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Emerging role of IL-16 in cytokine-mediated regulation of multiple sclerosis

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ABSTRACT

Cytokines are pleiotropic soluble mediators of cellular functions. Cytokines are critical in immune pathogenesis of human diseases, including autoimmune $CD4^+$ T cell mediated chronic inflammatory, demyelinating and neurodegenerative diseases of the central nervous system (CNS), multiple sclerosis (MS). In MS and its experimental model, experimental autoimmune encephalomyelitis (EAE), chronic persistence and/or reoccurrence of inflammation in the CNS causes chronic progressive or relapsing disease, accompanied with demyelination and damage to axons and oligodendrocytes, which ultimately leads to paralysis and disability. As opposed to other cytokines, whose effects are not limited to the $CD4^+$ T cell subset, IL-16 exerts its biological properties by exclusive binding and signaling through CD4 receptor. IL-16 selectively regulates migration of all CD4 expressing T cells regardless of their activation state, which is of critical importance for immune modulation and potential therapy of MS. Other major biological properties of IL-16 essential for the function of $CD4^+$ T cells include regulation of: T cell activation, CD25 expression, MHC class II expression, dendritic cell (DC)–T cell cooperation, B cell–T cell and T cell–T cell cooperation, inflammatory cytokine production and modulation of chemokine regulated T cell chemo-attraction. In this article we outline immune pathogenesis of the disease necessary to understand significance of cytokines and IL-16 in MS regulation. We revisit cytokine regulation with emphasis on involvement of IL-16 mechanisms, implicated in MS progression and important for development of new therapies. We emphasize the significance of similar IL-16 mechanisms for other chronic inflammatory CNS diseases.

1. Introduction

1.1. Multiple sclerosis (MS)

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, neurodegenerative and progressive paralytic disease of the central nervous system (CNS), caused by axonal degeneration and damage or dysfunction of neurons and oligodendrocytes [1,2]. The etiology of MS is not understood. Complex interactions between genetic, environmental and epigenetic factors are implicated in the regulation of the disease. The autoimmune nature of MS is strongly suggested by evidence of myelin-specific autoreactive T cells and antibodies and responsiveness of MS patients to immunomodulatory therapies.

Multiple sclerosis is the second most common neurological disorder leading to disability in young adults, surpassed only by trauma. MS affects working populations between 20 and 50 years of age. Accumulating clinical and epidemiologic data raises awareness of early and late onset disease in children and older adults, respectively. Incidence of childhood and late onset are lower compared to that in young adults. Nevertheless, MS poses a serious health concern. Differences in the clinical course of disease and in responses to therapy between age groups present additional challenges to understanding the complex pathophysiology of MS. MS affects about 2.5 million people world wide. Patients suffering from this progressive, debilitating disease require therapy, counseling, and rehabilitation. Most often, with the advancement of the disease, MS patients are unable to continue working and to maintain their basic daily activities [1]. The ratio of female to male MS patients is 2–3:1. Higher incidence of MS among women is suggestive of sex hormone regulation of the disease. Epidemiological studies and more recent studies of blood have also indicated a link between vitamin D insufficiency and MS [1,2].

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Genetic studies have made enormous progress in revealing risk alleles associated with MS. To date, many genome-wide-association studies (GWAS) supported the view of polygenic regulation of susceptibility to autoimmune diseases including MS. A large number of genes associated with immune functions show linkage to MS. The International Multiple Sclerosis Genetics Consortium (IMSGC) undertook an analysis of immune-related loci and reported on 48 new susceptibility variants for MS [3]. The strongest MS susceptibility locus is the major histocompatibility complex (MHC) in chromosome 6p21.3. In the MHC class II segment of the MHC locus, the HLA-DRB*1501 gene exhibits the strongest signal, with hierarchical allelic and haplotypic effects in different populations of MS patients. A cytokine IL-16 contributes to the regulation of expression of MHC class II on $CD4^+$ mononuclear cells. A protective linkage in the MHC Class I region has been identified. Association with MS has been suggested for many other genes including those encoding cytokines, their cognate receptors, cytokine receptor associated signaling molecules, some chemokines, chemokine receptors, co-stimulatory and inhibitory molecules expressed on the cell membrane of immune cells. These genes include tumor necrosis factor alpha (TNFα), IL-7R, IL-2Rα, tyrosine-protein kinase-2, macrophage chemoattractant protein-1 (MCP-1) and CC chemokine receptor-5 (CCR5). [4]. Functional studies are needed in order to evaluate and refine the genetic association with mechanisms of the disease in order to successfully translate accumulating knowledge into MS therapy. Recent data on epigenetic regulation of autoimmune diseases further add to the complexity of factors associated with MS. To our knowledge, data on MS linkage with IL-16 gene have not been reported.

Combination of genetic susceptibility and infectious environmental factors, such as bacteria, parasites, fungus and viruses, as triggers of autoimmune mediated CNS tissue damage has been proposed and reexamined [5]. It is outside the scope of this article to elaborate on all proposed environmental influences. We will discuss some data indicating association between viruses including MS-associated retrovirus (MSRV) with MS. A functional relationship between MSR, HERV-W, its endogenous family, has been reported [6]. Binding of viral proteins, including retroviruses, such as human delta-retrovirus T lymphotropic virus type 1 (HTLV-1) Tax oncoprotein, to PDZ (postsynaptic density/disc large/zona occludens-1) domain binding site of the precursor of IL-16 (pro-IL-16) in HTLV-1 infected T cells and subsequent deregulation of cell cycle, has been shown [7]. Pro-IL-16 contains three domains, which allow protein–protein interactions. After cleavage with active caspase-3, two PDZ domains remain in the N-terminal portion while one PDZ domain goes to C-terminal, bioactive IL-16. Bioactive IL-16 is the only PDZ domain containing secreted cytokine. This function of pro-IL-16 is important for similar mechanisms implicated in autoimmune diseases including MS and in cancer development.

Most immunomodulatory MS therapies work through non-specific immunosuppressive and anti-inflammatory effects [1,2,8]. Although these therapies provide reduction of relapse rate and in new lesions, as demonstrated by MRI along with showing of disability in some patients, there is a lack of noticeable effects in others. Better understanding of specific mechanisms of the disease progression is critical for development of new specifically targeted therapies. Development of therapies aimed at regulation of autoimmune and regulatory $CD4^+$ T cell subsets is of critical importance because of their central role in the pathogenesis of MS.

1.2. Experimental autoimmune encephalomyelitis

Experimental autoimmune encephalomyelitis (EAE) serves as a model to study primarily autoimmune mechanisms of MS. EAE is induced in genetically susceptible species and strains by immunization with myelin proteins or their encephalitogenic peptides or by adoptive transfer of in vitro re-stimulated myelin antigen cognate T cells. Myelin oligodendrocyte protein (MOG) is important for immune pathology of MS. Sequence of events in immune pathogenesis of EAE, initiated by challenge with myelin specific antigen, starts by the increase in permeability of the blood–brain barrier (BBB) and transmigration of antigen-specific T cells from the peripheral blood into the CNS. These interactions are coordinated by T cell chemoattractant cytokines and chemokines. Infiltrating T cells produce and locally release cytokines. Likewise, glia and other resident cell types produce inflammatory and some immune cytokines. Cytokines regulate complex cellular interactions between local antigen presenting cells (APC) and infiltrating lymphocytes. Interactions between autoreactive and regulatory T cells are central in the regulation of local inflammation and tissue damage. Strong immune responses to myelin oligodendrocyte glycoprotein (MOG) p35–55 ($MOG_{35–55}$) by $CD4^+$ Th1 cells and B cells are found in patients with MS. The encephalitogenic epitope of $MOG_{35–55}$ is highly conserved among species, including mouse and human, which makes data from mouse studies more relevant for human pathology. In response to $MOG_{35–55}$, a hybrid (B6 × SJL)F1 strain of mice develops severe, relapsing-remitting disease. In these mice, CNS inflammation is predominated by $CD4^+$ T cells, followed by B cells and demyelinating lesions and axonal damage are pronounced. A relationship between IL-16 and severity of $CD4^+$ T cell infiltration, occurrence of relapsing disease, and degrees of demyelination and axonal damage are demonstrated in (B6 × SJL) F1 mice with $MOG_{35–55}$ induced EAE [9]. We will mainly emphasize this particular EAE model because of similarities it shares with relapsing-remitting course of MS, histopathology of lesions that resemble the type III lesion of MS, and similarities in IL-16 mediated mechanisms of immune regulation.

1.3. Cytokine networks in MS and EAE

Cytokines comprise large families of small molecular glycoproteins, indispensable for regulation of developmental and immune functions. Cytokines are essential for the regulation of both innate and adoptive immune responses. Pleiotropic effects of cytokines include immune cell activation, differentiation and migration. By nature of their regulatory effects, cytokines may support, suppress or modulate inflammation. We will discuss cytokines in relation to their role in regulation of Th1, Th2, Th17, antigen presenting cells (APC), glial and neuronal function in MS and EAE. The complexity of cytokine interactions and networks are outside the scope of this article. We will revisit major mechanisms implicated in the regulation of progression of MS and CNS tissue damage.

1.4. Biological properties of IL-16

The lymphocyte chemotactic factor, interleukin-16 (IL-16), is a cytokine constitutive to T lymphocytes [10]. Other cell types including monocytes/macrophages, dendritic cells, mast cells, fibroblasts and microglia can produce IL-16. IL-16 is a key regulator of the biological properties of $CD4^+$ T cells including, migration, T cell activation, CD25 (IL-2Rα) expression, MHC class II expression, cytokine synthesis, DC-T cell cooperation, B cell–T cell cooperation, T cell–T cell cooperation, inflammatory cytokine production and modulation of chemokine regulated T cell migration by heterologous receptor cross-desensitization of chemokine G-protein-coupled receptor-signaling of CCR5, CXCR4 and CXCR3 [11]. Each of these pleiotropic functions of IL-16 will be discussed in the following sections, alongside mechanisms pertinent for MS immune pathology. Thus, IL-16 is postulated to be a proinflammatory and immunoregulatory molecule with an important role in recruitment and activation of $CD4^+$ T cells at the site of inflammation [12]. In