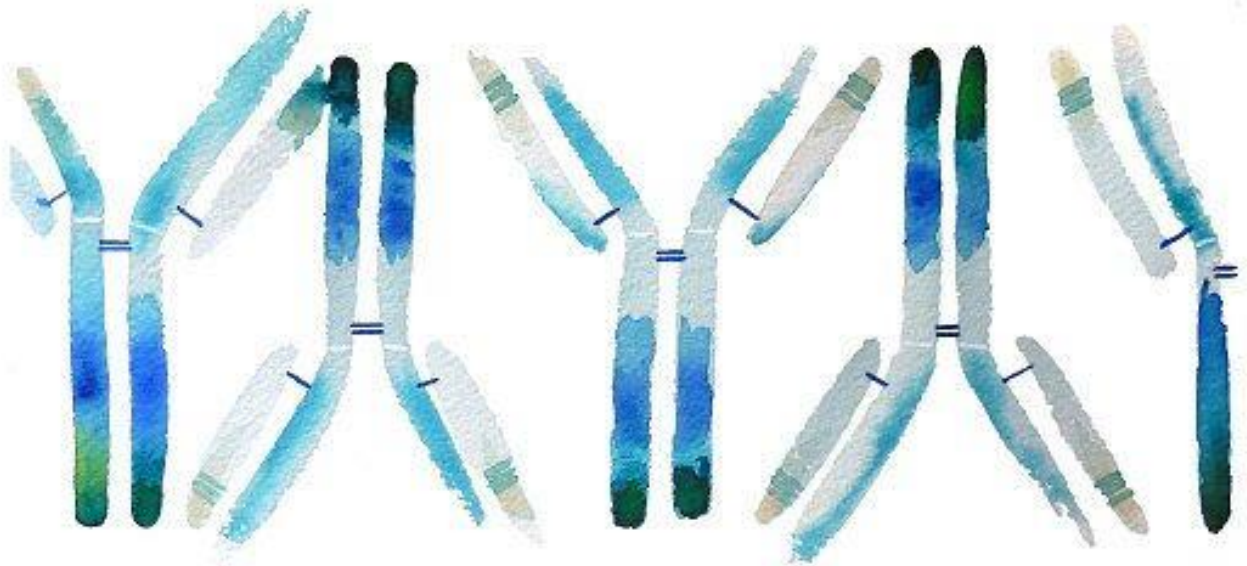
Medical Immunology



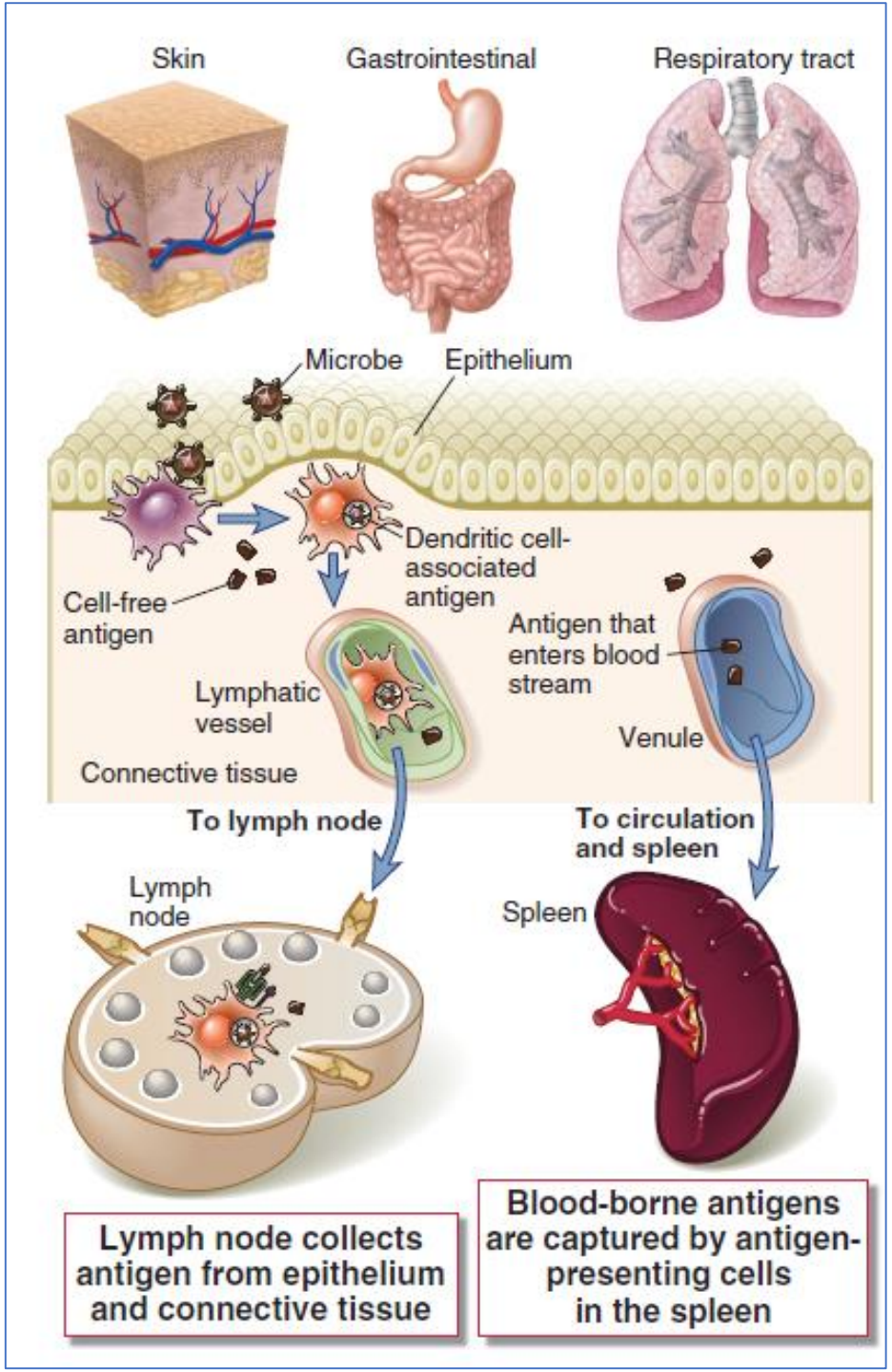
Anas Abu-Humaidan
M.D. Ph.D.

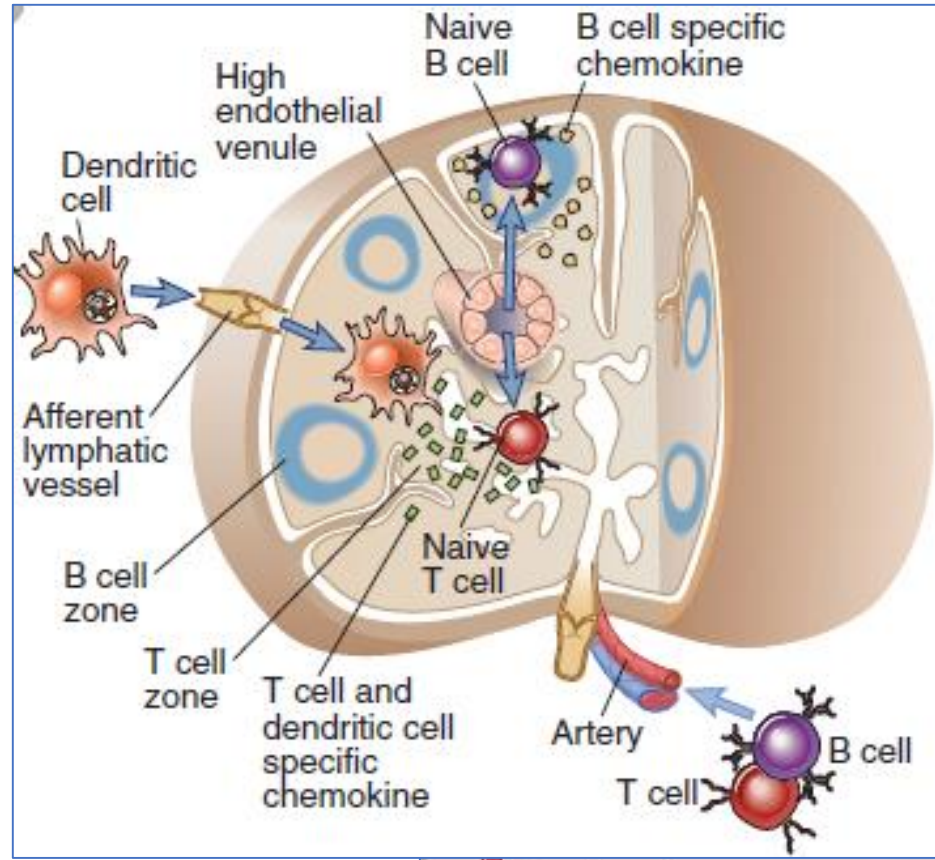
Lecture 13

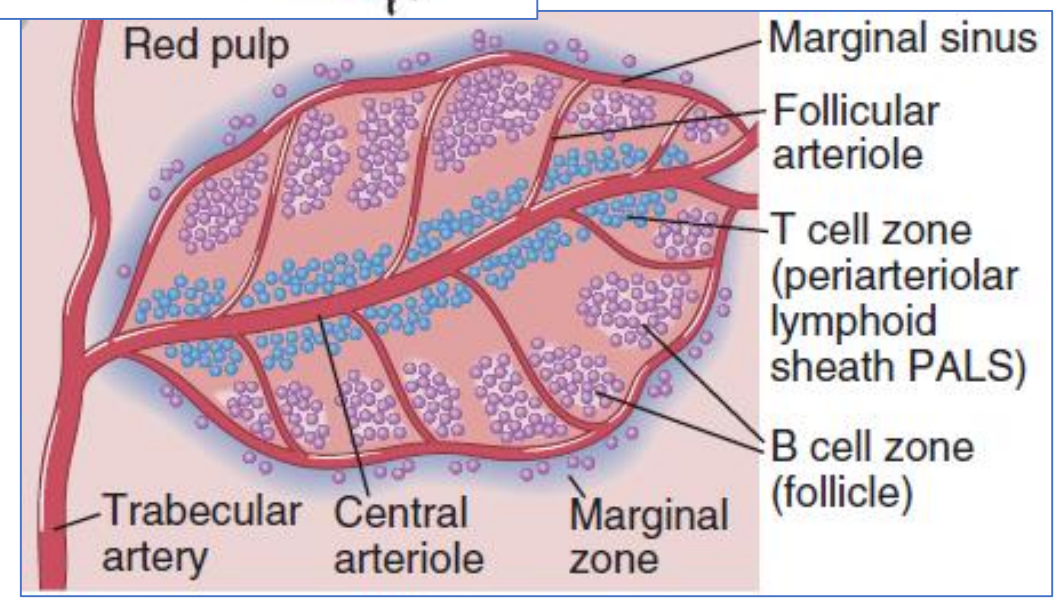
B cell response

In this lecture we will discuss:

- B-cell response
- Active and passive immunity


Skin
Gastrointestinal
Respiratory tract
Microbe
Epithelium
Dendritic cell-associated antigen
Cell-free antigen
Antigen that enters blood stream
Lymphatic vessel
Venule
Connective tissue
To lymph node
To circulation and spleen
Lymph node
Spleen
Lymph node collects antigen from epithelium and connective tissue
Blood-borne antigens are captured by antigen-presenting cells in the spleen


Naive B cell
B cell specific chemokine
High endothelial venule
Dendritic cell
Afferent lymphatic vessel
B cell zone
T cell zone
Naive T cell
T cell and dendritic cell specific chemokine
Artery
B cell
T cell

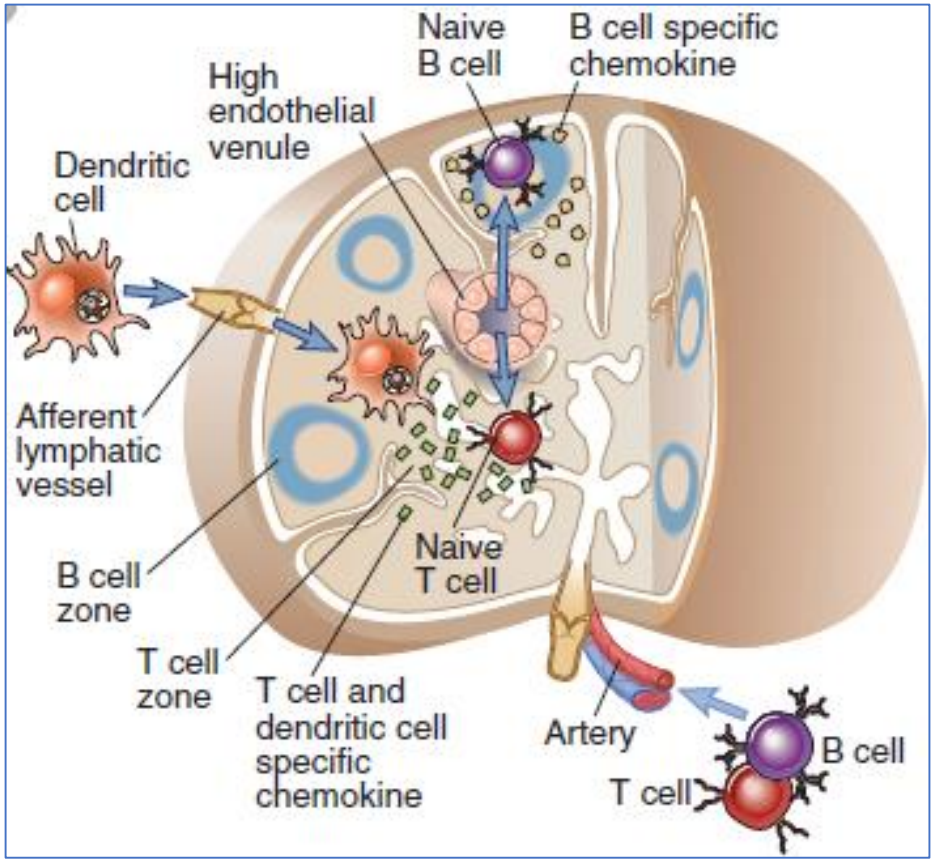

Red pulp
Marginal sinus
Follicular arteriole
T cell zone (periarteriolar lymphoid sheath PALS)
B cell zone (follicle)
Trabecular artery
Central arteriole
Marginal zone

B cell response/ Antigen Capture and Delivery to B Cells

- Mature B lymphocytes migrate from one secondary lymphoid organ to the next in search of antigen.

- Most B cells enter follicles guided by the chemokine **CXCL13** secreted by follicular dendritic cells and are called follicular B cells or recirculating B cells. CXCL13 binds to the **CXCR5** chemokine receptor on recirculating naive B cells and attracts these cells into the follicles

- Naive follicular B cells survive for limited periods until they encounter antigen, survival depends on **signals** from the **BCR** as well as on inputs received from a cytokine called **BAFF** (B cell–activating factor of the TNF family, also known as BLyS, for B lymphocyte stimulator), which provides maturation and survival signals through the BAFF receptor.



B cell response/ Antigen Capture and Delivery to B Cells

- Soluble antigens, generally smaller than 70 kD, may reach the B cell zone through conduits that extend between the subcapsular sinus and the follicle and **interact directly with specific B cells.**

- **Subcapsular sinus macrophages** capture large microbes and antigen-antibody complexes and deliver these to follicles, which lie under the sinus

- Medium sized antigens may be captured in the medullary region by resident dendritic cells and transported into follicles, where they can activate B cells.

- Antigens in immune complexes may bind to complement receptors (in particular the complement receptor type 2 or **CR2**) on **marginal zone B cells**, and these cells can transfer the immune complex–containing antigens to **follicular B cells**.

- In all these cases, the antigen that is presented to B cells is generally in its **intact, native conformation** and is not processed by antigen-presenting cells

B cell response/ Antigen Capture and Delivery to B Cells

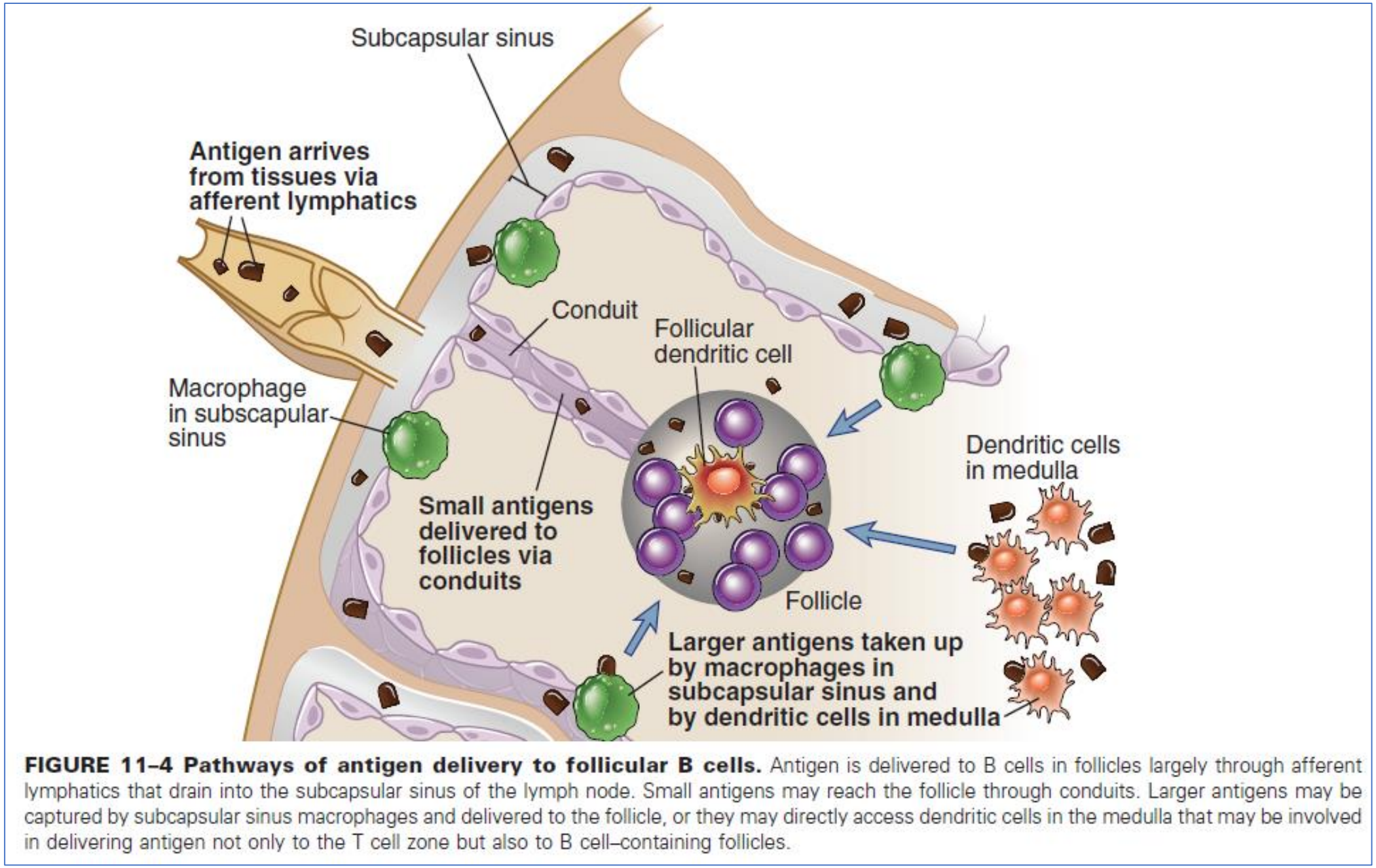


FIGURE 11–4 Pathways of antigen delivery to follicular B cells. Antigen is delivered to B cells in follicles largely through afferent lymphatics that drain into the subcapsular sinus of the lymph node. Small antigens may reach the follicle through conduits. Larger antigens may be captured by subcapsular sinus macrophages and delivered to the follicle, or they may directly access dendritic cells in the medulla that may be involved in delivering antigen not only to the T cell zone but also to B cell–containing follicles.

B cell response/ Activation of B Cells

- Membrane **IgM** and **IgD**, the antigen receptors of **naïve B cells**, have short cytoplasmic tails consisting of only three amino acids (lysine, valine, and lysine).

- Ig-mediated signals are transduced by two other molecules, called **Igα and Igβ**, that are disulfide linked to one another and are expressed in B cells noncovalently **associated with membrane Ig**

- **B cell receptor complexes** in class-switched B cells, including memory B cells, contain membrane immunoglobulins that may be of the IgG, IgA, or IgE classes

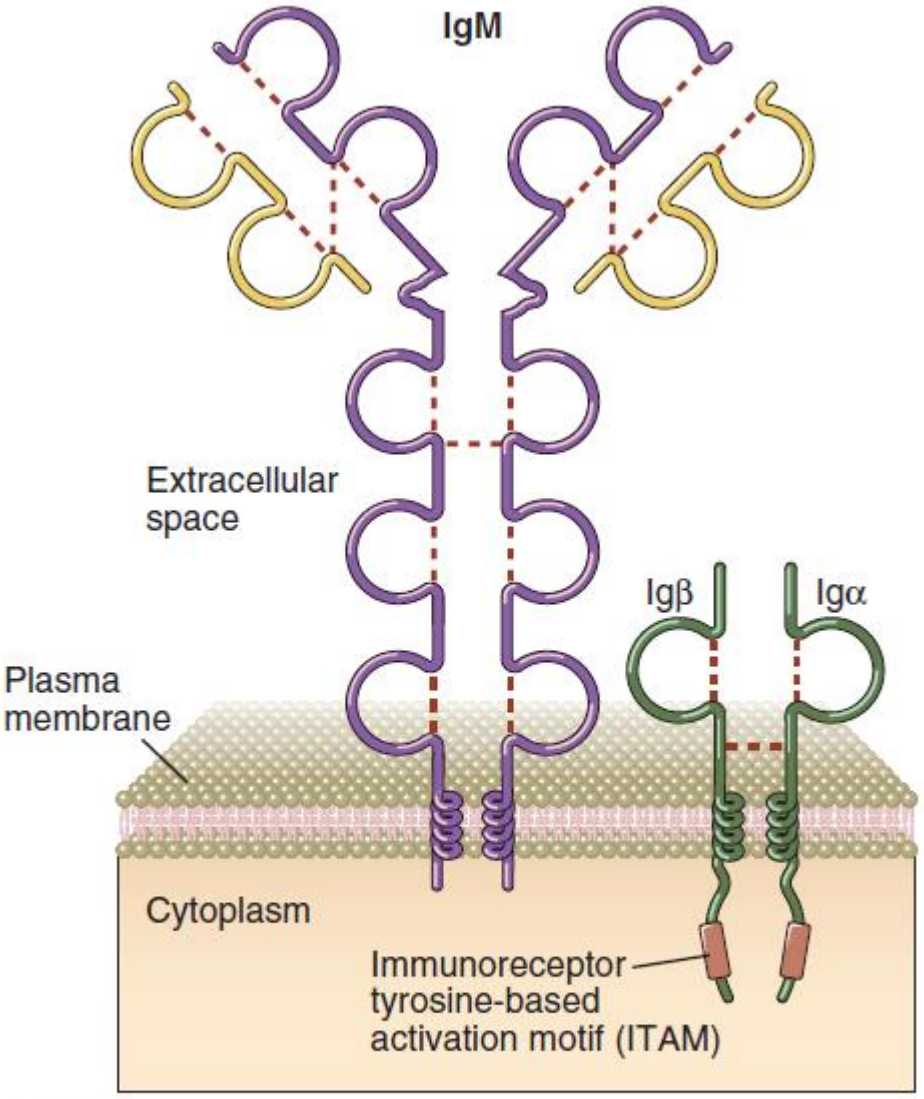


FIGURE 7–18 B cell antigen receptor complex. Membrane IgM (and IgD) on the surface of mature B cells is associated with the invariant Igβ and Igα molecules, which contain ITAMs in their cytoplasmic tails that mediate signaling functions. Note the similarity to the TCR complex.

B cell response/ Activation of B Cells

- The activation of antigen-specific B lymphocytes is initiated by the binding of antigen to membrane Ig molecules, which, in conjunction with the associated Igα and Igβ proteins, make up the antigen receptor complex of mature B cells.

- **Binding** of antigen to the receptor **delivers biochemical signals to the B cells that initiate the process of activation**. It also **internalizes the bound antigen** into endosomal vesicles, and if the antigen is a protein, it is processed into peptides that may be presented on the B cell surface for recognition by helper T cells.

- For full responses to be induced, other stimuli cooperate with BCR engagement, including **complement proteins**, **pattern recognition receptor**s, and, in the case of protein antigens, **helper T cells**.

B cell response/ Activation of B Cells

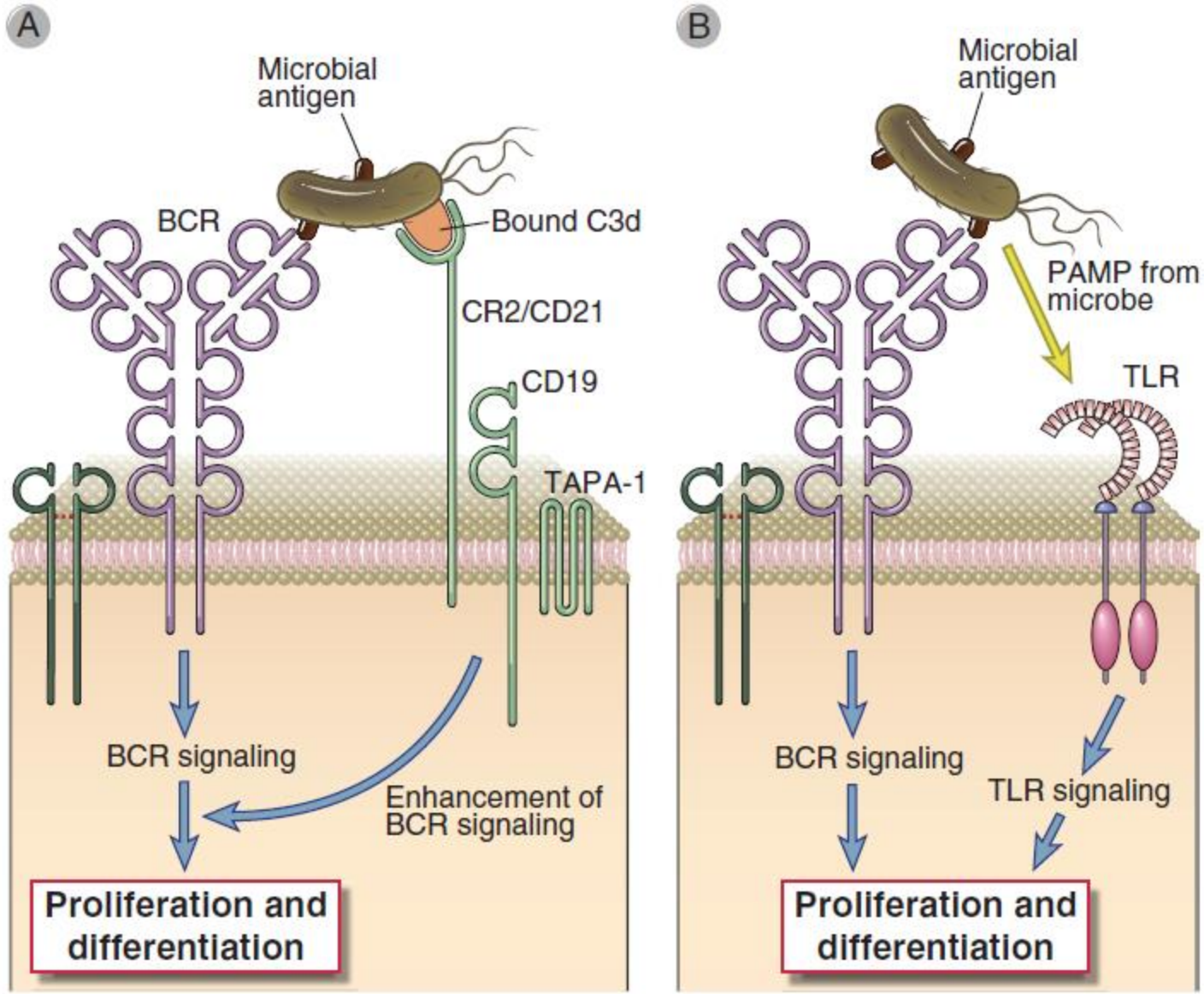


FIGURE 11–5 Role of CR2 and TLRs in B cell activation. In immune responses to microbes, activation of B cells through the BCR may be enhanced by complement-coated antigen that can simultaneously ligate the BCR and complement receptor 2 (CR2) **(A)**, and may also involve the contemporaneous activation of Toll-like receptors (TLRs) on B cells by molecules (so-called pathogen-associated molecular patterns [PAMPs]) derived from the microbe **(B)**.

B cell response/ Functional Responses of B Cells to Antigens

- Antigen receptor cross-linking by some antigens can stimulate several important changes in B cells . The previously resting cells enter into the G1 stage of the cell cycle, and this is accompanied by **increases in cell size**, **cytoplasmic RNA**, and biosynthetic organelles such as **ribosomes.** The survival of the stimulated B cells is enhanced as a result of the production of **various antiapoptotic proteins**, notably **Bcl-2**, and the cells may proliferate and secrete some antibody.

- The expression of receptors for several T cell–derived cytokines is also increased.

- Response of b-cells varies with the nature of the antigen, Most T-independent antigens, such as **polysaccharides**, display **multiple identical epitopes** on each molecule or on a cell surface. Therefore, such multivalent antigens effectively cross-link many B cell antigen receptors and initiate responses even though they are not recognized by helper T lymphocytes

- Damage to the Bcl-2 gene has been identified as a cause of a number of cancers, including chronic lymphocytic leukemia.

B cell response/ Functional Responses of B Cells to Antigens

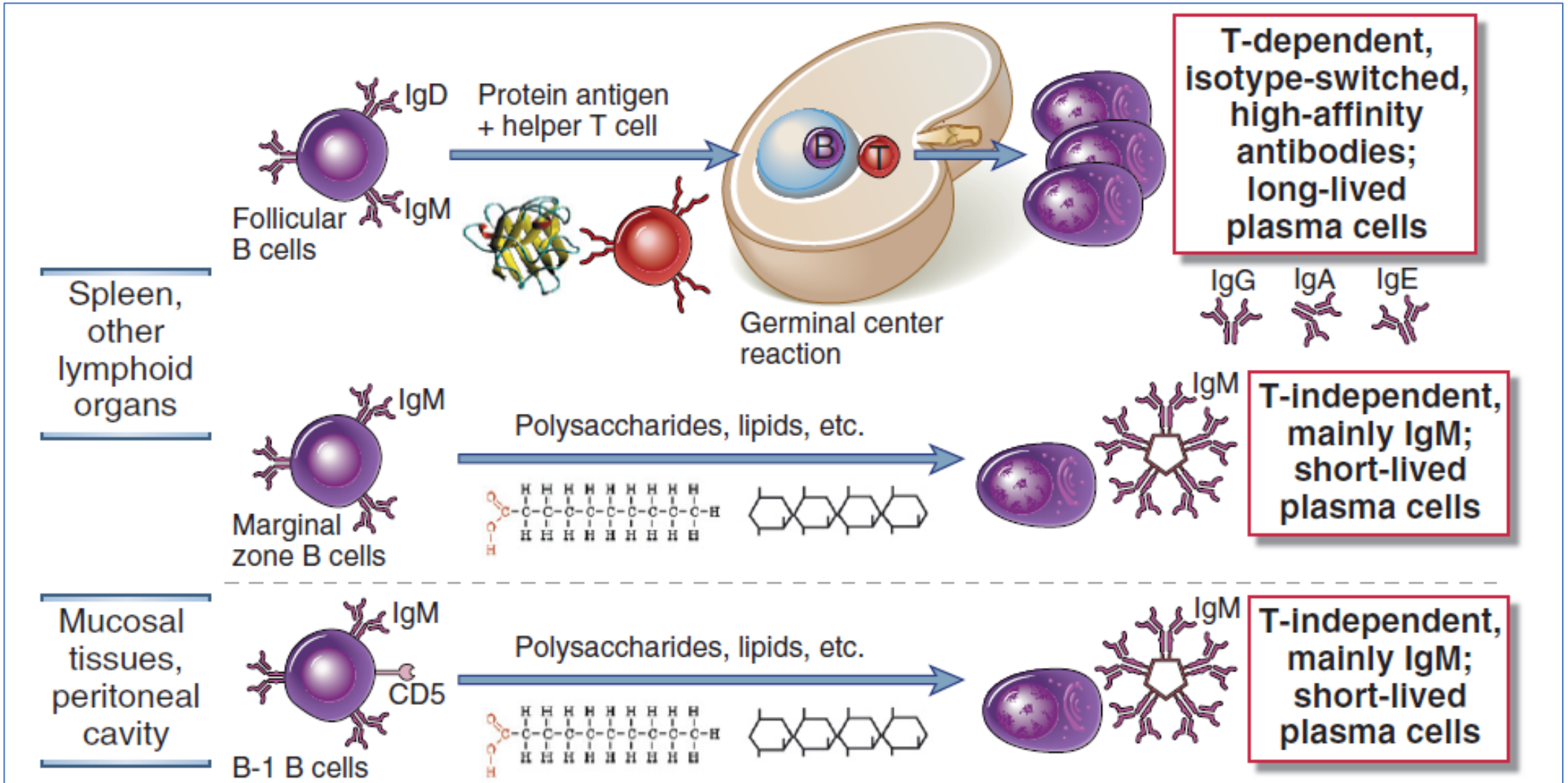


FIGURE 11–3 Distinct B cell subsets mediate different types of antibody responses. Follicular B cells are recirculating cells that receive T cell help when they respond to protein antigens and thus initiate T-dependent antibody responses. These responses can lead to the formation of germinal centers, where class switching and somatic mutation of antibody gene occur, resulting in specialized high-affinity antibody responses. T-independent responses to multivalent antigens such as lipids, polysaccharides, and nucleic acids are mediated mainly by marginal zone B cells in the spleen and B-1 cells in mucosal sites. These functional distinctions between subsets are not absolute.

B cell response/ B cell subsets

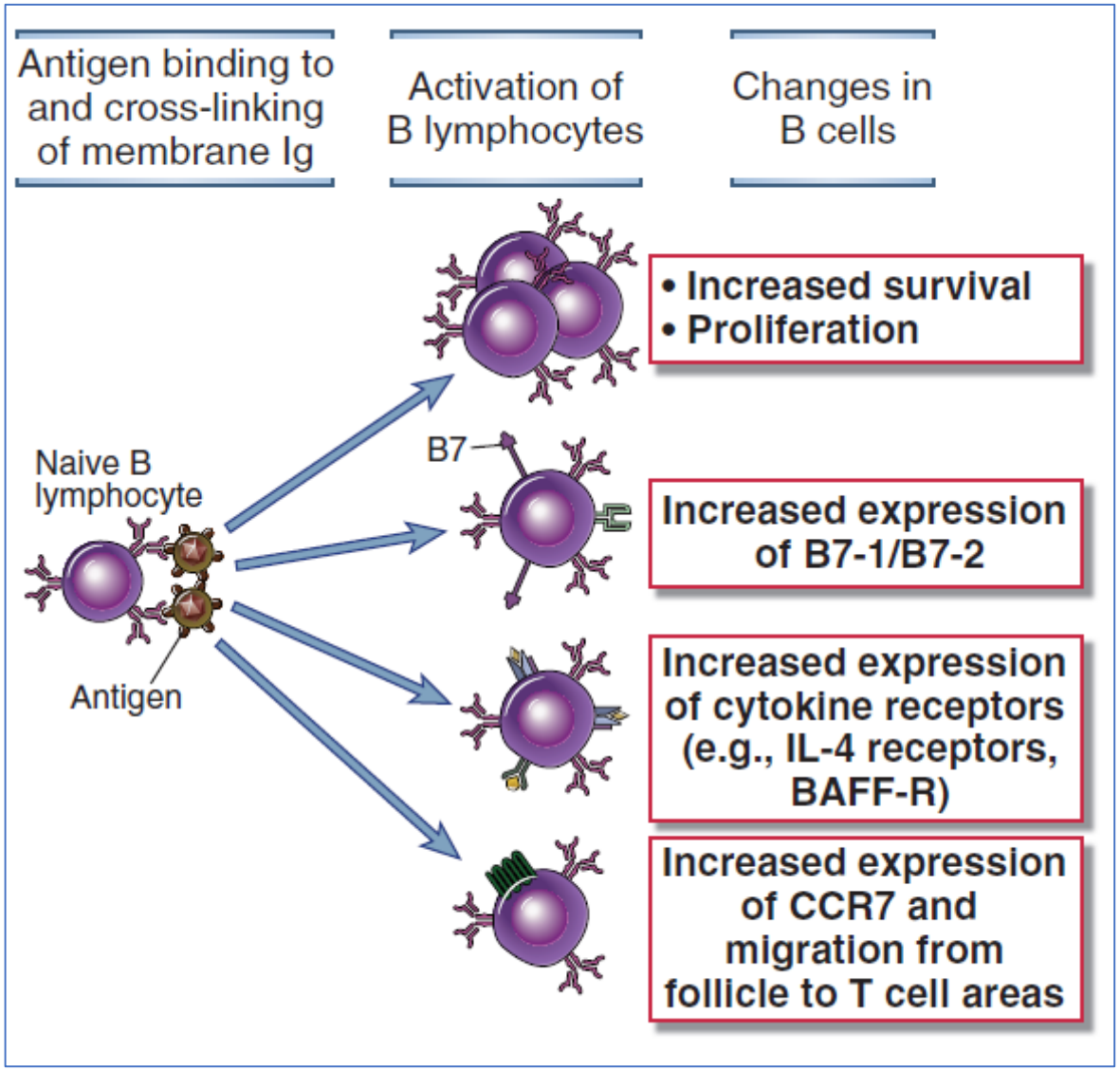
- **Follicular B Cells**: Most mature B cells belong to the follicular B cell subset and produce IgD in addition to IgM. Follicular B cells are also often called recirculating B cells because they migrate from one lymphoid organ to the next, residing in specialized niches known as B cell follicles.

- **B-1 B cells**, differs from the majority of B lymphocytes and develops in a unique manner. These cells develop from **fetal liver–derived HSCs.** B-1 cells as well as marginal zone B cells **spontaneously secrete IgM antibodies** that often react with microbial polysaccharides and lipids. B-1 cells contribute to rapid antibody production against microbes in particular tissues, such as the peritoneum. At mucosal sites, **as many as half the IgA-secreting cells** in the lamina propria may be **derived from B-1 cells**.

- **Marginal zone B cells** are located primarily in the vicinity of the **marginal sinus in the spleen** and are similar to B-1 cells in terms of their **limited diversity** and their ability to **respond to polysaccharide antigens** and to **generate natural antibodies**.

- The activation of B cells results in their proliferation, leading to **clonal expansion**, followed by **differentiation**, culminating in the generation of **memory B cells** and **antibody-secreting plasma cells**.

- A **single B cell** may, within a week, give rise to as many as **5000 antibody-secreting cell**s, which produce more than 10^{12} antibody molecules per day.



B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- Antibody responses to **protein antigens** require **recognition and processing** of the antigen **by B cells**, followed by presentation of a peptide fragment of the antigen to helper T cells, leading to cooperation between the antigen specific B and T lymphocytes.

- The frequency of naive B cells or T cells specific for a given epitope of an antigen is as low as 1 in 10^5 to 1 in 10^6 lymphocytes, and both populations have to be activated and the specific B and T cells have to find each other and physically interact to generate strong antibody responses.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- Antigen is taken up by dendritic cells that have also been activated by microbial products and presented to naive helper T cells in the T cell zones of lymphoid organs.
- Helper T cells are initially activated by the dendritic cells presenting antigenic peptides on class II MHC molecules and also expressing costimulatory ligands such as the B7 molecules (see Chapters 6 and 9).
- Activated helper T cells express CD40L and also chemokine receptors that promote their migration toward the follicle following a chemokine gradient.
- B cells in the lymphoid follicles are activated by antigen, which may be in soluble form or displayed by other cells.
- B cells process and present the antigen, alter their cell surface chemokine receptor profile, and migrate toward the T cell zone.
- Activated helper T cells and B cells interact at the boundary of the T cell zone and follicle, where the B cells are activated by CD40L on the helper T cells and by cytokines that the T cells secrete.
- Small extrafollicular B cell foci form in the medulla of the lymph node or between the periarteriolar lymphoid sheath and the red pulp of the spleen. B cells in these foci undergo low levels of isotype switching and somatic mutation and generate short-lived plasma cells that secrete antibodies.
- Some activated helper T cells are induced during B:T interactions to differentiate into T follicular helper cells (T_{FH} cells).
- Activated B cells and T_{FH} cells migrate into the follicle, where the B cells are activated by T_{FH} cells. Germinal centers form within the follicles and are the sites of extensive B cell proliferation, isotype switching, somatic mutation, selection events that lead to affinity maturation, memory B cell generation, and induction of long-lived plasma cells that migrate to the bone marrow.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

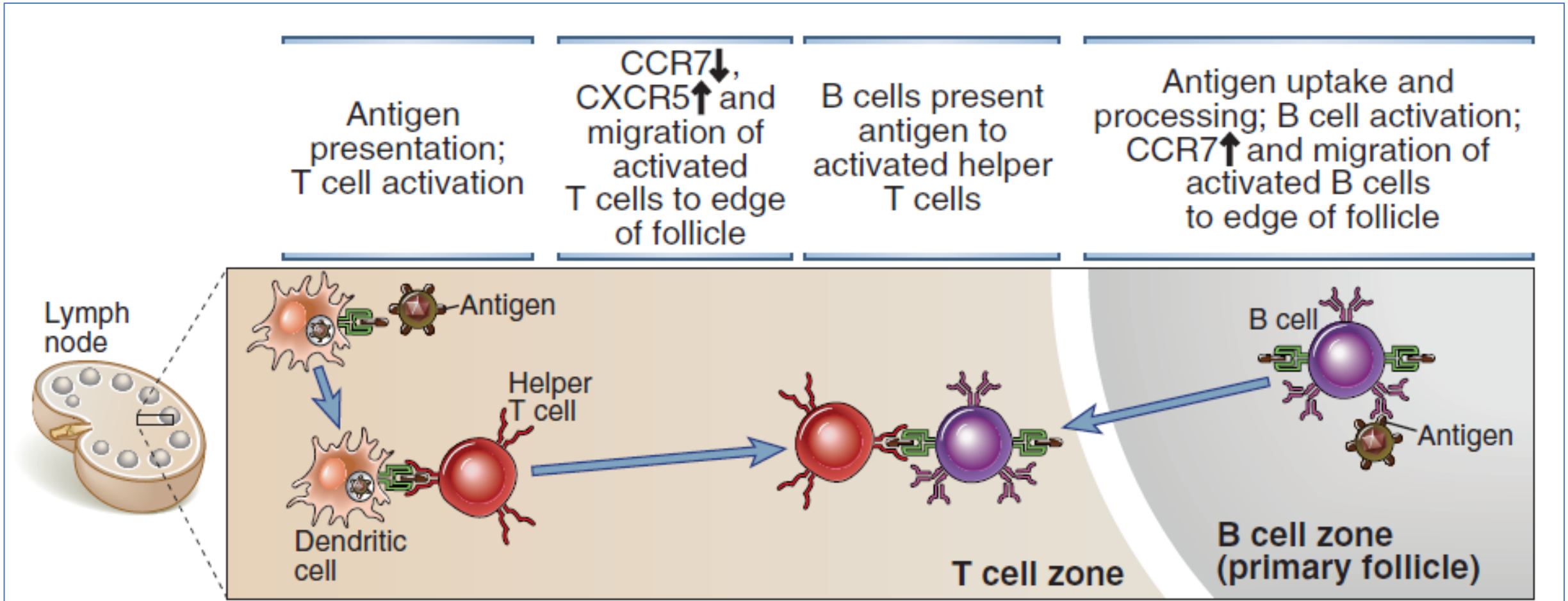


FIGURE 11–8 Migration of B cells and helper T cells and T-B interaction. Antigen-activated helper T cells and B cells move toward one another in response to chemokine signals and make contact adjacent to the edge of primary follicles. In this location, the B cell presents antigen to the T cell, and the B cell receives activating signals from the T cell.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

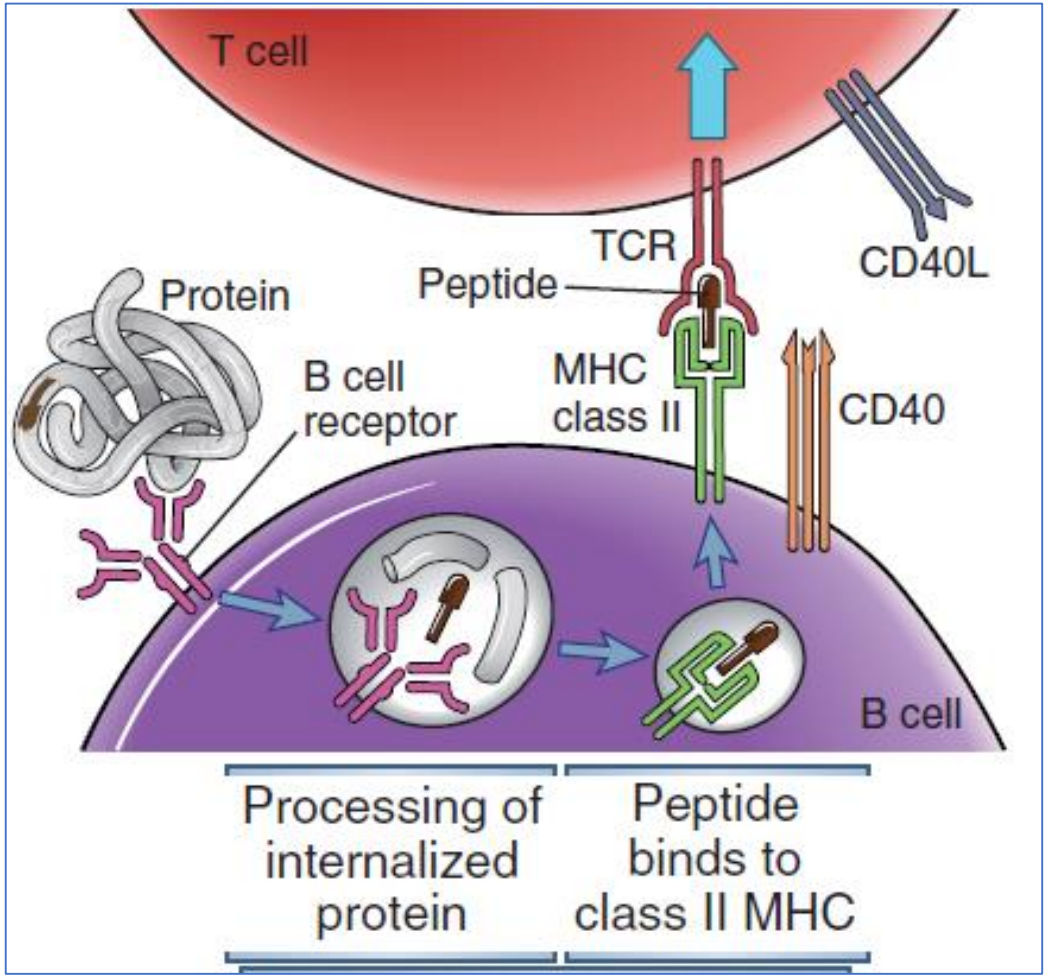
- **Helper T cells** that have been activated by antigen and costimulation are induced to **proliferate**, express **CD40L**, and **secrete cytokines**. They also **downregulate** the chemokine receptor **CCR7** and increase the expression of **CXCR5** and as a result **leave the T cell zone** and **migrate toward the follicle**. **CXCL13**, the ligand for CXCR5, is secreted by **follicular dendritic cells** and other follicular stromal cells, and it contributes to the migration of activated CD4+ T cells toward the follicle.

- BCR engagement by these antigens results in **reduced** cell surface expression of the chemokine receptor **CXCR5** and **increased** expression of **CCR7**, which is normally expressed on T cells. As a result, activated B cells migrate toward the T cell zone drawn by a gradient of CCL19 and CCL21, the ligands for CCR7.

B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- A protein antigen that elicits a T-dependent B cell response therefore makes use of at least two epitopes when activating specific B cells. A surface epitope on the **native protein** is recognized with **high specificity by a B cell**, and an **internal linear peptide** epitope is subsequently released from the protein, binds class II MHC molecules, and is **recognized by helper T cells**.

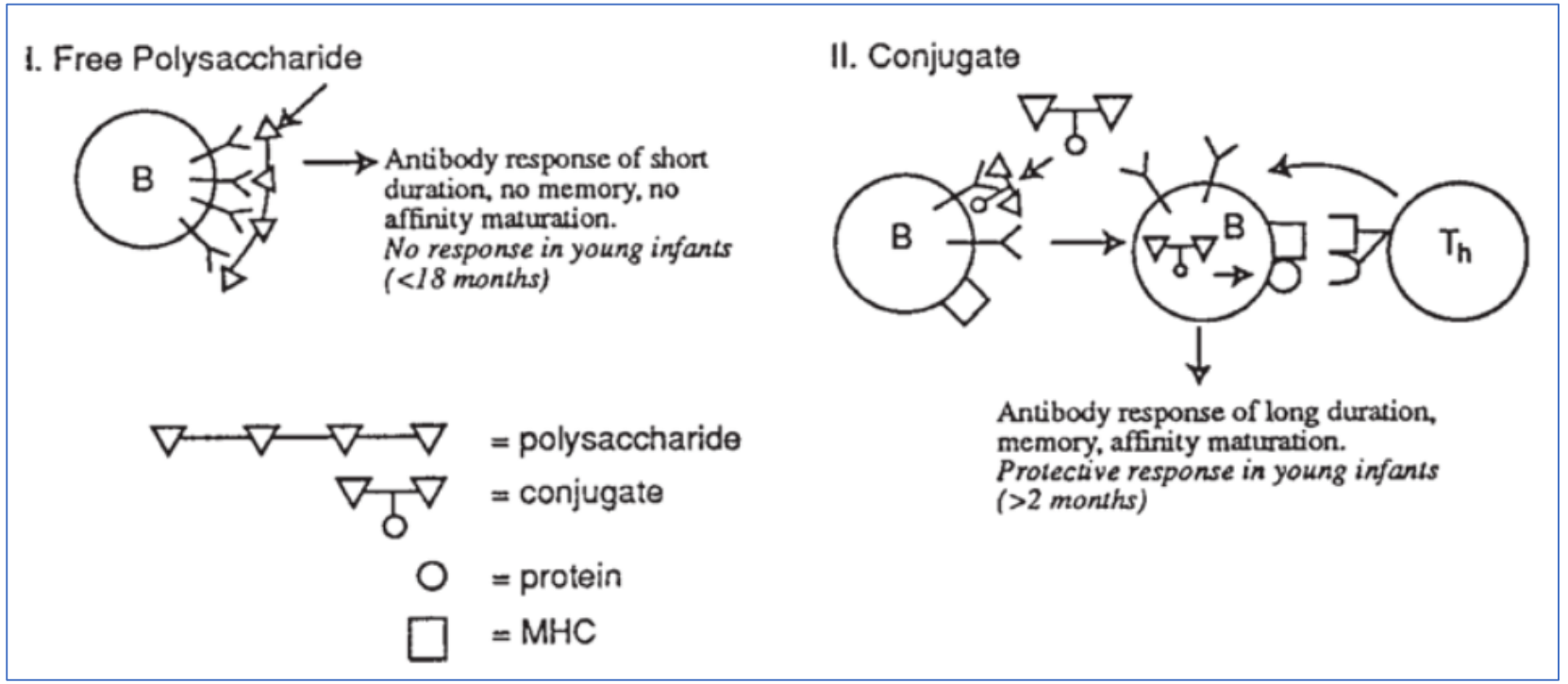
- The antibodies that are subsequently secreted are usually **specific for conformational determinants of the native antigen.**



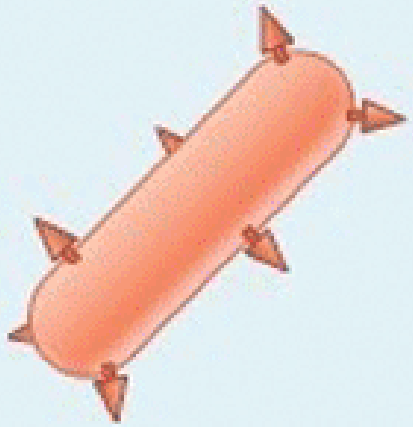
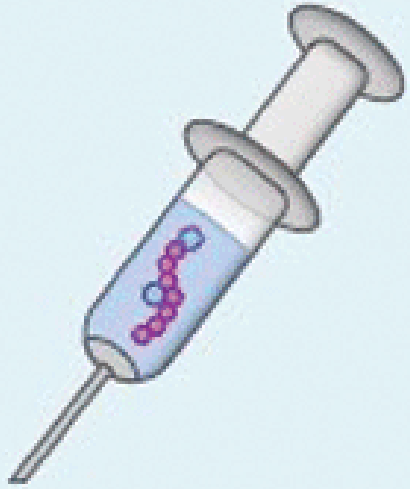
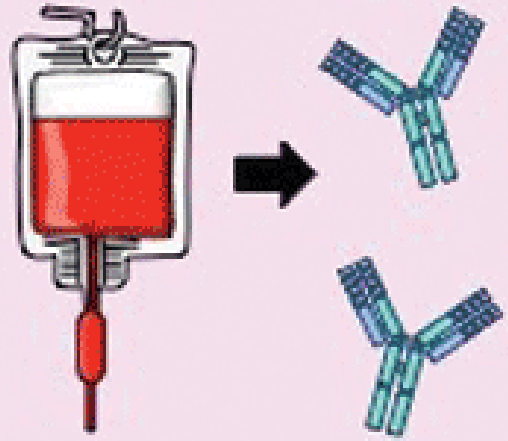
B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- This interaction is involved in the **Hapten-carrier effect. Haptens** are small chemicals that can be bound by specific antibodies but are not immunogenic by themselves. If, however, haptens are coupled to proteins, which serve as carriers, the conjugates are able to induce antibody responses against the haptens.

- This can be used in the production of conjugate vaccines. A **conjugate vaccine** consists of a **polysaccharide antigen** that is conjugated to a **carrier molecule**.



Active Immunity VS Passive Immunity

Natural	Artificial	Natural	Artificial
			
Infection	Vaccination	Maternal antibodies	Monoclonal antibodies

Passive vs. active immunity

Acquired immunity is attained through either **passive** or **active** immunization.

- **Passive immunization** refers to the transfer of **"ready-made" antibodies**, from one individual to another. It can occur:

1) **naturally** by **transplacental transfer** of **maternal** antibodies to the **developing fetus**, or through **colostrum** and **breast milk** rich in IgA.
2) it can be induced **artificially** by **injecting** a recipient with **exogenous antibodies** targeted to a specific pathogen or toxin.

- Examples:

Natural: Maternal antibodies protect against some diseases such as measles, rubella, and tetanus for the first few months of life.
Artificial: Pooled human immunoglobulins used intravenously (**IVIG**) can be used prophylactically in the case of **immunodeficiency diseases**, or specific antibodies used in the treatment of several types of acute infections such as **rabies**.

Passive vs. active immunity

Acquired immunity is attained through either **passive** or **active** immunization.

- **Active immunity** refers to the process of exposing the body to an antigen to **generate an adaptive immune response**: the response takes days/weeks to develop but may be long lasting—even lifelong (**unlike passive immunity**). It can occur:

1) Naturally through infection with a certain pathogen.
2) Artificially through administration of vaccines containing weekend or inactive pathogen.

Examples:
Natural: Wild infection with hepatitis A virus (HAV) and subsequent recovery gives rise to an active immune response usually leading to lifelong protection.
Artificial: In a similar manner, administration of two doses of hepatitis A vaccine generates an acquired active immune response leading to long-lasting (possibly lifelong) protection.

If you went back to 1796, when Edward Jenner was about to inject an 8 year old with an extract from a milk maid's cowpox lesion, in order to provide protection from smallpox in a process known then as variolation. **How would you describe to Jenner the immunology of vaccines**? Starting from the injury to the epithelial barrier and **activation of innate immunity** to the **formation of protective antibodies.**

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 11. B Cell Activation and Antibody Production

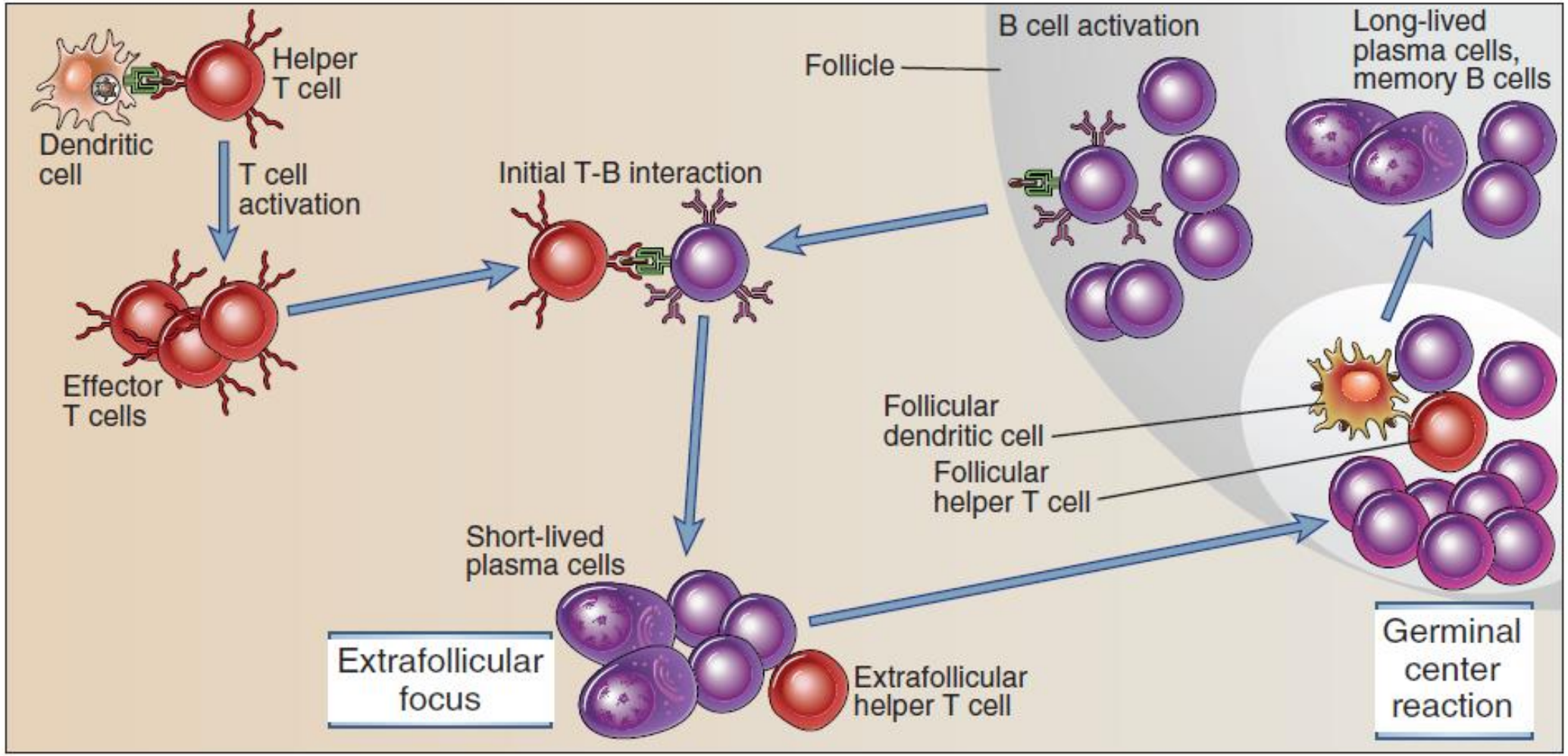
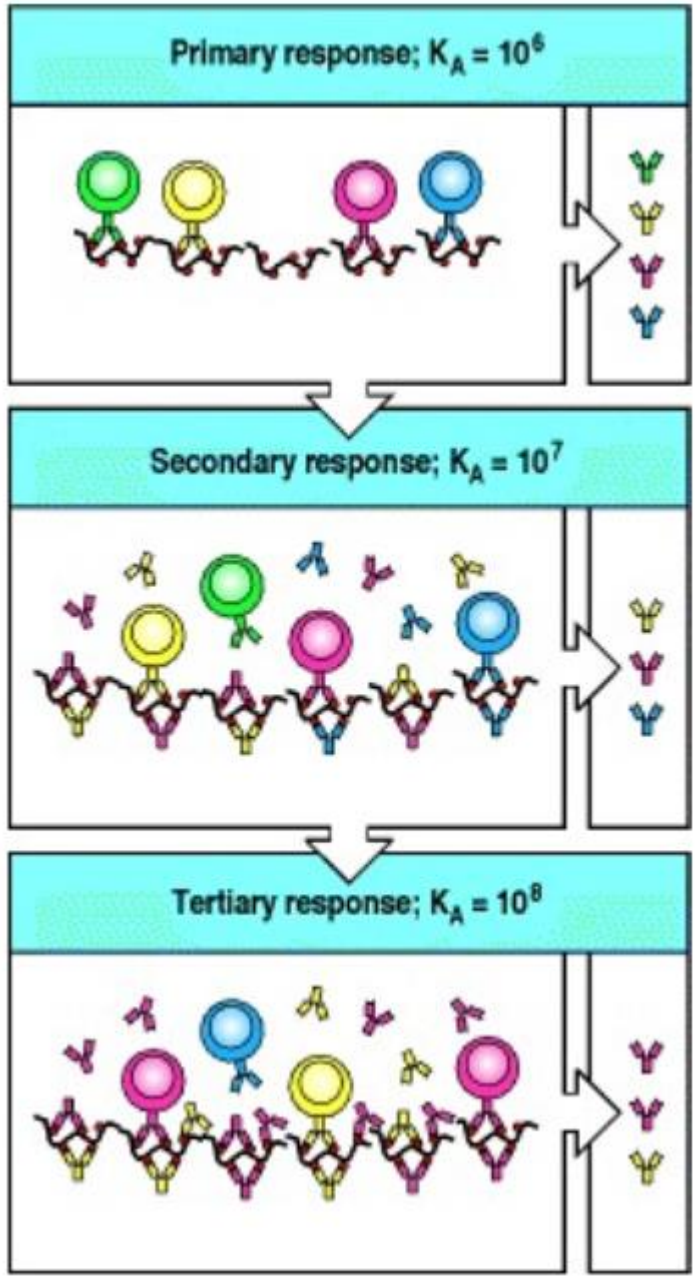


FIGURE 11–7 Sequence of events in humoral immune responses to T cell–dependent protein antigens. Immune responses are initiated by the recognition of antigens by B cells and helper T cells. The activated lymphocytes migrate toward one another and interact, resulting in B cell proliferation and differentiation. Restimulation of B cells by helper T cells in extrafollicular sites leads to early isotype switching and short-lived plasma cell generation. The late events occur in germinal centers and include somatic mutation and the selection of high-affinity cells (affinity maturation), additional isotype switching, memory B cell generation, and the generation of long-lived plasma cells.


Primary response; $K_A = 10^6$
Secondary response; $K_A = 10^7$
Tertiary response; $K_A = 10^8$