B-cell mediated disease

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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 diabe**tes 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**).