility is that susceptible MHC haplotypes may have structural similarities in presenting myelin proteins and microbial epitopes, increasing the rate of molecular mimicry and the potential for a dysregulated immune response to an endogenous protein (Lang et al., 2002).

CD4+ T helper (Th) cells play a critical role in MS (Zhang et al., 1994) and EAE (Hjelmstrom et al., 1998; Chu et al., 2000). The major types of Th cell are type 1 helper T (Th1) cells that produce interleukin (IL)-2, tumor necrosis factor-α (TNF-α), and IFN-γ, type 2 helper T (Th2) cells that produce IL-4, IL-5, IL-10 and IL-13 and type 3 helper T (Th3) cells that primarily secrete transforming growth factor-β (TGF-β; Fukaura et al., 1996; Hafler et al., 1997). Studies in STAT protein-deficient mice have helped to elucidate the role of Th1 and Th2 cytokines in EAE, with implications for MS.

Intracellular signaling mechanisms provide the link between the binding of the cytokine with its receptor and the effect of the cytokine on cellular function. The Janus kinase and signal transducer and activator of transcription (Jak/STAT) family of transducer/transcription-activating factors play a critical role in the signaling of many cytokine receptors. Cytokine binding to the specific receptor activates the Jak molecule associated with the receptor causing phosphorylation of tyrosine residues. This facilitates binding of STAT proteins to the phosphorylated receptor, which subsequently dissociates from the receptor and activates