B cell dysregulation in autoimmune diseases: From immunopathogenesis to targeted therapy.

Priya N. Sharma*

Division of Hematopathology, University of Michigan Health System, Ann Arbor, MI, USA.

Introduction

B cells play a central role in the immune system by producing antibodies, presenting antigens, and regulating immune responses through cytokine secretion. However, in autoimmune diseases, B cell function becomes dysregulated, contributing significantly to immunopathogenesis. Aberrant B cell activation, survival, and differentiation lead to the production of pathogenic autoantibodies, loss of immune tolerance, and sustained inflammation, all hallmarks of autoimmunity.

In healthy individuals, B cells undergo strict selection processes in the bone marrow and peripheral lymphoid organs to eliminate self-reactive clones. However, in autoimmune conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS), these checkpoints fail, allowing autoreactive B cells to persist. These cells recognize self-antigens and differentiate into plasma cells that secrete autoantibodies, which can form immune complexes, activate complement, and mediate tissue damage.

The immunopathological contribution of B cells extends beyond antibody production. B cells are efficient antigen-presenting cells (APCs) and are capable of activating autoreactive T cells. They also secrete a wide range of pro-inflammatory cytokines, including IL-6, TNF-α, and lymphotoxin, which amplify the immune response and sustain chronic inflammation. Additionally, defects in regulatory B cell (Breg) populations—normally responsible for suppressing immune responses—have been observed in several autoimmune disorders, further contributing to immune dysregulation [1-5].

B cell hyperactivity is often associated with elevated levels of B cell activating factor (BAFF), a cytokine that promotes B cell survival and maturation. Overexpression of BAFF has been linked to the persistence of autoreactive B cells in diseases like SLE. Moreover, genetic polymorphisms affecting B cell receptor (BCR) signaling pathways have also been implicated in the pathogenesis of autoimmunity, highlighting the multifactorial nature of B cell dysfunction [6-10].

The recognition of B cells as key drivers of autoimmunity has led to the development of targeted therapies aimed at depleting or modulating B cell activity. **Rituximab**, a monoclonal antibody against CD20, depletes mature B cells and has shown efficacy in RA, ANCA-associated vasculitis, and off-label use in SLE. Other agents, such as **belimumab**, a BAFF inhibitor, target B cell survival pathways and are approved for SLE and lupus nephritis.

Emerging therapies are becoming more precise, targeting specific B cell subsets or functions while preserving protective immunity. For example, **obinutuzumab** and **ofatumumab** are newer anti-CD20 agents with enhanced B cell-depleting activity. In addition, research is underway to develop therapies that specifically eliminate autoreactive B cells or modulate Breg function, offering a more selective approach to treatment.

Despite these advances, challenges remain. Not all patients respond equally to B cell–targeted therapies, and long-term immunosuppression can increase the risk of infections. Biomarkers predicting therapeutic response and monitoring disease activity are needed to optimize treatment strategies and minimize adverse effects.

Conclusion

In conclusion, B cell dysregulation is a critical component of autoimmune disease pathogenesis. Understanding the mechanisms underlying B cell involvement has paved the way for novel therapies that improve outcomes while preserving immune balance. Continued research into B cell biology promises to refine and personalize treatment approaches for autoimmune diseases.

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***Correspondence to:** Priya N. Sharma, Division of Hematopathology, University of Michigan Health System, Ann Arbor, MI, USA. E-mail: pnsharma@umichpath.org

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