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B-Cell Dysregulation in Neuroinflammatory Diseases: From Autoantibodies to Immunotherapy

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Abstract

Neuroinflammatory disorders, encompassing a diverse group of conditions affecting the central nervous system (CNS), are increasingly recognized to involve a significant B-cell component. This review synthesizes current findings regarding the role of B cells in the pathogenesis of these disorders, including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and other autoimmune encephalitides. It explores the diverse functions of B cells in neuroinflammation, from autoantibody production to cytokine secretion and antigen presentation, and discusses the therapeutic implications of targeting B cells in these conditions.

Keywords: B cells; Neuroinflammation; Multiple sclerosis; Neuromyelitis optica; Autoantibodies; Cytokines; Antigen presentation; B-cell therapies

Introduction

Neuroinflammatory disorders are a heterogeneous group of conditions characterized by inflammation within the CNS, leading to neuronal damage and neurological dysfunction [1]. While T cells have historically been the primary focus of research in these disorders, accumulating evidence highlights the crucial role of B cells in their pathogenesis. B cells contribute to neuroinflammation through a variety of mechanisms, including the production of autoantibodies, secretion of pro-inflammatory cytokines, antigen presentation to T cells, and formation of ectopic lymphoid structures within the CNS [2]. This review synthesizes current findings regarding the diverse roles of B cells in several key neuroinflammatory disorders, including multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and other autoimmune encephalitides, and discusses the therapeutic implications of targeting B cells in these conditions.

Results

B cells contribute to neuroinflammation through several distinct mechanisms. The most well-established role of B cells is the production of autoantibodies that target CNS antigens. In NMOSD, autoantibodies against aquaporin-4 (AQP4), the most abundant water channel in the CNS, are pathogenic. These AQP4-IgG antibodies bind to AQP4 on astrocytes, leading to complement activation, astrocyte damage, and subsequent demyelination and inflammation. In some forms of autoimmune encephalitis, such as N-methyl-D-aspartate receptor (NMDAR) encephalitis, autoantibodies targeting neuronal surface antigens, like the GluN1 subunit of the NMDAR, directly impair neuronal function [3]. In MS, while a specific pathogenic autoantibody has not been definitively identified, evidence suggests a role for autoantibodies against myelin components and other neuronal antigens in disease pathogenesis. Beyond autoantibody production, B cells also contribute to neuroinflammation through the secretion of pro-inflammatory cytokines, such as TNF-α, IL-6, and lymphotoxin-α (LTα). These cytokines can exacerbate inflammation, promote demyelination, and contribute to neuronal damage. B cells can also act as antigen-presenting cells (APCs), presenting CNS antigens to T cells and activating them within the CNS . This interaction between B cells and T cells can amplify the inflammatory response and contribute to disease progression. In some neuroinflammatory conditions, B cells can organize into ectopic lymphoid structures, such as meningeal inflammation, within the CNS. These structures can serve as local sites for B-cell activation, proliferation, and autoantibody production, further contributing to neuroinflammation . Studies have shown that B cells can also influence the function of other immune cells within the CNS. For instance, B cells can interact with microglia, the resident immune cells of the brain, and modulate their activation state [4-6]. This interaction can contribute to both pro-inflammatory and anti-inflammatory processes within the CNS. Genetic studies have also implicated B-cell-related genes in the susceptibility to neuroinflammatory disorders. Polymorphisms in genes encoding B-cell receptors, signaling molecules, and cytokines have been associated with an increased risk of developing MS and other autoimmune conditions [7]. The efficacy of B-cell depletion therapies in several neuroinflammatory disorders provides strong evidence for the pathogenic role of B cells. Rituximab, an anti-CD20 monoclonal antibody that depletes B cells, has shown efficacy in treating NMOSD and some forms of autoimmune encephalitis. Ocrelizumab and ofatumumab, also anti-CD20 antibodies, are approved for the treatment of relapsing forms of MS . These therapies reduce the number of circulating B cells and subsequently decrease autoantibody production, cytokine secretion, and antigen presentation, leading to a reduction in inflammation and clinical improvement. Recent research has also focused on identifying specific B-cell subsets that contribute to neuroinflammation. Studies have shown that certain B-cell subsets, such as memory B cells and plasmablasts, may play a more prominent role in disease pathogenesis .

Discussion

The findings summarized in this review highlight the diverse and crucial roles of B cells in the pathogenesis of neuroinflammatory disorders. B cells contribute to neuroinflammation through multiple mechanisms, including autoantibody production, cytokine secretion,

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antigen presentation, and formation of ectopic lymphoid structures. The efficacy of B-cell depletion therapies in several of these conditions provides strong evidence for the pathogenic role of B cells [8,9]. While targeting CD20 has proven effective, ongoing research aims to identify more specific B-cell targets to improve therapeutic efficacy and minimize off-target effects. Understanding the specific B-cell subsets and their contributions to different neuroinflammatory disorders is crucial for developing personalized therapeutic strategies. Future research should also focus on elucidating the interactions between B cells and other immune cells within the CNS, as well as the role of environmental factors in modulating B-cell responses in these conditions.

Conclusion

B cells play a critical role in the pathogenesis of various neuroinflammatory disorders, contributing to neuroinflammation through diverse mechanisms. Targeting B cells has proven to be an effective therapeutic strategy in several of these conditions. Further research is needed to fully understand the complex roles of different B-cell subsets and their interactions with other immune cells in the CNS, paving the way for the development of more targeted and effective therapies for these debilitating disorders.

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