Lec4 Summary. B cell activation & antibody production

Created by; Dr. Mohammad Al-Zuraiqi

Antigen Binding in B Cells:

1. **B cell (B2) binds antigens**:
    - Antigens are always proteins.
    - B cell activation is dependent on T cells.
2. **Antigen presentation**:
    - Antigens are presented to B cells by follicular dendritic cells (DCs) in their native, intact form.
3. **C3d involvement**:
    - The antigen binds to the BCR and C3d binds to another receptor, CR2, on the B cell.
4. **Internalization and processing**:
    - The bound antigen is internalized into endosomal vesicles.
    - If the antigen is a protein, it is processed into peptides, which are presented on the B cell surface for recognition by helper T cells.

T-Dependent (TD) B Cell Activation (Humoral Immune Response):

1. **B cell activation by antigens**:
    - Increases expression of class II MHC molecules and B7 costimulators.
    - Expresses CD40, which engages CD40 ligand (CD40L) on T cells (necessary for isotype switch).
    - Activated B cells increase expression of cytokine receptors.
2. **Helper T cell involvement**:
    - Requires initial activation of naive T cells by the same antigen in T cell zones.
3. **Migration and interaction**:
    - Activated lymphocytes migrate and interact at follicle edges, where B cells present antigens to helper T cells.
4. **Bidirectional activation**:
    - Helper T cell activation results in Th2 cells.
    - B cell activation results in plasma cells.

Germinal Center Activity:

1. **Migration to germinal centers**:
    - Activated B cells migrate to germinal centers after T cell activation.
2. **Proliferation and differentiation**:
    - Each B cell proliferates in response to one antigen, forming clones with identical receptors.
    - B cells switch from membrane-bound IgM to secreting IgM.
    - B cells undergo isotype switching, secreting different antibody types.
3. **Memory and plasma cell formation**:
    - B cells differentiate into memory B cells and plasma cells.
    - The produced antibody's affinity increases via somatic hypermutation.

Isotype Switching:

1. **Naive B cells**:
    - B cell receptors (IgM) are formed by combining constant μ gene with V-D-J genes of the heavy chains.
2. **Activated B cells**:
    - In the germinal center, isotype switching occurs to other antibody types (e.g., IgG, IgA, IgE) while specificity remains the same.
3. **Mechanism**:
    - Isotype switching involves DNA recombination, retaining the variable regions by allelic exclusion.
4. **Key enzyme**:
    - Activation-induced cytidine deaminase (AID) is required for isotype switching and affinity maturation.
5. **CD40 role**:
    - CD40 on B cells binds CD40L on T cells to induce isotype switching.
6. **Defects and diseases**:
    - AID deficiency causes hyper-IgM syndrome.
    - Mutations in the CD40L gene result in X-linked hyper-IgM syndrome, leading to antibody production defects.

Isotype Determinants:

1. **Switching based on antigen type and location**:
    - Protein antigens and T-dependent B cell activation are needed.
    - B cells in mucosal tissues and secretory glands switch to IgA.
2. **Prior antigen exposure**:
    - First exposure leads to more IgM production;
    - repeated exposure leads to more IgG.
3. **Microbial type**:
    - Most bacteria and viruses lead to IgG antibody production.
    - Helminthic parasites and allergens drive IgE antibody responses.

Somatic Hypermutation (Affinity Maturation):

1. **Affinity maturation process**:
    - Leads to increased antibody affinity without changing specificity.
2. **Point mutations**:
    - Germinal center B cells undergo high rates of point mutations (hypermutation) in Ig V genes.
    - Produces high-affinity antibodies, making the immune response stronger over time.
3. **Selection of high-affinity B cells**:
    - B cells with high-affinity antibodies survive and become plasma or memory cells.
    - Low-affinity B cells die (selection process).

Plasma Cells:

1. **Long-lived plasma cells**:
    - Generated in T-dependent responses to protein antigens.
    - Can maintain antibody production for decades or a lifetime without needing antigen restimulation.
2. **Formation and migration**:
    - Plasma cells are identified as antibody-secreting cells that do not express CD20.
    - Some plasma cells remain in the lymph nodes, while others enter circulation and home to the bone marrow.
3. **Short-lived plasma cells**:
    - Rapidly formed in secondary lymphoid organs, undergo apoptosis after a few days.

Memory B Cells:

1. **T-dependent activation**:
    - B cells activated in a T-dependent manner differentiate into memory cells.
2. **Resting state**:
    - Memory B cells survive in a resting state for years, ready to mount rapid responses upon re-exposure to the same antigen.
3. **High anti-apoptotic protein**:
    - Memory B cells express high levels of Bcl-2, contributing to their long lifespan.
4. **Role in infections and vaccines**:
    - Infections and effective vaccines induce long-lived plasma cells and memory B cells.
    - Conjugate vaccines are used for antigens like capsular polysaccharides, linking them to proteins to activate T cells.

B1 Cells (CD5+ B Cells):

1. **Characteristics**:
    - Comprise 5-10% of blood B cells, present from fetal life.
    - Respond to non-protein antigens (polysaccharides, lipids, nucleic acids).
    - Self-renewing and located in mucosal tissues and peritoneum.
2. **T-independent response**:
    - Do not require helper T cells.
    - Respond by engaging BCR and Toll-like receptors (TLRs) on B cells.
3. **Short-lived plasma cells**:
    - Some B1 cells differentiate into short-lived plasma cells.
    - Do not undergo isotype switching or affinity maturation.

Primary and Secondary Immune Responses:

1. **Primary response**:
    - Activates naive B and T cells, producing more IgM.
2. **Secondary response**:
    - Activates memory B and T cells, resulting in faster, stronger IgG production.
    - Isotype switching and affinity maturation increase with repeated exposure.

Factors Influencing B Cell as APC to T Cells:

1. **Antigen binding**:
    - Receptor and coreceptor binding to antigen enhances B cell activation.
2. **Co-receptor involvement**:
    - The CR2-CD19-CD81 complex on B cells enhances antigen binding.
    - Immunoglobulin alpha and beta also assist in signal transduction inside B cells.
3. **B7 proteins and CD40**:
    - B7-1 (CD80) and B7-2 (CD86) on B cells bind CD28 on T cells for activation (signal 2).
    - CD40 binds CD40L on T cells, promoting isotype switching and B cell activation.

Inhibition of B Cells:

1. **Negative feedback via IgG**:
    - Secreted IgG inhibits B cell activation by binding to the inhibitory CD32 (FcγRIIB) receptor.
2. **Link to autoimmune disease**:
    - Polymorphisms in FcγRIIB are associated with systemic lupus erythematosus (SLE).
3. **CD22 inhibitory receptor**:
    - B cells express another inhibitory receptor called CD22.