

4+5) B-cell Activation

1. Antigen Capture and Delivery

- **Cell Migration:** Mature B cells circulate between secondary lymphoid organs searching for antigens.
- **Follicular Entry:** B cells enter follicles guided by the chemokine **CXCL13**, which is secreted by follicular dendritic cells (FDCs).
- **Receptors:** Recirculating naive B cells express the **CXCR5** receptor, which binds to CXCL13 to attract them into the follicle.
- **Survival Factors:** B-cell survival depends on BCR signals and a cytokine called **BAFF** (B cell-activating factor), which provides maturation signals.
- **Native Conformation:** B cells recognize antigens in their **intact, native conformation**; unlike T cells, the antigen is **not processed** by APCs before recognition.
- **Delivery Pathways:**
 - Small antigens reach the follicle through **conduits**.
 - Large antigens are captured by **subcapsular sinus macrophages** and delivered to the follicles.

2. B-Cell Receptor (BCR) Complex and Signaling

- **Signaling Components:** Membrane **IgM** and **IgD** have very short cytoplasmic tails. Signals are actually transduced by two associated molecules, **Ig α** and **Ig β** , which are disulfide-linked.
- **ITAMs:** The tails of Ig α and Ig β contain **immunoreceptor tyrosine-based activation motifs (ITAMs)** that mediate signaling.
- **Enhancement Signals:**
 - **Complement:** The receptor **CR2 (CD21)** binds to complement-coated antigens, significantly enhancing BCR signaling.
 - **TLRs:** B cells express **Toll-like receptors** that recognize microbial **PAMPs**, contributing to proliferation and differentiation.

3. Functional Responses and B-Cell Subsets

- **Early Changes:** Activated B cells enter the **G1 stage** of the cell cycle, increase in size, and produce antiapoptotic proteins like **Bcl-2** to enhance survival.
- **Follicular B Cells:** These are the most common; they produce **IgM** and **IgD** and mediate **T-dependent** responses to protein antigens.
- **Marginal Zone B Cells & B-1 Cells:**
 - They respond to **non-protein antigens** (polysaccharides, lipids) in a **T-independent** manner.
 - They produce mainly **IgM** and differentiate into **short-lived plasma cells**.

4. Helper T-Cell Dependent Responses (Protein Antigens)

- **The Interaction:** Protein antigens require B cells to process the antigen and present peptides on **Class II MHC** molecules to helper T cells.
- **Migration to the Boundary:**
 - Activated T cells increase **CXCR5** to move toward the follicle.
 - Activated B cells increase **CCR7** expression to migrate toward the T-cell zone.
 - They meet and interact at the **boundary of the follicle**.
- **CD40-CD40L:** Activated T cells express **CD40 ligand (CD40L)**, which binds to **CD40** on B cells; this interaction is essential for B-cell proliferation and the initiation of the germinal center reaction.
- **Hapten-Carrier Effect:** Small chemicals (**Haptens**) only become immunogenic when coupled to a protein carrier. This principle is used to create **conjugate vaccines**.

5. The Germinal Center Reaction

Occurring a few days after activation, this is the site for specialized B-cell evolution:

- **TFH Cells:** Follicular helper T cells are the specific subset that triggers B-cell changes within the germinal center.
- **Affinity Maturation:** The process of increasing antibody affinity through **somatic mutation** of Ig genes followed by the selective survival of B cells with the highest affinity receptors.
- **Isotype Switching:** Regulated by T-cell cytokines:
 - **IFN- γ** induces switching to **IgG**.
 - **IL-4** induces switching to **IgE**.
 - **TGF- β** and **BAFF** induce switching to **IgA** in mucosal tissues.

6. Plasma Cells and Memory B Cells

- **Plasma Cells:** Terminally differentiated cells with a high cytoplasm-to-nucleus ratio and prominent **endoplasmic reticulum** for secretory activity.
 - **Short-lived:** Generated in extrafollicular foci; produce primarily **IgM**.
 - **Long-lived:** Generated in germinal centers; home to the **bone marrow** and secrete antibodies for years.
- **Memory B Cells:** Express high levels of **Bcl-2** for long-term survival. They respond rapidly upon secondary exposure to antigen.

7. Antibody Feedback and Effector Mechanisms

- **Antibody Feedback:** Secreted **IgG** inhibits further B-cell activation by binding to the inhibitory **Fc γ RIIB** receptor, blocking BCR signaling.
- **Key Effector Functions:**
 - **Neutralization:** Blocking microbes and toxins from binding to cellular receptors.
 - **Opsonization:** Coating microbes for phagocytosis.
 - **ADCC:** NK cells kill antibody-coated cells by recognizing IgG via **Fc γ RIII**.
 - **Complement Activation:** Initiated primarily by **IgM and IgG**.