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The Study Progress of B Cells and Neuroimmunological Diseases

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Abstract

B cells have both positive and negative regulatory roles during immune responses; they have role in the pathogenesis of various neuroimmunological diseases such as Myasthenia gravis (MG), Multiple sclerosis (MS), Guillain-Barre syndrome (GBS), and Lambert-Eaton myasthenic syndrome (LEMS). B cells can positively regulate immune responses by producing antigen-specific antibody, inducing optimal T cell activation and cytokine production. The pathogenic role of B cells and autoantibodies in neuroimmunological diseases, as reviewed here, provides information towards the research progress in the progressive role of B cells in neuroimmunological diseases. It is expected that the ongoing research on B cells and neuroimmunological diseases will contribute to the clinical applications, and better understanding of the etiology of neuroimmunogical diseases.

Keywords: Neuroimmunological diseases; Myasthenia gravis; Multiple sclerosis; Guillain-Barre syndrome; B cells; Regulatory B cells; Lambert-Eaton myasthenic syndrome

Introduction

B cells are now well established to have both positive and negative regulatory roles during immune responses [1]. B cells can positively regulate immune responses by producing antigen-specific antibody and inducing optimal T cell activation [2,3]. B cells can also negatively regulate cellular immune responses through their production of immune modulatory cytokines. B cell-negative regulation of immune responses has been demonstrated in a variety of mouse models of autoimmunity and inflammation [1,4-13]. The important negative regulatory roles of B cells in immune responses are now broadly recognized [1,14,15]. The regulatory role of B cells in autoimmune diseases was first reported by Janeway and colleagues in EAE. The existence of regulatory B cells were subsequently confirmed by other investigators [4,16-18]. These studies indicate that, like their T cell counterparts, B cells can be divided into functionally distinct regulatory subsets capable of inducing immune tolerance [1,15,18-21]. Autoimmune disorders affect 5-10% of the general population [22], and often involve central nervous system (CNS) and peripheral nervous system (PNS). In the context of autoimmune neurological disorders, B cells have traditionally been associated with the production of auto-antibodies from plasma cells, the end products of B cell differentiation [23-25]. In most autoimmune neurological disorders, the auto-antibodies are directed against cytosolic antigens and might not be directly involved in tissue injury. In such cases, B cells might still participate in the autoimmune process through antibody-independent mechanisms that include antigen presentation, co-stimulation, cytokine production, and coordination of T cell functions [25,26].

B cells Overview

B cells or B lymphocytes are the critical component of adaptive immune response. B cells are functioned to produce antibody to a specific antigen in response of pathogen such as bacteria, viruses; release interleukin (IL) producing cytokines (Figure 1). B cells can be involved in cell mediated immune responses. B cells express clonally distributed antigen presenting receptors (BCRs) that binds to one particular antigen. Naive B cells (not exposed to antigen) are able to recognize their cognate antigen. Since there are millions of B cells in the body, and naive B cells only live a few days, and more than 90% of these cells die before they have come into contact with an antigen. Once the B cell reaches maturity, it has a B cell receptoron its surface. The B cell receptor (BCR) is a protein that distinguishes the B cell from other lymphocytes. The mature B cell expresses both the Immunoglobulin M (IgM) and the Immunoglobulin M (IgD) [27-29]. The B cell receptor is critical for B cell function, toward production of antibodies, as well as for their functioning as antigen-presenting cells (APCs).

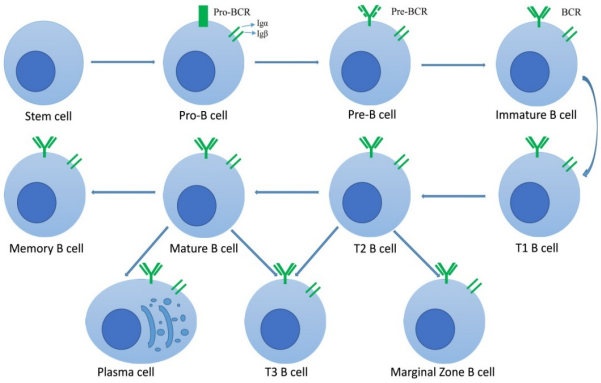

Figure 1: B cells overview.

The mature B cells circulate in the bloodstream and lymph nodes, searching for foreign substances like bacteria, viruses that may harm the body. These B cells are also called naive cells because they have not encountered an antigen yet [30,31]. A mature B cell can differentiate

into several types of B cells, most common being plasma and memory B cells [32,33].

Regulatory B cells

Regulatory B cells (Bregs) are those immunosuppressive cells, which support immunological tolerance. Over the last decade, the role of Bregs in suppressing pathological immune responses has been widely recognized. In these recent years multiple studies in both mice and humans have demonstrated that Bregs suppress inflammatory responses primarily via the provision of IL-10 [14]. These cells regulate the immune system by various mechanisms. The main mechanism is through the production of IL-10, IL-35, and transforming growth factor (TGF-β) [34]. The regulatory effects of Bregs were described in various models of inflammation, autoimmune diseases, transplantation reactions, and in anti-tumor immunity. Bregs can develop from different subsets of B cells [35]. B cells generally are considered to act as positive regulators of immune responses by promoting antigen presentation for optimal T cell activation and by producing antibodies, but now it is clear that Bregs are essential for inducing immune tolerance by negatively regulating immune responses via IL-10 production [12].

B cells and Neuroimmunological diseases

In several neurological diseases, including Myasthenia gravis and certain neuropathies, the autoantibodies are pathogenetic, exerting a direct effect on self-antigens either by functioning as neutralizing antibodies or by activating and fixing complement on the targeted tissues [25,26,36]. B cell functions in neuroimmunological diseases through production of antibodies that cause tissue damage; acting as APCs that cause cytokine production; production of proinflammatory cytokines that cause activation of macrophages and enhance tissue damage; neolymphogenesis [37]. Therefore, further research on neuroimmunogical diseases such as Myasthenia gravis, Multiple sclerosis, Guillain-Barre syndrome, and Lambert-Eaton myasthenic syndrome may be an advantage in new therapeutic role in future.

B cells and Myasthenia Gravis

Myasthenia gravis is an autoimmune disease that affects the transmission of signals from nerves to muscles. It is caused by a defect in the transmission of nerve impulses to muscles. It occurs when normal communication between the nerve and muscle is interrupted at the neuromuscular junction - the place where nerve cells connect with the muscles they control. Approximately 15-20% of people with Myasthenia gravis develop severe, potentially life-threatening respiratory impairment, often within the first year of illness which is a medical emergency called Myasthenia crisis and necessitates mechanical ventilation. The onset of the disorder can be sudden. The diagnosis of MG may be delayed if the symptoms are subtle or variable [37]. MG can be difficult to diagnose, as the symptoms can be subtle and hard to distinguish from both normal variants and other neurological disorders [38]. Approximately 85% of patients with generalized myasthenia gravis have circulating anti-AChR antibodies [39]. Autoantibodies to muscle-specific tyrosine kinase (MuSK) [38-40] are found in 38-47% of patients with MG who do not have detectable antibodies to the acetylcholine receptor (AChR) [40-42]. Anti-AChR or MuSK autoantibodies are produced by B cells with the help of T cells and other lymphocytes [43]. It has been reported that B cell depletion with rituximab treatment has long-lasting effects on MuSK MG [44]. The outcome in cohort was consistent with the finding. Interestingly, MuSK MG patients also had a tendency for faster B10 cell repopulation during the course of rituximab therapy. It has been found that, a subset of regulatory B (B10) cells is highly relevant to the pathogenesis of MG [43]. The concept of regulatory B cells has been strongly associated with IL-10 productions. The regulatory function of B cells has been associated with the presence and activation of molecules such as CD19, CD1d. Alterations in signaling by any of these pathways leads to a marked defect in Bregs and to increased clinical symptoms and pro-inflammatory signs in autoimmune diseases in humans [45]. To determine whether breakdown in immune tolerance in Myasthenia gravis may be attributable to a reduction in B10 cells. Through an observation may be noticed a whether reduction of B cells capable of producing IL-10 in patients with MG. A compare studies can be made between healthy controls and patients with Myasthenia gravis by which expression of B10 cells such as IL-10 expression, and B cells subsets such as CD19, CD5, CD1d expression can be studied. The reduction of expression in MG could be secondary to the pathogenesis of MG and the outcome of these studies may lead to an effective treatment progress of Myasthenia gravis patients.

B cells and multiple sclerosis

Multiple sclerosis is an inflammatory demyelinating disease affecting the CNS. In MS, the immune system attacks the myelin sheath that covers nerve fibers and causes communication problems between the brain and rest of the body. Eventually, MS can cause the nerves themselves to deteriorate or become permanently damaged. B cells are thought to play a pathogenic role in MS, and this idea is supported by the reduction of disease in MS patients undergoing antibody mediated B cell depletion therapy. In contrast, in EAE, a mouse model of MS, B cells have been shown to play a regulatory role. This is suggestive of a dual role for B cells in CNS autoimmunity. It is possible that a critical balance between the pathogenic and regulatory populations of B cells might be involved in the manifestation of the disease [46]. While the majority of B cells stimulate the immune system and contribute to antigen clearance and inflammation, some B cells suppress immune functions. These Bregs are a small subset of B cells with CD19, CD5, CD1d surface markers in mice [13], and it has been shown that treatment with autologous Bregs in mice ameliorates EAE [47]. A study found that the levels of IL-10 are lower in untreated MS patients compared to patients receiving anti-inflammatory drugs [48,49]. In a recent study, the phenotype and frequency of B cell subsets in peripheral blood from 32 MS patients and 34 healthy controls were examined using flow cytometry and findings were suggestive to altered blood B cell homeostasis in MS patients [50]. In addition, the researchers found that when B cells were reduced to below a threshold of 64 cells per micro liter, disease activity, as measured by appearance of new brain lesions, was significantly reduced [51]. These awaiting findings and ongoing research on immune regulatory function of B cells and MS, could contribute to reasoning about MS pathogenesis; various B cell related mechanisms including investigation of B cell effectors and regulatory functions; understanding of the mechanisms of formation and persistence of tertiary lymphoid tissues in Multiple sclerosis patients.

B cells and Guillain-Barre syndrome

GBS is a neurological disorder in which the body's immune system attacks part of the PNS. Symptoms of GBS vary from person to person and may be mild or severe. Most often, the first prominent symptom is weakness felt in both legs. The weakness is accompanied by paresthesia

[52]. Up to two thirds of cases may have an antecedent flu-like illness or gastroenteritis triggering the immune response. Elevated titers of anti-nerve antibodies are frequently found but their presence usually has limited clinical significance. Clinically, GBS manifests as an acute peripheral neuropathy with symmetric weakness reaching a peak by 4 weeks from onset, hyporeflexia or areflexia and cytoalbuminemic dissociation in the cerebrospinal fluid (CSF) with an elevated protein content and normal cell count. Diagnosis can usually be made on clinical grounds, but lumbar puncture and electrophysiological studies can help to substantiate the diagnosis and to differentiate demyelinating from axonal subtypes of GBS [53] (Table 1).

Subtypes	Antibodies
Acute inflammatory demyelinating polyneuropathy (AIDP)	various antibodies
Acute motor axonal neuropathy (AMAN)	GM1a, GM1b, GD1a, GalNAc-GD1a
Acute motor sensory axonal neuropathy (AMSAN)	GM1, GD1a
Pharyngeal-cervical brachial variant	GT1a, GQ1b, GD1a
Miller fisher syndrome (MFS)	GQ1b, GT1a

Table 1: The subtypes of GBS and relevant antibodies are recognized [54-57].

In a recent study, 59 GBS cases were compared to 58 neurological controls and 60 non-neurological controls to investigate the association of anti-ganglioside antibodies in GBS and other neurological disorders. Anti-gangliosid1e IgG was present in 82% and IgM in 46% in AIDP patients, 70% and 44% respectively in AMAN subgroup and 38% each in AMSAN subgroup [58]. In GBS, it is possible that the virus has changed the nature of cells in the nervous system so that, the immune system treats them as foreign cells. Through the investigation of lymphocyte subsets in patients with GBS in comparison with healthy controls and other autoimmune diseases may lead to the key role of activation of immune system inappropriately. A compared study of the peripheral blood B lymphocyte subsets such as CD19 expression and counting by flow cytometric analysis may show the characteristic features of cell subsets in relation with the pathogenesis of Guillain-Barre syndrome.

B cells and Lambert-Eaton Myasthenic syndrome

In the LEMS, antibodies against voltage-gated calcium channels (VGCC), decrease the amount of calcium that can enter the nerve ending, hence less acetylcholine (ACh) can be released from the neuromuscular junction. Apart from the skeletal muscle, the autonomic nervous system also requires ACh neurotransmission; this explains the occurrence of autonomic symptoms in LEMS [59,60]. To assess the treatment effects of rituximab in patients with Lambert-Eaton myasthenic syndrome, two patients with LEMS were treated with rituximab. The LEMS antibody patients improved following rituximab treatment. As a selective, B cell targeted therapy; rituximab should be considered as a treatment option for patients with LEMS if standard immunosuppressive treatments have been unsuccessful [61]. Further studies may contribute to the treatment progress of patients with Lambert-Eaton myasthenic syndrome.

Conclusion and Expectation

B cells play significant regulatory roles during immune responses. B cells have both their positive and negative regulatory roles in neuroimmunological diseases including Myasthenia gravis, Multiple sclerosis, Guillain-Barre syndrome, and Lambert-Eaton myasthenic syndrome, etc. B cells function through production of antibodies, acting as APCs, proinflammatory cytokines production. Studies of B10 expressions from MG patients and healthy controls expected to be effective on MG treatment progress in future. Through further studies of B cells and MS in comparison with healthy controls may contribute to reasoning about MS pathogenesis. Studies of GBS, LEMS, and other neuroimmunological diseases with B cells are growing significantly which can lead to new treatment options. As of expectation, in near future, the current studies on B cells will contribute to the new therapeutic options for these neuroimmunological diseases.

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