NOVA

Charting New Horizons in Education

B cells activation & antibody production

04

Immunology

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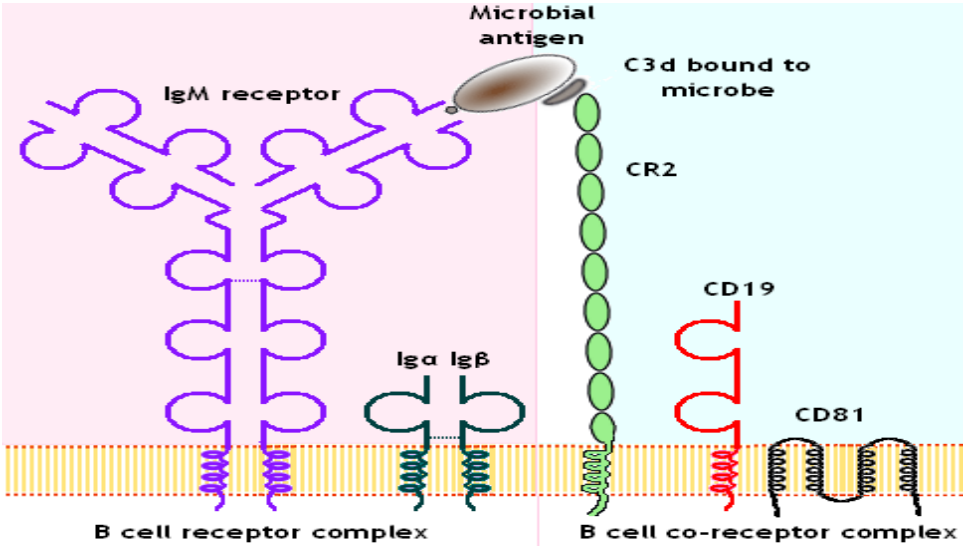
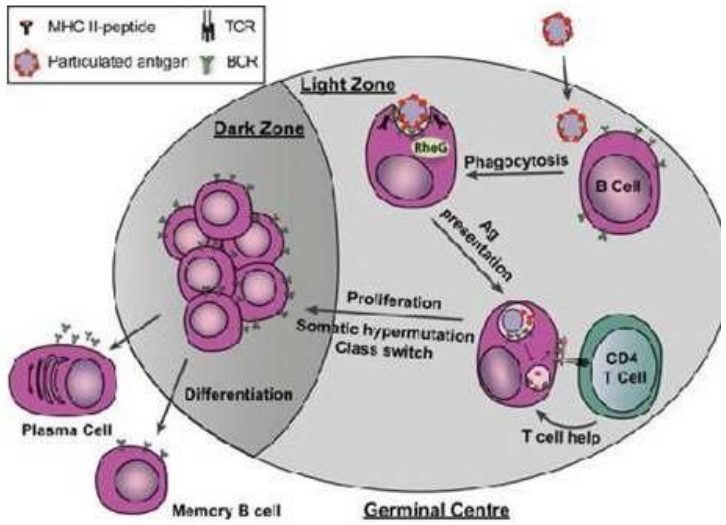
Antigen Binding in B Cells

- B cell (B2) bind Antigens (always proteins) then B cell activation is T cell dependent.
- **Steps in Activation:**
  - **Antigen Presentation:**
    - Antigen is presented to B cells in the follicle by follicular dendritic cells (DCs).
    - The antigen binds to the B cell receptor (BCR) in its intact, native conformation and is not processed by antigen-presenting cells.
  - **Complement Binding:**
    - The antigen carries **C3d**, which binds to another receptor on the B cell (CR2).
  - **Internalization and Processing:**
    - The receptor internalizes the bound antigen into endosomal vesicles.
    - If the antigen is a protein, it is processed into peptides that are presented on the B cell surface for recognition by helper T cells (B cell acts as an antigen-presenting cell to T helper cells).



T- dependent (TD) B cell activation (Humoral immune response)

- **Activation of B Cells by Antigen result in**
  1. Increases expression of class II MHC molecules and B7 costimulators.
  2. B cells express CD40, which engages CD40 ligand (CD40L) on T cells (needed for isotype switching).
  3. Increased cytokine receptors on activated B cells.
- **Helper T Cell–Dependent B cell Activation**
  - Requires initial activation of naive T cells by the same antigen as B cells in T cell zones.
  - Activated lymphocytes migrate toward one another and interact at the edges of follicles.
  - B cells present antigen to helper T cells.
- **Bidirectional Activation**
  - Th cell activation results in Th2 cells.
  - B cell activation results in plasma cells.



In germinal center

- Activated B cells by T cells migrate to the germinal centers.
- Each B cell proliferates in response to one antigen, resulting in a clone of cells with receptors of identical specificities.
- **Differentiation to Plasma Cells**
  - B cells switch from membrane-bound IgM to secreting IgM.
  - B cells perform immunoglobulin isotype switching, secreting different types of antibodies.
- Some B cells differentiate into memory B cells.
- The affinity of the produced antibodies increases through somatic hypermutation (affinity maturation).

Isotype switch

- During B cell development in the bone marrow, naïve B cell receptors (IgM) are formed by combining the constant μ gene to the V-D-J genes of the heavy chains.
- In activated B cells within the germinal center, isotype switching occurs to other antibody isotypes by combining other constant regions such as Cγ for IgG, Cα for IgA, and Cε for IgE to the variable part of the heavy chain, while the specificity of the antibodies (determined by the variable regions) remains unchanged.
- The molecular mechanism of isotype switching involves DNA recombination, where B cells change the isotype of the antibodies they produce by altering constant genes while keeping the variable regions unaltered through allelic exclusion.
- The key enzyme required for isotype switching and affinity maturation is activation-induced cytidine deaminase (AID), and deficiencies of AID underlie some forms of the hyper-IgM syndrome.
- CD40 expression on B cells and its binding to CD40L on helper T cells work to induce isotype switching, and mutations in the CD40L gene result in a disease called X-linked hyper-IgM syndrome, which is characterized by defects in antibody production.

Isotype Determinants

- Isotype switching occurs in response to different types of microbes, requiring protein antigens and T-dependent B cell activation.
- B cells in different anatomical sites switch to various isotypes:
  - In mucosal tissues and secretory glands, B cells switch to IgA.
- Antigen exposure history influences isotype switching:
  - First exposure: more IgM.
  - second exposures: more IgG.
- Microbe type affects isotype switching:
  - Viruses and bacteria: IgG antibodies.
  - Helminthic parasites and allergens: IgE antibodies.

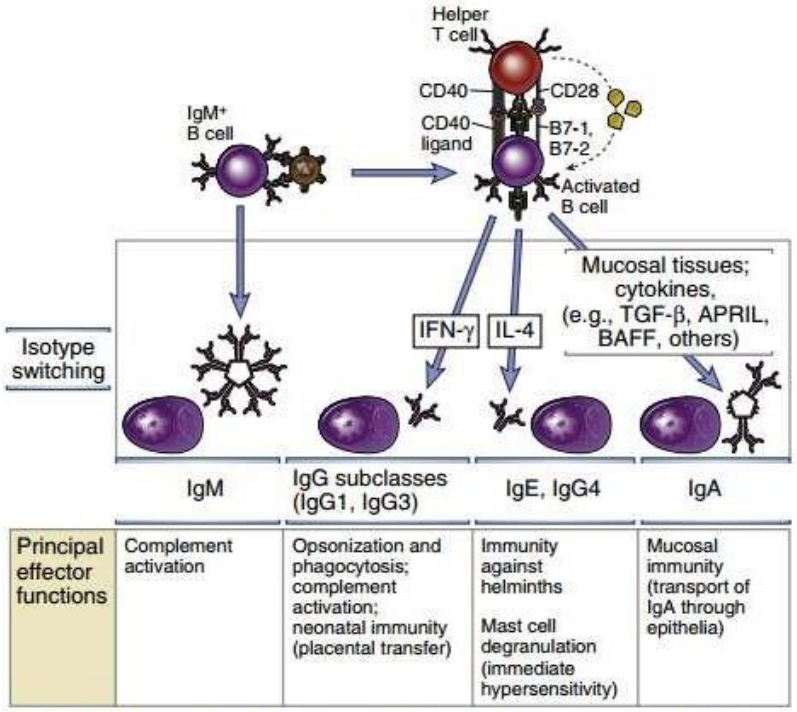


FIGURE 12-14 Ig heavy chain isotype switching. B cells activated by helper T cell signals (CD40L, cytokines) undergo switching to different Ig isotypes, which mediate distinct effector functions. Selected examples of switched isotypes are shown. The role of IFN-γ in directing specific isotype switching events has been established only in rodents.

Somatic hyper mutation

- Somatic hypermutation, or affinity maturation, leads to increased affinity of produced antibodies.
- In proliferating germinal center B cells:
  - Ig V genes undergo point mutations at an extremely high rate (hypermutation) to produce high-affinity antibodies, enhancing binding strength without changing specificity.
- As a result, with increased duration of infection or repeated infections:
  - The produced antibodies become stronger and more specific.
- Cells are exposed to antigens on follicular dendritic cells, leading to the following outcomes:
  - B cells producing high-affinity antibodies proliferate and differentiate into:
    - Antibody secretors (plasma cells)
    - Non-antibody secretors (memory B cells)
  - B cells producing low-affinity antibodies die. This process is known as selection.

Activated B cells migrate into the germinal center

B cell proliferation in the dark zone

Somatic hypermutation of Ig V genes

B cell recognition of antigen on follicular dendritic cells and selection of high-affinity B cells

Apoptosis of B cells that do not bind to antigens

High-affinity B cells exit lymph node

Generation of antibody secreting B cells and memory B cells

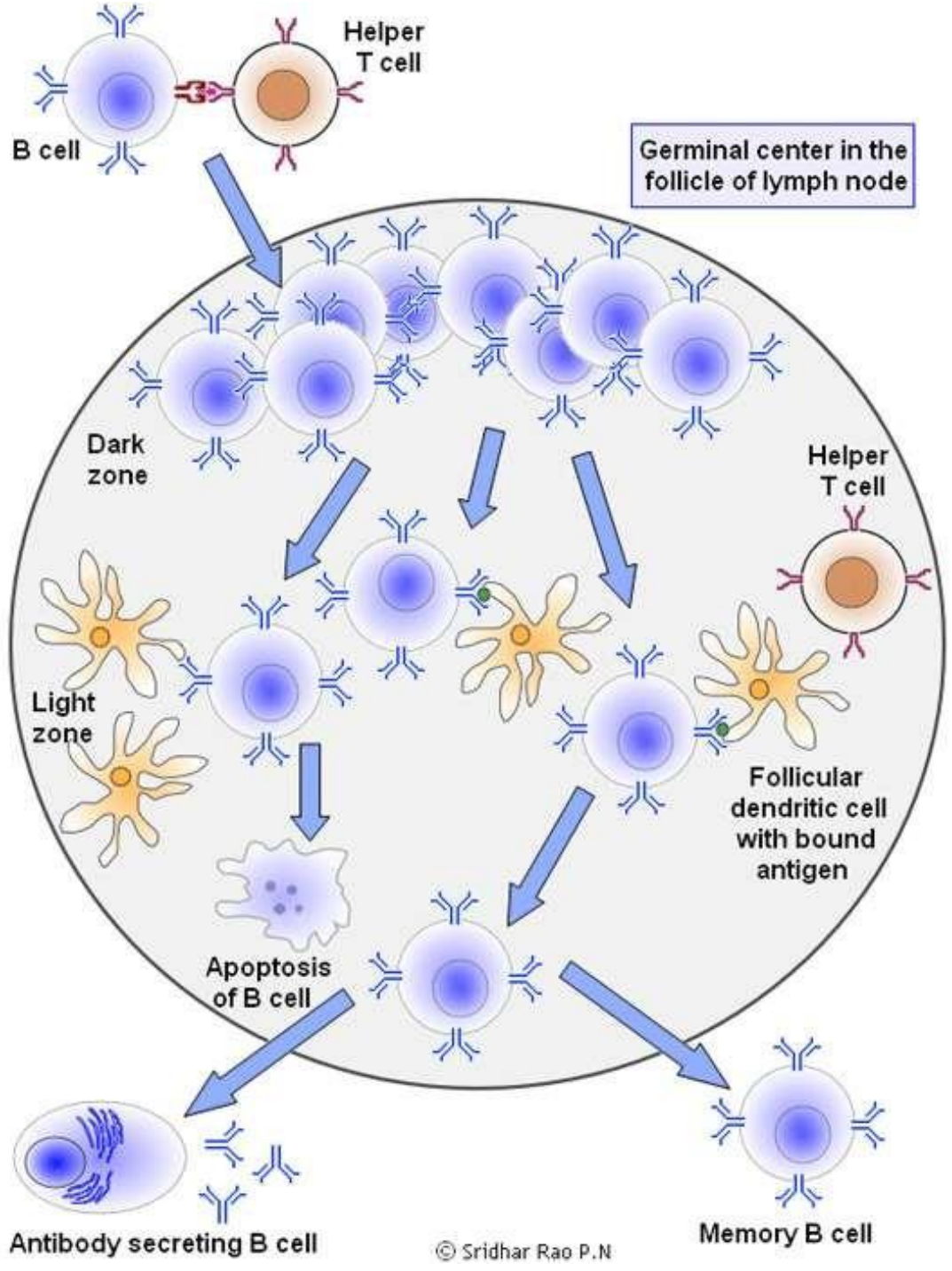


TABLE 11-2 Properties of thymus-dependent and thymus-independent antigens

Property	TD antigens	TI antigens	
		Type 1	Type 2
Chemical nature	Soluble protein	Bacterial cell- wall components (e.g., LPS)	Polymeric protein antigens; capsular polysaccharides
Humoral response			
Isotype switching	Yes	No	Limited
Affinity maturation	Yes	No	No
Immunologic memory	Yes	No	No
Polyclonal activation	No	Yes (high doses)	No

Table 11-2
Kuby IMMUNOLOGY, Sixth Edition

Plasma Cells

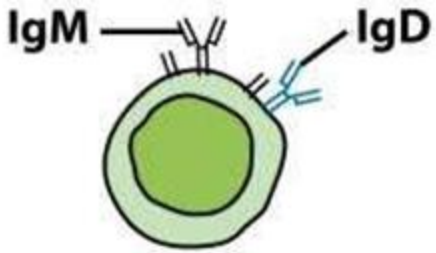
- **Long-lived plasma cells** are generated in T-dependent germinal center responses to protein antigens.
  - They maintain antibody production for decades or even for the lifetime of an individual.
  - Unlike B cells, long-lived plasma cells do not require antigen restimulation to generate antibodies.
- Signals from the B cell antigen receptor and IL-21 cooperate in the generation of plasma cells.
  - Plasma cells are identified as antibody-secreting cells that do not express CD20, a marker of mature B cells.
- Some plasma cells generated in germinal centers:
  - Remain in the medulla of secondary lymph nodes.
  - Enter circulation and home to the bone marrow.
- **Short-lived plasma cells** are rapidly formed in secondary lymphoid organs, where they undergo apoptosis after a few days.

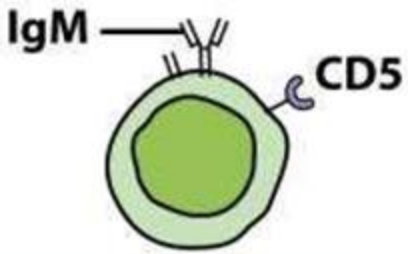
Memory B Cells

- **B cells activated only in a T-dependent manner** may differentiate into memory cells.
  - Memory B cells survive in a resting state in peripheral lymph nodes or bone marrow without secreting antibodies for many years.
  - They mount rapid responses upon subsequent encounters with the same antigen (secondary immune response).
- **Characteristics of memory B cells**:
  - High levels of the anti-apoptotic protein Bcl-2 contribute to their long lifespan.
  - High expression of the CD27 protein.
- **Infections or effective vaccines** against microbes and microbial toxins must induce long-lived plasma cells and memory B cell formation:
  - These events occur only if helper T cells are activated.
- **Application in vaccine design**:
  - For some bacterial infections, the target antigen is a capsular polysaccharide or hapten, which cannot stimulate T cells.
  - In these cases, the polysaccharide is covalently linked to a foreign protein to form a conjugate, which does activate helper T cells.
  - Such vaccines are called conjugate vaccines.

B1 cells (CD5+ B cells)

- **B-1 cells** constitute 5-10% of blood B cells and are naturally present from fetal life.
- **Characteristics of B-1 cells**:
  - Respond to non-protein antigens (T-independent antigens) with repeating determinants, such as: Polysaccharides, Some lipids, Nucleic acids
- These cells are **self-renewing** and found in the peritoneum and mucosal sites.
- B-1 cells do not require antigen-specific helper T lymphocytes:
  - Their responses are elicited by:
    - Engagement of the B cell receptor (BCR) with the antigen.
    - Activation of Toll-like receptors (TLRs) on B cells by pathogen-associated molecular patterns (PAMPs) derived from microbes.
- Some activated B cells differentiate into **short-lived antibody-secreting plasma cells**:
  - They do not undergo isotype switching or affinity maturation.
  - Some antibodies switch to IgM, IgA, and IgG2 (natural antibodies).



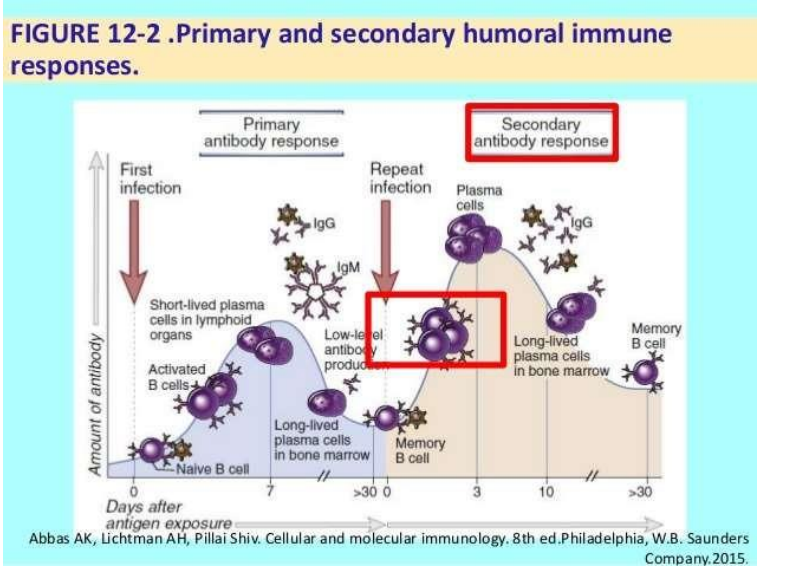


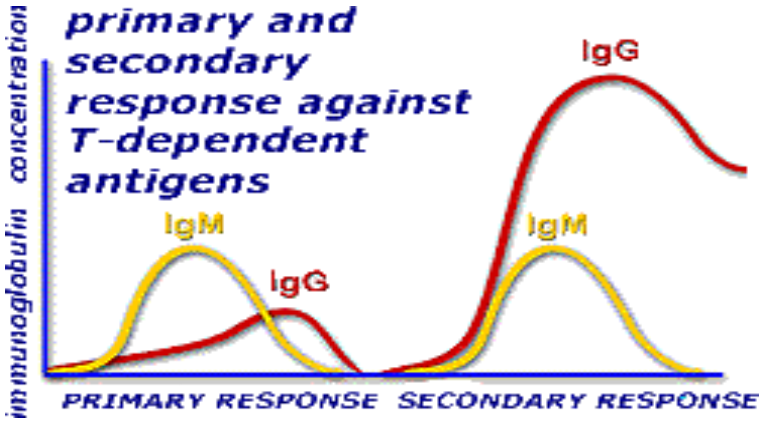
Attribute	Conventional B cells (B-2 B cells)	B-1 B cells
Major sites	Secondary lymphoid organs	Peritoneal and pleural cavities
Source of new B cells	From precursors in bone marrow	Self-renewing (division of existing B-1 cells)
V-region diversity	Highly diverse	Restricted diversity
Somatic hypermutation	Yes	No
Requirements for T-cell help	Yes	No
Isotypes produced	High levels of IgG	High levels of IgM
Response to carbohydrate antigens	Possibly	Definitely
Response to protein antigens	Definitely	Possibly
Memory	Yes	Very little or none
Surface IgD on mature B cells	Present on naive B cells	Little or none

Figure 11-5
Kuby IMMUNOLOGY, Sixth Edition

Primary and Secondary Immune Response

- Primary and secondary antibody responses to protein antigens differ qualitatively and quantitatively:
  - **Primary Response:**
    - Results from the activation of previously unstimulated naive B and T cells.
    - Characterized by the production of IgM antibodies.
  - **Secondary Response:**
    - Due to the stimulation of memory B and T cells.
    - Develops more rapidly than the primary response.
    - Produces larger amounts of antibodies, primarily IgG.
    - Isotype switching and affinity maturation increase with repeated exposure to protein antigens.
- Studies show that IgG+ memory B cells preferentially generate plasma cells, whereas IgM+ cells re-initiate germinal center reactions.





Difference Between Primary Response and Secondary Response.

	Primary Response	Secondary Response
Exposure to antigen	first exposure to a specific antigen	*after second exposure to the same a*ntigen
Time of onset	1-week delay	Within hours
Strength	weak potency	more potent
Duration	Short life , for only a few weeks	forms antibodies for many months
Type of antibody	IgM	IgG

Factors influencing the Strength binding of B Cell as antigen presenting cell (APC) to T cells

- Antigen binding increase by (First signal for cells activation).
- Key components involved in this process:
  - **Receptors and Coreceptors (**enhances the strength of interaction)
  - **Transmembrane Signaling Protein (**transmitting signals within the cell)
- **Coreceptor:**
  - A protein on the surface of the cell that binds to the antigen simultaneously with the receptor.

Costimulatory Receptors on B Cells

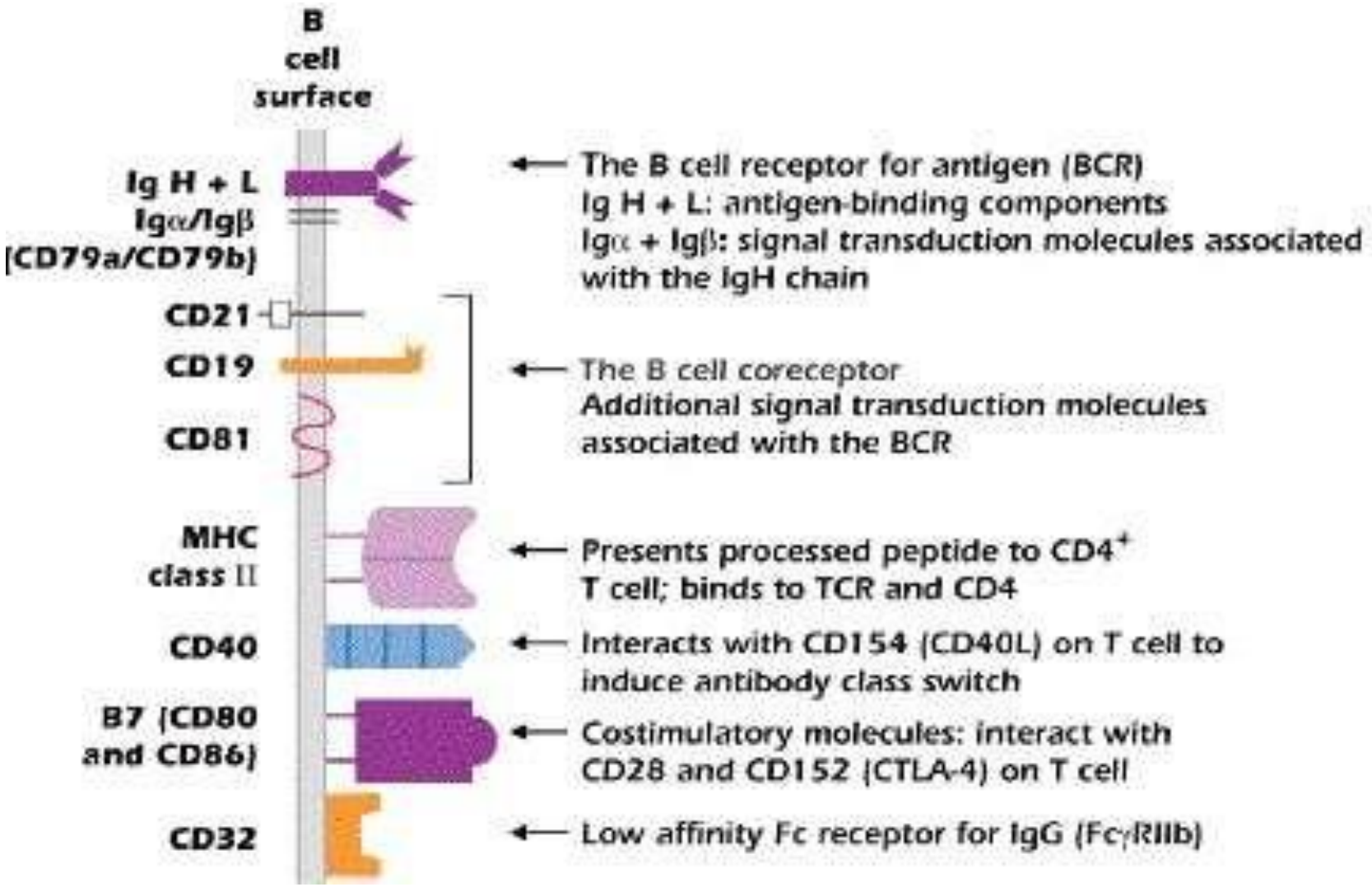
- **B Cell Co-receptor Complex:**
  - The B cell co-receptor, CR2 (CD21), is expressed on mature B cells as a complex (TAPA-1) with two other membrane proteins:
    - **CD19**
    - **CD81**
  - This complex is often referred to as the B cell coreceptor complex.
- **Functionality:**
  - **CD21:** Binds complement proteins C3d on microbes.
  - **CD19:** Transduces the signal into the cell.
  - **CD81:** Stabilizes both CD21 and CD19 molecules.
- **Signal Transduction:**
  - Immunoglobulin alpha and beta, alongside the B cell receptor (BCR), also participate in signal transduction within B cells.

Costimulatory Receptors on B Cells

- **Costimulatory Signals:**
  - **B7-1 (CD80) and B7-2 (CD86):**
    - Ligands on B cells and antigen-presenting cells (APCs).
    - Bind to CD28 on T helper (Th) cells, providing signal 2 in T-B cell interaction, leading to B cell activation.
  - **CD40:**
    - A glycoprotein present on B cells that binds to CD40L on T cells.
    - This interaction leads to B cell activation and isotype switching.

Inhibition of B cells

- **Mechanism of Inhibition:**
  - Secreted antibodies (IgG) inhibit ongoing B cell activation by binding to the inhibitory receptor **CD32 (FcγRIIB)** on B cells, which serves as a negative feedback mechanism.
- **Genetic Link:**
  - A polymorphism in the FcγRIIB gene has been linked to susceptibility to the autoimmune disease **systemic lupus erythematosus (SLE)**.
- **Additional Inhibitory Receptor:**
  - B cells also express another inhibitory receptor called **CD22**.


B cell surface
Ig H + L
Igα/Igβ (CD79a/CD79b)
CD21
CD19
CD81
MHC class II
CD40
B7 (CD80 and CD86)
CD32
The B cell receptor for antigen (BCR)
Ig H + L: antigen-binding components
Igα + Igβ: signal transduction molecules associated with the IgH chain
The B cell coreceptor
Additional signal transduction molecules associated with the BCR
Presents processed peptide to CD4+ T cell; binds to TCR and CD4
Interacts with CD154 (CD40L) on T cell to induce antibody class switch
Costimulatory molecules: interact with CD28 and CD152 (CTLA-4) on T cell
Low affinity Fc receptor for IgG (FcγRIIb)

Thank you

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