B-cell mediated disease

Ali Roghanian, University of Southampton Faculty of Medicine, UK

B cells play an important role in regulating the immune response in both physiological and pathological conditions. Dysregulation of B-cell function can lead to severe consequences for the host, which are discussed below.

Cancer
Many different B-cell malignancies have been described, such as non-Hodgkin’s lymphoma (NHL) and Hodgkin’s lymphoma (HL). B-cell NHL is the most common haematological cancer in adults. Some NHLs are indolent, or slow-growing, yet incurable (e.g., advanced stage follicular lymphoma and some chronic lymphocytic leukaemias). In contrast, others are aggressive with the potential to be rapidly fatal, yet are often curable (e.g., Burkitt’s lymphoma or diffuse large B-cell lymphoma).

Autoimmunity
A primary feature of autoimmune diseases is the loss of B-cell tolerance and the inappropriate production of autoantibodies. More than 80 distinct autoimmune diseases have been described, such as multiple sclerosis (MS), rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Clonally silent B cells could escape cell death and be induced to proliferate and secrete self-reactive antibodies in otherwise healthy individuals in the setting of a random event, such as a virus that induces strong activation signals (e.g., cytokines). Activated B cells also secrete a variety of proinflammatory cytokines and chemokines, e.g., IL-6, tumour necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and macrophage migration inhibitory factor (MIF), which participate in the inflammatory cascade of autoimmune pathology.

Non-autoimmune inflammatory disease
B-cell cytokines also play roles in other non-autoimmune inflammatory diseases, such as type 2 diabetes and periodontal disease.

Transplantation
B cells are thought to play a role in the pathophysiology of chronic graft-versus-host diseases (GVHDs). B cells could be pathogenic through a variety of effector pathways, including antigen presentation to T cells, dysregulated autoimmune antibody synthesis, and allogeneic antibody induction. B-cell depletion therapy is beneficial for patients with GVHD. Moreover, B cells exert a pivotal influence during the initiation of alloimmunity in pre-clinical animal transplant models and B-cell depletion significantly protects organ recipients from chronic rejection.

Spread of human immunodeficiency virus (HIV)
The impact of HIV-associated immunopathogenesis on B cells has been largely associated with indirect consequences of viral replication, such as B-cell hyperactivation. However, emerging experimental and clinical data indicate that HIV interacts directly with CD21 (also known as complement receptor 2; CR2) on B cells in both lymphoid tissues and peripheral blood via complement proteins bound to circulating HIV virions. Other potential receptors present on B cells such as DC-specific ICAM3-grabbing non-integrin (DC-SIGN) and surface immunoglobulins of the variable heavy chain 3 (VH3) family have also been shown to interact with HIV. Through these interactions, B cells could facilitate cell-to-cell transmission of HIV in vivo., though there is little evidence that HIV can productively replicate in B cells in vivo.

B-cell depletion therapy
Due to their known roles in the pathogenesis of a wide spectrum of disorders as highlighted above, B cells are an important therapeutic target. The use of monoclonal antibody (mAb) therapy, to selectively deplete B cells is well-established in the treatment of B-cell malignancies. In recent years, mAb therapy has also been vigorously tested in an increasing number of autoimmune disorders. B cell-directed therapies are being tested in clinical trials for a variety of autoimmune disorders including MS, RA and SLE.

The most widely used mAb in the clinic to treat certain B-cell cancers/autoimmune conditions to date is rituximab (Rituxan/Mabthera). Rituximab is a human/murine chimeric mAb that specifically targets the transmembrane protein CD20 on B cells, leading to a significant depletion of peripheral cancerous/auto-reactive B cells. However, under some circumstances prolonged B-cell depletion may significantly increase the risk of infection. Besides targeting CD20, the newer B cell-directed therapies for a range of B-cell disorders target CD22, CD19, CD40 and CD40 ligand (CD154).