Microbiology 1

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B-cell Response / T-dependent B-cell Response

- **T-dependent activation** of B cells involves two distinct epitopes: a surface epitope recognized by B cells and an internal peptide epitope recognized by helper T cells after processing the antigen.
  - Helper T cells express *CD40 ligand (CD40L)* upon activation, which binds to *CD40* on B cells, triggering their *proliferation and differentiation*.
  - T-helper cytokines (e.g., *IFN-γ, IL-4*) regulate *isotype switching* and B cell proliferation.
  - The interaction between *helper T cells* and *B cells* occurs at the *T-B interface* in secondary lymphoid tissues, with key events happening in *extrafollicular foci* and *germinal centers* (sites for affinity maturation, isotype switching, and memory B cell generation).

- **Isotype Switching:**
  - *Cytokines* produced by helper T cells influence which immunoglobulin (Ig) class a B cell will produce. Different cytokines drive switching to specific isotypes (IgM, IgG, IgA, IgE).
    - ✓ *IgM* is primarily produced in response to polysaccharide antigens.
    - ✓ *IFN-γ* (from TH1) induces IgG production.
    - ✓ *IL-4* (from TH2) induces IgE production, important for defense against helminths.
    - ✓ *IgA* is predominantly produced in mucosal tissues.

- **Affinity Maturation:**
  - *Affinity maturation* refers to the process where the affinity of antibodies for an antigen increases during a T-dependent response.
  - This is driven by *somatic mutations* in the *V region* of immunoglobulin genes, leading to the selection of *high-affinity antibodies*.
  - This process is regulated by interactions between *CD40L on T cells* and *CD40 on B cells* and involves the selection of B cells that bind the antigen with the highest affinity.

- **B Cell Differentiation into Antibody-Secreting Plasma Cells:**
  - After activation, B cells differentiate into *plasma cells*, which are responsible for producing antibodies.
    - ✓ *Short-lived plasma cells* are generated early during the immune response in *extrafollicular foci* and during T-independent responses.
    - ✓ *Long-lived plasma cells* are produced in *germinal centers* and are responsible for sustained antibody production. These cells migrate to the *bone marrow*, where they continue to secrete antibodies even after the antigen is cleared.

- **Plasma Cell Differentiation:**
  - Differentiation involves dramatic *cell enlargement* and a prominent *endoplasmic reticulum* for antibody production.
  - Plasma cells secrete antibodies, transitioning from producing *membrane-bound immunoglobulin to secreted antibodies.*

- **Germinal Centers and Follicular Dendritic Cells (FDCs):**
  - *Germinal centers* are critical sites for *affinity maturation, isotype switching*, and *generation of memory B cells.*
  - Follicular dendritic cells *(FDCs)* present antigens to B cells in germinal centers and assist in the selection of high-affinity B cells.

- **Helper T Cell Role in T-dependent Responses:**
  - *Follicular helper T cells (TFH)* are specialized for supporting B cells in the germinal center.
  - TFH cells express *CXCR5* and migrate towards the follicle, where they interact with activated B cells to support their differentiation.

- **B Cell Response / Generation of Memory B Cells and Secondary Humoral Immune Responses:**
  - *Memory B Cells:*
    After encountering an antigen and undergoing activation in *germinal centers*, some B cells differentiate into *memory B cells*. These cells:
    - ✓ Have the ability to *survive long-term* due to high expression of *antiapoptotic proteins* like *Bcl-2*
    - ✓ Do not require continued antigenic stimulation to persist.
    - ✓ Can *recirculate* between the *blood* and *lymphoid organs* or stay in the site where they were generated.
    - ✓ Are *produced during T-dependent responses*, usually alongside memory helper T cells.
  - *Secondary Humoral Immune Response:*
    - ✓ When *memory B cells* encounter the antigen again (secondary exposure), they *reactivate quickly.*
    - ✓ These cells rapidly differentiate into *plasma cells*, produce large quantities of *high-affinity*, *isotype-switched antibodies*, and *re-enter germinal centers* to further refine the antibody affinity.
    - ✓ This results in a *faster and more robust* immune response, providing *enhanced protection*.

- **B Cell Response / Antibody Feedback:**
  - *Inhibition of Continued Activation (Negative Feedback):*
    - ✓ Secreted antibodies can inhibit further B cell activation. They do this by forming *antigen-antibody complexes*, which bind to:
      - The *antigen receptor* (on the B cell) through the antigen.
      - *Inhibitory Fcγ receptors (FcγRIIB*) on antigen-specific B cells through the antibody.
    - ✓ This dual binding brings *inhibitory phosphatases* close to the antigen receptors, blocking the signaling required for further activation and preventing over-activation of the B cell.

- **Effector Mechanisms of Humoral Immunity / Antibody-Dependent Cellular Cytotoxicity (ADCC):**
  - *Natural Killer (NK) Cells in ADCC:*
    - ✓ NK cells, and other leukocytes, can recognize and bind to cells coated with antibodies via *Fc receptors* (specifically *FcγRIII*).
    - ✓ This *binding* activates the NK cells, leading to:
      - Synthesis and secretion of cytokines like *IFN-γ*.
      - Release of cytotoxic *granules* from NK cells, which are responsible for *killing* the antibody-coated target cells.
    - ✓ This process is known as *antibody-dependent cellular cytotoxicity (ADCC*), which is an important mechanism for eliminating infected or cancerous cells in the body.

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