B cell activation and the germinal centre response

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**B cell activation**

B cells are activated when their B cell receptor (BCR) binds to either soluble or membrane bound antigen. This activates the BCR to form microclusters and trigger downstream signaling cascades. The microcluster eventually undergoes a contraction phase and forms an immunological synapse, this allows for a stable interaction between B and T cells to provide bidirectional activation signals.

Once activated B cells may undergo class switch recombination. In their inactivated state B cells express IgM/IgD but once activated they may express IgA, IgE, IgG or retain IgM expression. They do this by excision of the unwanted isotypes (Figure 1). Cytokines produced by T cells and other cells are important in determining what isotype the B cells express.

![Diagram](image_url)

**Figure 1: Class switch recombination.** After VDJ recombination class switch recombination may occur. In this process unwanted Immunoglobulin (Ig) genes are excised so that the desired gene can be expressed. In this depiction excision occurs and IgE is expressed. There are five isotypes which can be found in difference circumstances. For example, IgE is common in allergic responses such as asthma.
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The germinal centre

B cells have two main types of immune responses. In a T-Independent immune response B cells can respond directly to the antigen. In a T-dependent immune response the B cells need assistance from T cells in order to respond.

In this situation activated B cells move to the border of the T cell zone to interact with T cells (Figure 2). CD40 ligand is found on these T helper cells and interacts with CD40 on the B cells to form a stable attraction. Cytokines secreted by T cells encourage proliferation and isotype switching and maintain germinal centre size and longevity. Without these signals the germinal centre response will quickly collapse.

B cells that have encountered antigen and begun proliferating may exit the follicle and differentiate into short-lived plasma cells called plasmablasts (Figure 2). They secrete antibody as an early attempt to neutralize the foreign antigen. They do not survive more than three days but the antibody produced can provide important assistance to stop fast-dividing pathogens such as viruses.

The germinal centre has a light zone and a dark zone. The germinal centre response begins in the dark zone where the B cells rapidly proliferate and undergo somatic hypermutation. During somatic hypermutation, random mutations are generated in the variable domains of the BCR by the enzyme activation-induced cytidine deaminase (AID). B cells then enter the light zone and compete with each other for antigen. If the mutation resulted in a BCR with an improved affinity to the antigen the B cell clone can out-compete other clones and survive. The light zone is also thought to be where B cells undergo class switch recombination, although a germinal centre is not crucial for this process. The B cells may migrate between both zones to undergo several rounds of somatic hypermutation and class switch recombination. The ultimate goal of the germinal centre is to produce B cells with a BCR which has high affinity for the initial antigen.

Figure 2: The migration of B cells in an immune response. When B cells (B) first encounter antigen (★) they migrate to the T-B border to receive survival signals from T cells (T). If they receive survival signals they will begin to proliferate and either become plasmablasts (Bl) or form a germinal centre (Blue). B cells can migrate between the light zone and dark zone of the germinal centre to undergo somatic hypermutation and class switch recombination. Eventually they may leave the GC as high-affinity memory cells (M) or plasma cells (P).
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Plasma and memory cells
B cells leave the germinal centre response as high-affinity plasma cells and memory B cells (Figure 3). Plasma cells secrete antigen-binding antibodies for weeks after activation. They migrate to the bone marrow soon after formation where they can reside indefinitely ready to encounter the antigen again and respond. Memory B cells circulate throughout the body on the lookout for antigen with a high-affinity for their BCR and then quickly respond to the antigen, stopping infection. This is how vaccination works. As your body has been previously exposed to the antigen the immune cells can quickly respond to remove the antigen if it is encountered again, stopping you getting sick.

Figure 3: B cell differentiation after activation. When a mature B cell encounters antigen that binds to its B cell receptor it becomes activated. It then proliferates and becomes a blasting B cell. These B cells form germinal centres. The germinal centre B cells undergo somatic hypermutation and class switch recombination. Plasma cells and memory B cells with a high-affinity for the original antigen stimuli are produced. These cells are long lived and plasma cells may secrete antibody for weeks after the initial infection.