Medical Immunology

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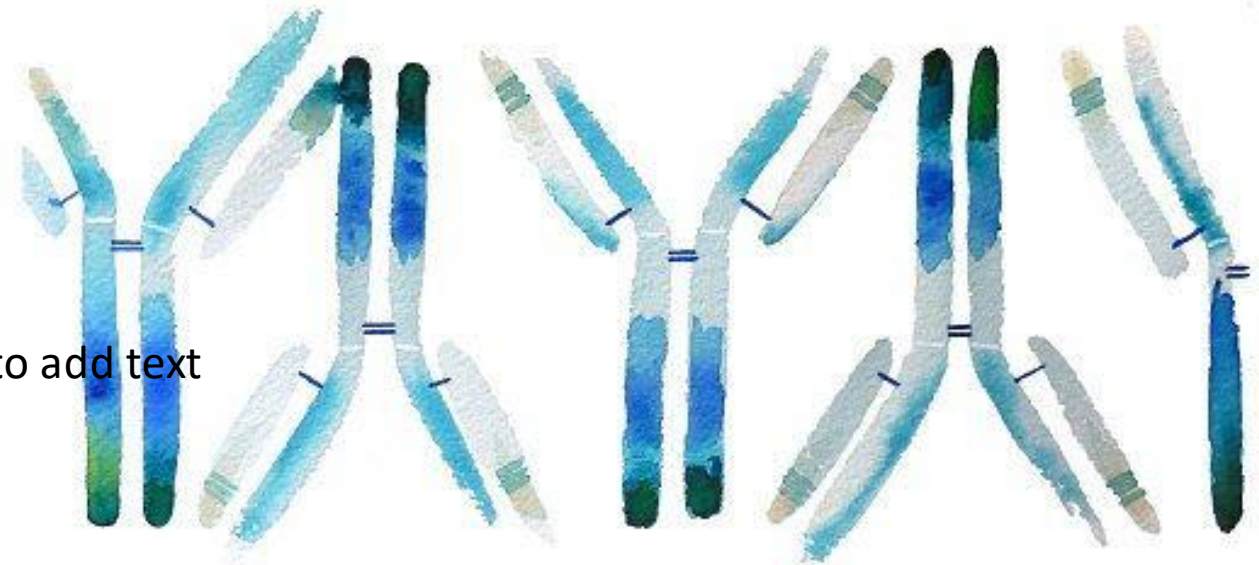


Anas Abu-Humaidan
M.D. Ph.D.

Lecture 12

B cell response

In this lecture we will discuss:

- B-cell response / T-dependent B-cell response
- Effector mechanisms of humoral immunity

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

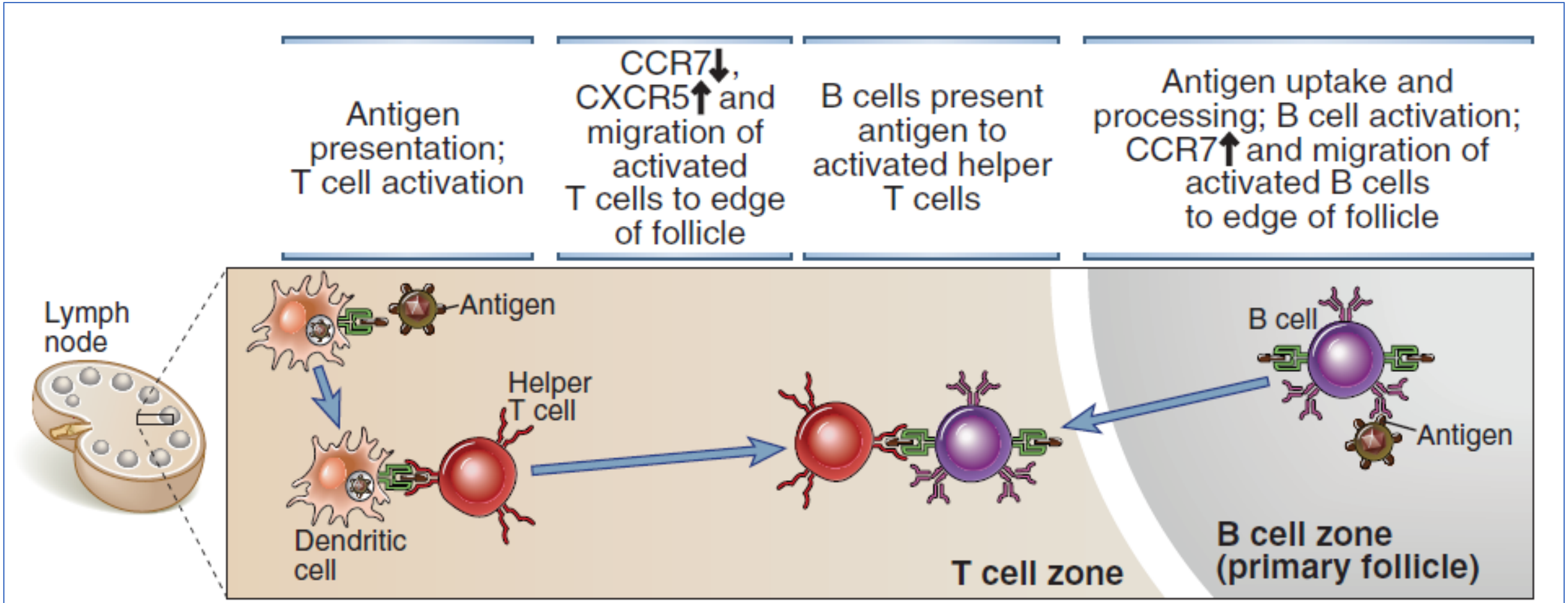
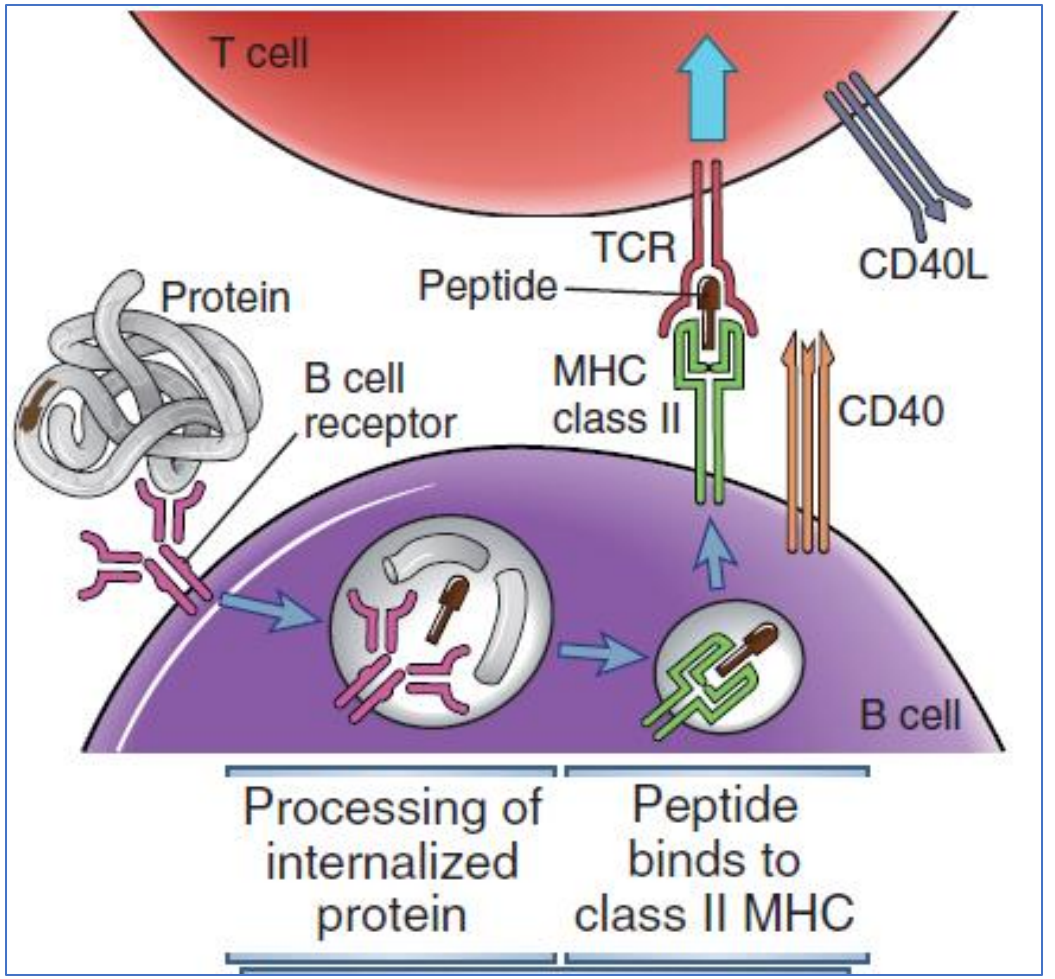


FIGURE 11–8 Migration of B cells and helper T cells and T-B interaction. Antigen-activated helper T cells and B cells move toward one another in response to chemokine signals and make contact adjacent to the edge of primary follicles. In this location, the B cell presents antigen to the T cell, and the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

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

- 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.**

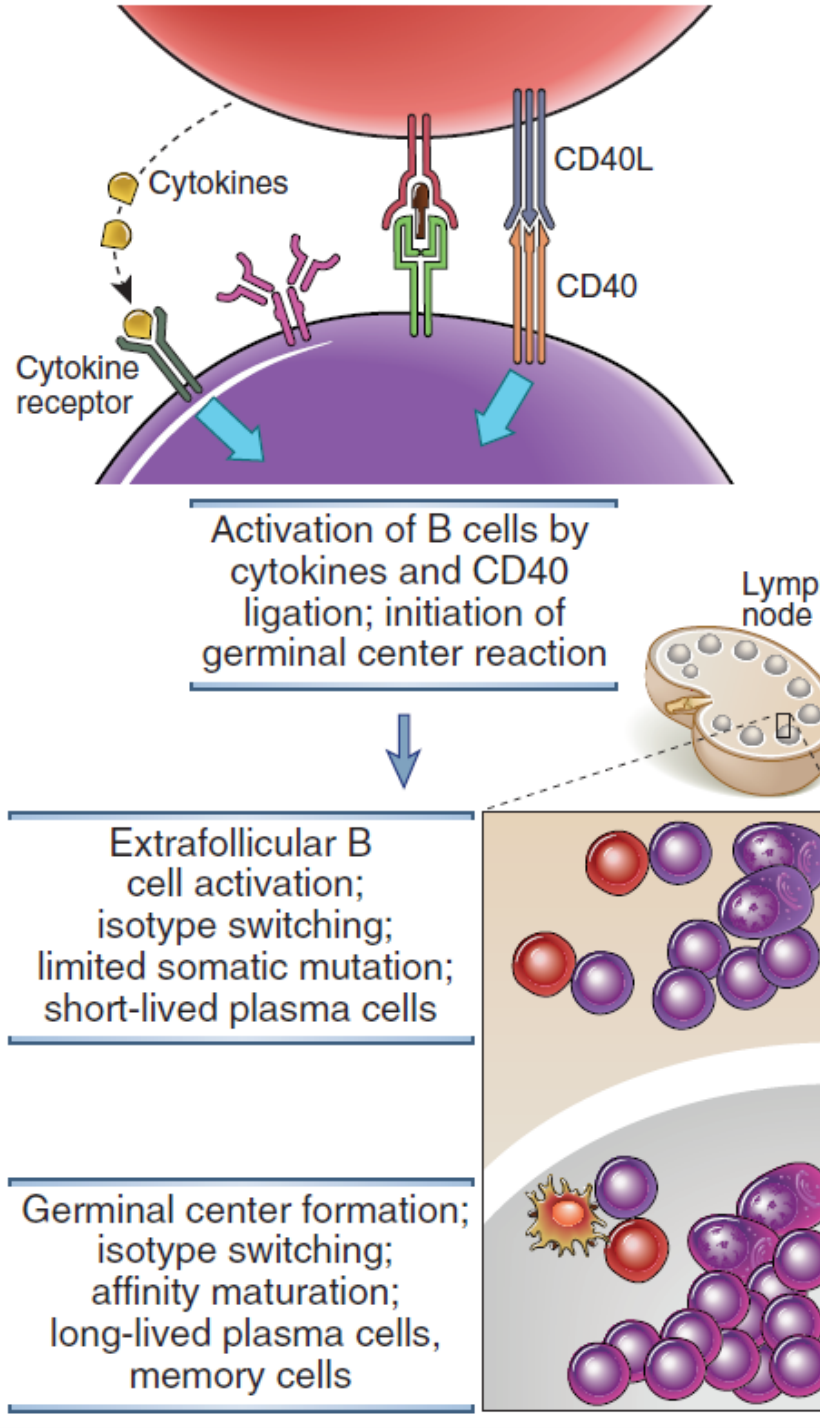


B cell response/ HELPER T CELL–DEPENDENT ANTIBODY RESPONSES TO PROTEIN ANTIGENS

- On activation, helper T cells express CD40 ligand (CD40L), which engages its receptor, CD40, on antigen-stimulated B cells at the T-B interface and induces subsequent proliferation and differentiation **initially in extrafollicular foci** and later **in germinal centers**.

- CD40 is constitutively expressed on B cells, and **CD40L is expressed on the surface of helper T cells after activation** by antigen and costimulators.

- helper T cells also **secrete cytokines** that contribute to B cell responses. The best defined roles of T cell derived cytokines in humoral immune responses are in isotype switching, with roles in differentiation and proliferation as well.



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

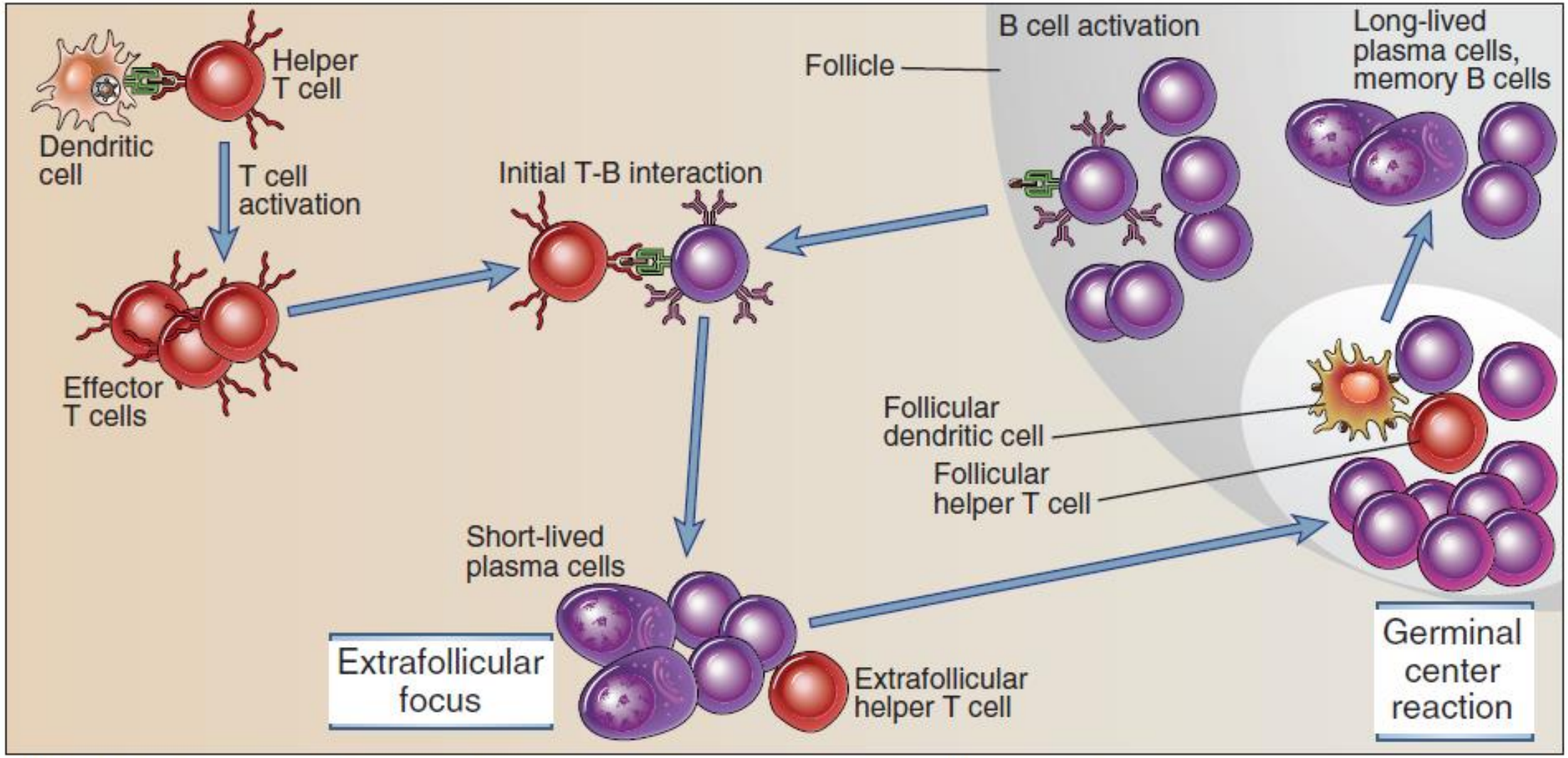


FIGURE 11–7 Sequence of events in humoral immune responses to T cell–dependent protein antigens. Immune responses are initiated by the recognition of antigens by B cells and helper T cells. The activated lymphocytes migrate toward one another and interact, resulting in B cell proliferation and differentiation. 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.

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

- **Extrafollicular foci of T-dependent B cell activation** are generated **relatively early** in an immune response**. Germinal centers**, in which specialized **follicular helper T (TFH)** cells trigger B cells to undergo numerous changes, **appear a few days later**.

- The characteristic events of helper T cell–dependent antibody responses, including **affinity maturation**, **isotype switching**, **generation of memory B cells**, and **long-lived plasma cell differentiation**, occur primarily in the **germinal centers** of lymphoid follicles.

- Each fully formed germinal center contains cells derived from only one or a few antigen-specific B cell clones

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

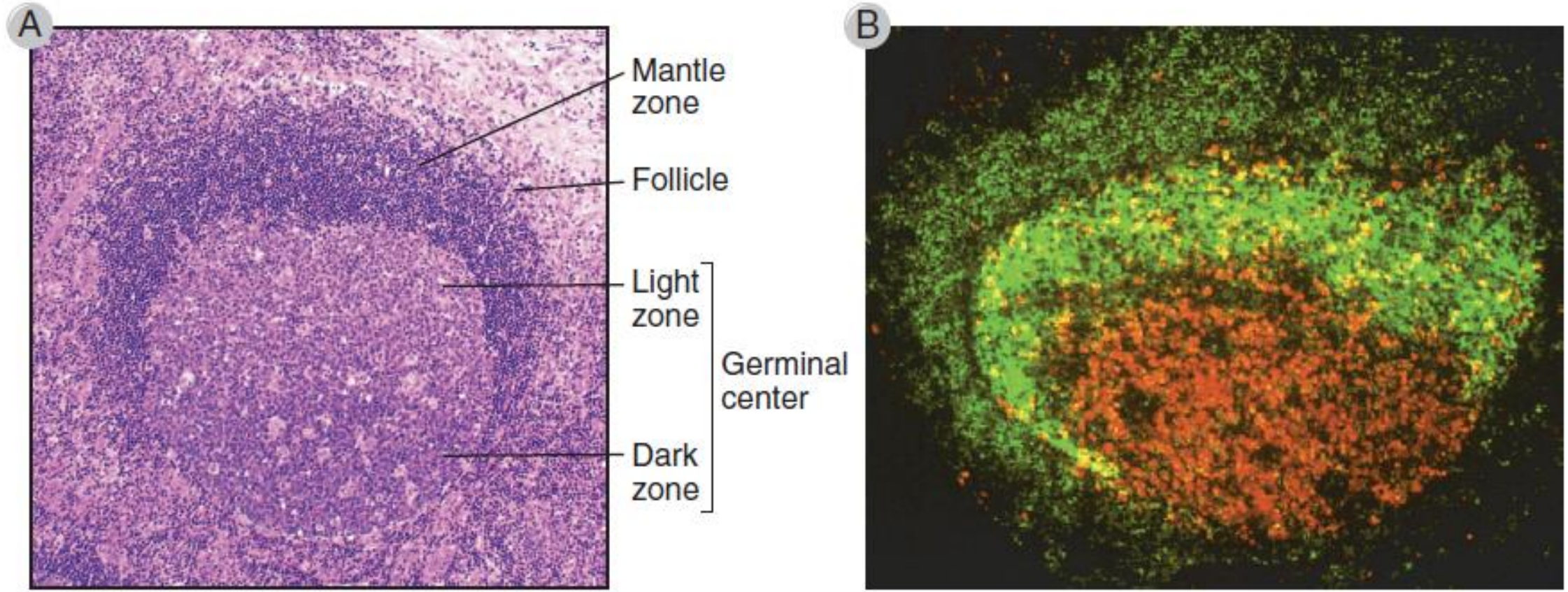


FIGURE 11–11 Germinal centers in secondary lymphoid organs. A, Histology of a secondary follicle with a germinal center in a lymph node. The germinal center is contained within the follicle and includes a basal dark zone and an adjacent light zone. The mantle zone is the parent follicle within which the germinal center has formed. *(Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)* **B,** Cellular components of the germinal center. A secondary follicle has been stained with an anti-CD23 antibody (green), which brightly stains follicular dendritic cells in the light zone and dimly stains naive B cells in the mantle zone. Anti-Ki67 (red), which detects cycling cells, stains mitotically active B cell blasts in the dark zone. *(Modified from Liu YJ, GD Johnson, J Gordon, and IC MacLennan. Germinal centres in T-cell–dependent antibody responses. Immunology Today 13:17-21, Copyright 1992, with permission from Elsevier.)*

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

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- Each fully formed germinal center contains cells derived from only one or a few antigen-specific B cell clones.

- **follicular dendritic cells (FDCs).** FDCs are found only in lymphoid follicles and express complement receptors (CR1, CR2, and CR3) and Fc receptors. These molecules are involved in displaying antigens for the selection of germinal center B cells

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

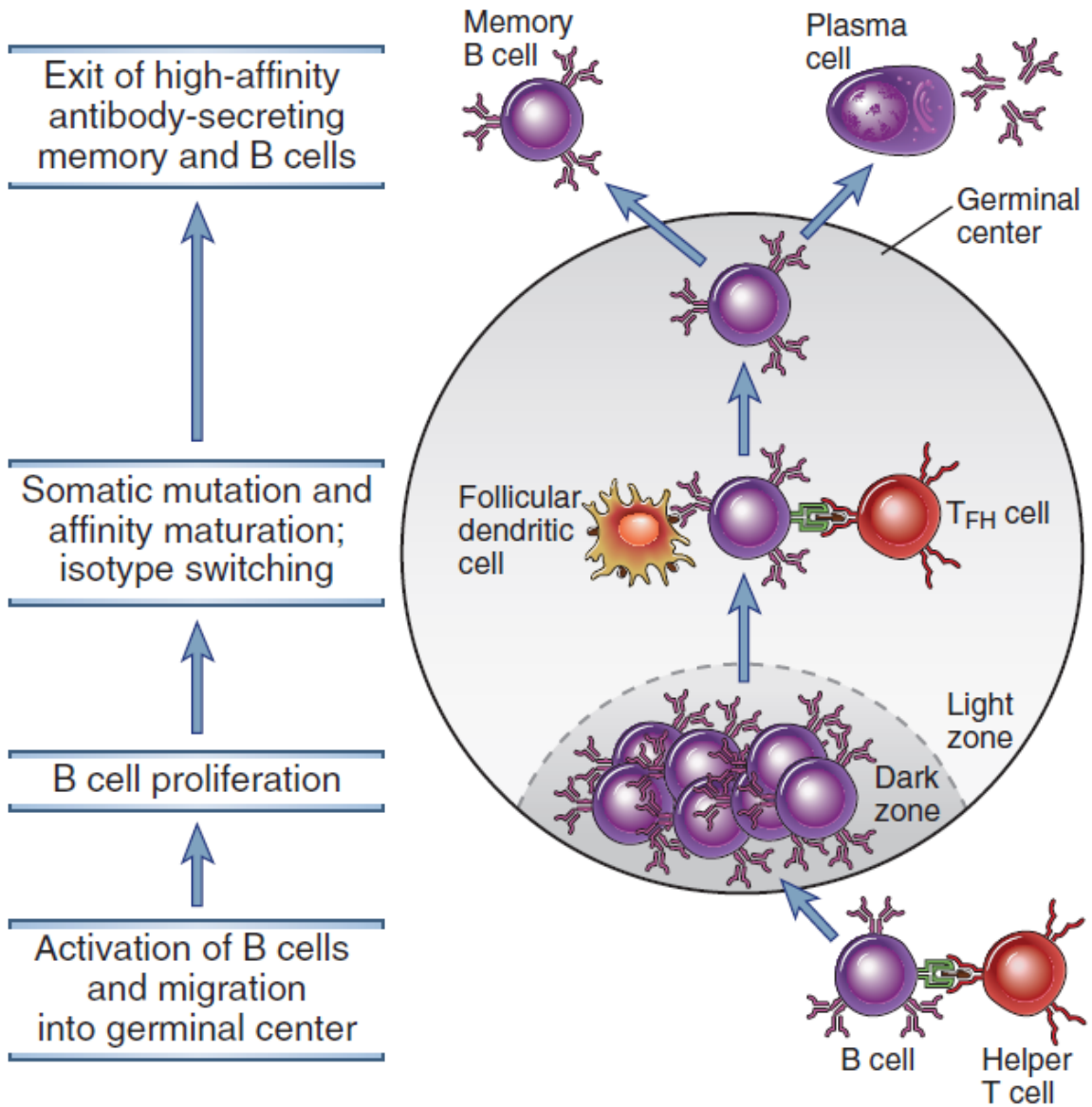


FIGURE 11–12 The germinal center reaction in a lymph node. B cells that have been activated by T helper cells at the edge of a primary follicle migrate into the follicle and proliferate, forming the dark zone of the germinal center. Germinal center B cells undergo extensive isotype switching. Somatic hypermutation of Ig V genes occur in these B cells, and they migrate into the light zone, where they encounter follicular dendritic cells displaying antigen and T_{FH} cells. B cells with the highest affinity Ig receptors are selected to survive, and they differentiate into antibody-secreting or memory B cells. The antibody-secreting cells leave and reside in the bone marrow as long-lived plasma cells, and the memory B cells enter the recirculating pool.

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

TABLE 11–1 Extrafollicular and Germinal Center B Cell Responses

Feature	Follicular/Germinal Center	Extrafollicular
Localization	Secondary follicles	Medullary cords of lymph nodes and at junctions between T cell zone and red pulp of spleen
CD40 signals	Required	Required
Specialized T cell help	T_{FH} cells in germinal center	Extrafollicular T helper cells
AID expression	Yes	Yes
Class switching	Yes	Yes
Somatic hypermutation	High rate	Low rate
Antibody affinity	High	Low
Terminally differentiated B cells	Long-lived plasma cells and memory cells	Short-lived plasma cells (life span of ~3 days)
Fate of plasma cells	Bone marrow or local MALT	Most die by apoptosis in secondary lymphoid tissues where they were produced
B cell transcription factors	Bcl-6	Blimp-1

AID, activation-induced cytidine deaminase; Bcl-6, B cell lymphoma 6; Blimp-1, B lymphocyte–induced maturation protein 1; IL-21R, interleukin-21 receptor; MALT, mucosa-associated lymphoid tissue; T_{FH}, follicular helper T cell.
Data from Vinusa CG, I Sanz, and MC Cook. Dysregulation of germinal centres in autoimmune disease. Nature Reviews Immunology 9:845-857, 2009.

B cell response/ Isotype switching

- **Isotype switching** in response to **different types of microbes** is regulated by cytokines produced by the helper T cells that are activated by these microbes.

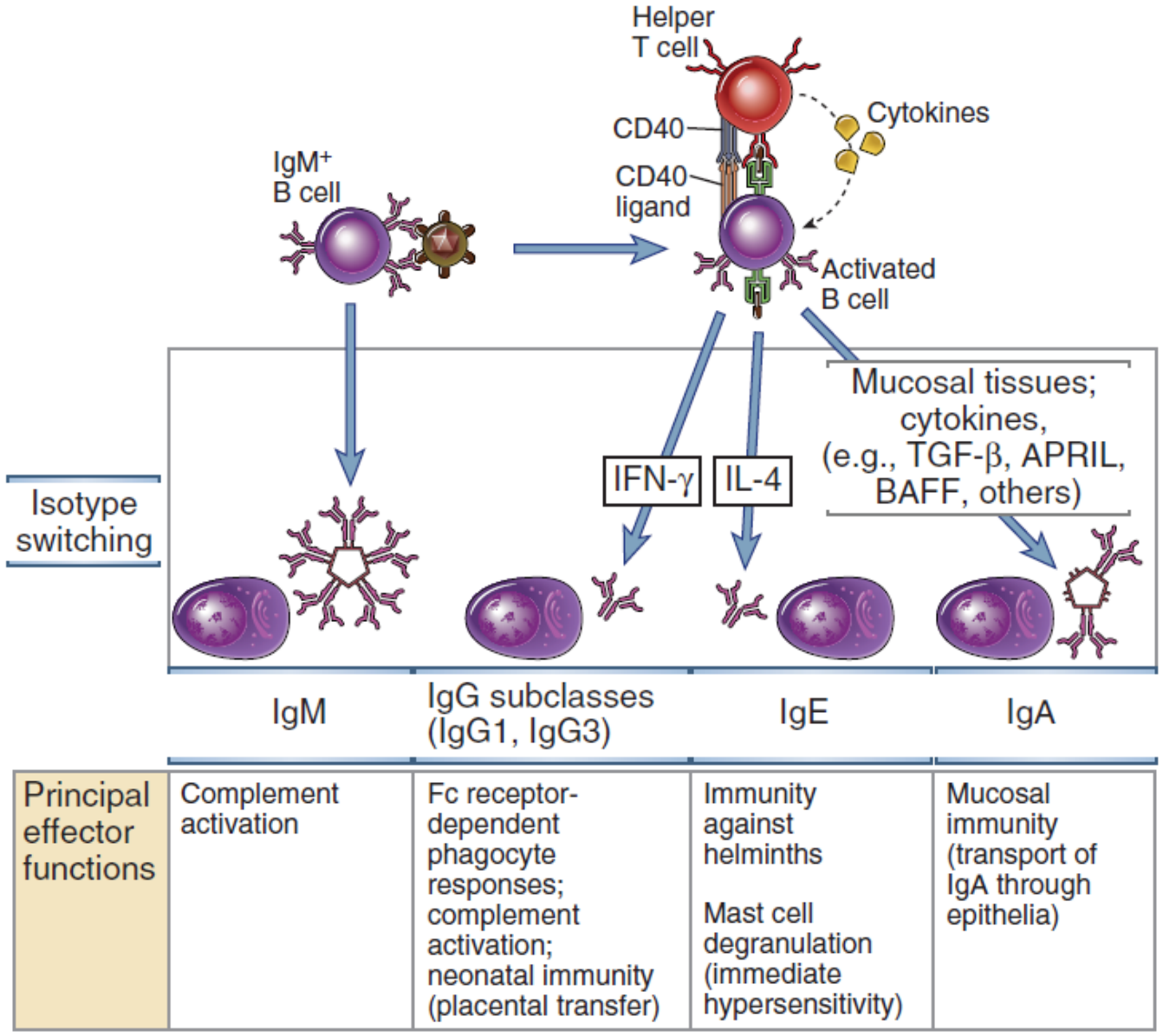
- Polysaccharide antigens, which do not elicit T cell help, stimulate mainly IgM antibodies, with little if any isotype switching to some IgG subclasses

- Viruses and many bacteria activate helper T cells of the TH1 subset, which produce the cytokine IFN-γ.

- Helminths activate the TH2 subset of helper T cells, which produces IL-4, the cytokine that induces switching to IgE.

- **B cells in different anatomic sites switch to different isotypes.** Specifically, B cells in mucosal tissues switch to IgA, which is the antibody class that is most efficiently transported through epithelia into mucosal secretions, where it defends against microbes that try to enter through the epithelia

B cell response/ Isotype switching



	IgM	IgG subclasses (IgG1, IgG3)	IgE	IgA
Principal effector functions	Complement activation	Fc receptor-dependent phagocyte responses; complement activation; neonatal immunity (placental transfer)	Immunity against helminths Mast cell degranulation (immediate hypersensitivity)	Mucosal immunity (transport of IgA through epithelia)

FIGURE 11–14 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.

B cell response/ Affinity Maturation

- **Affinity maturation** is the process that leads to **increased affinity of antibodies** for a particular antigen as a T-dependent humoral response progresses and is the result of **somatic mutation of Ig genes** followed by **selective survival of the B cells** producing the antibodies with the highest affinities.

- Helper T cells and CD40:CD40L interactions are required for somatic mutation to be initiated, and as a result, affinity maturation is observed only in antibody responses to T-dependent protein antigens.

- This rate is estimated to be 1 in 1000 V gene base pairs per cell division, which is about a thousand times higher than the spontaneous rate of mutation in other mammalian genes. The mutations are clustered in the V regions, mostly in the antigen-binding complementarity-determining regions.

B cell response/ Affinity Maturation

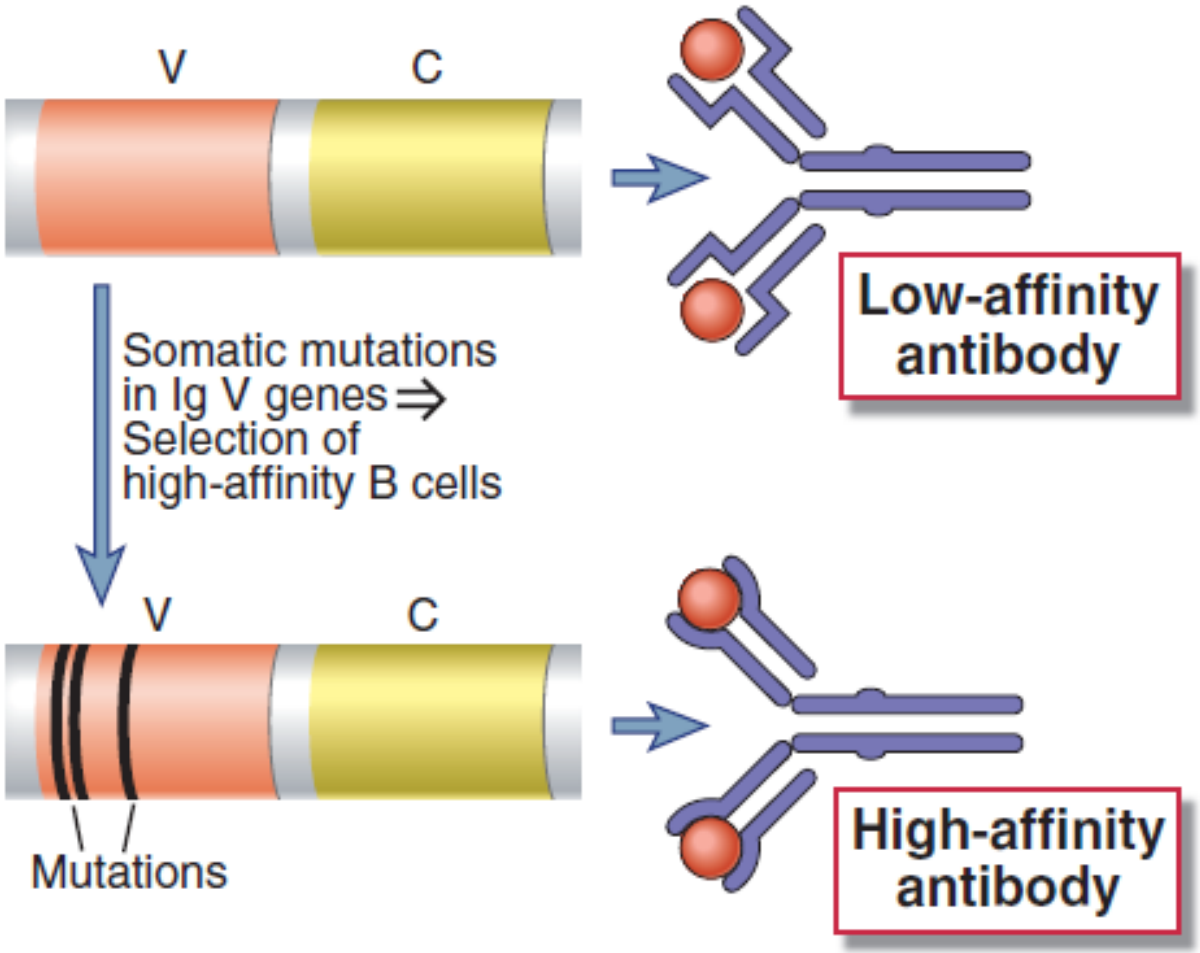
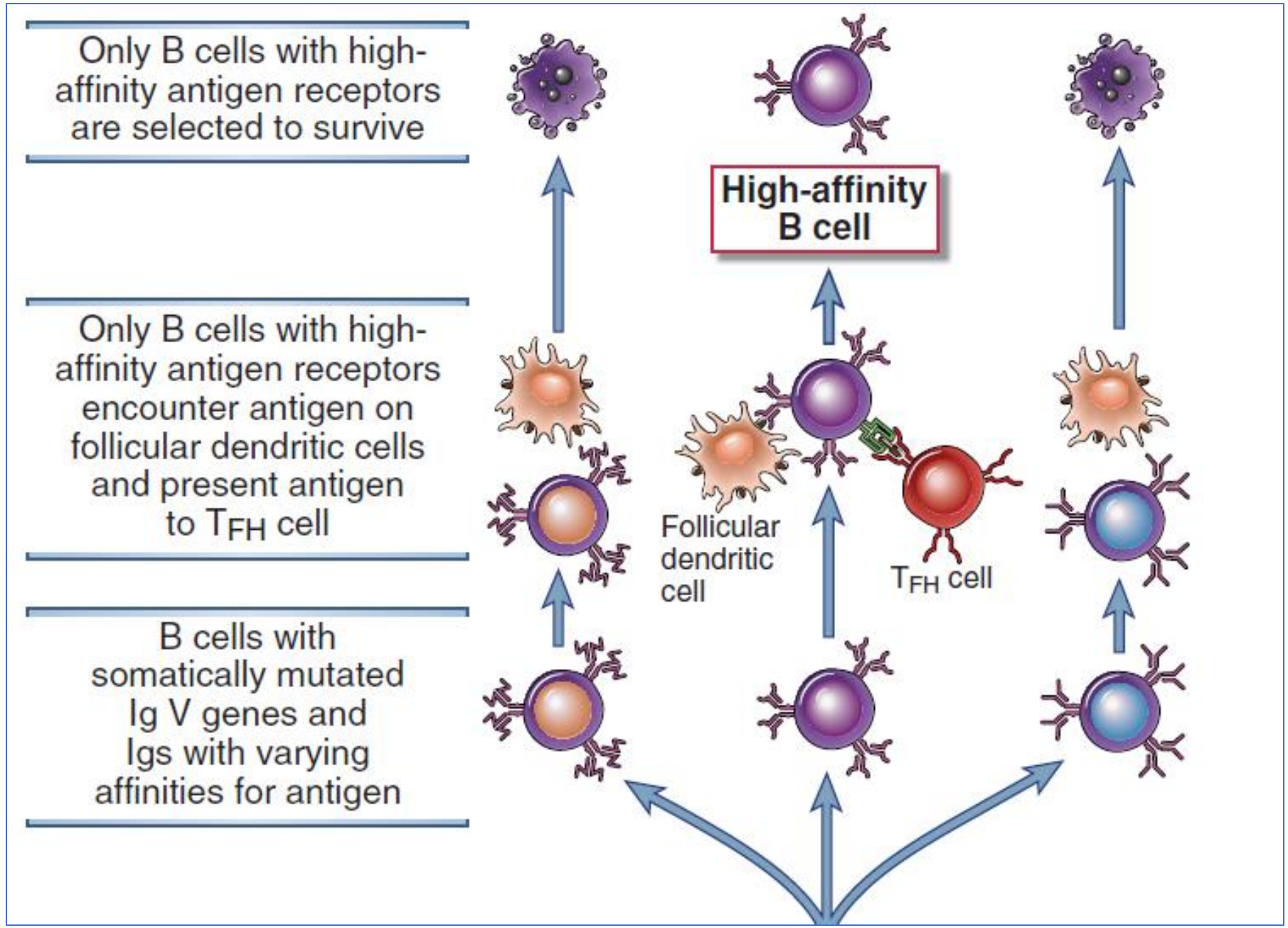


FIGURE 11–17 An overview of affinity maturation. Early in the immune response, low-affinity antibodies are produced. During the germinal center reaction, somatic mutation of Ig V genes and selection of mutated B cells with high-affinity antigen receptors result in the production of antibodies with high affinity for antigen.

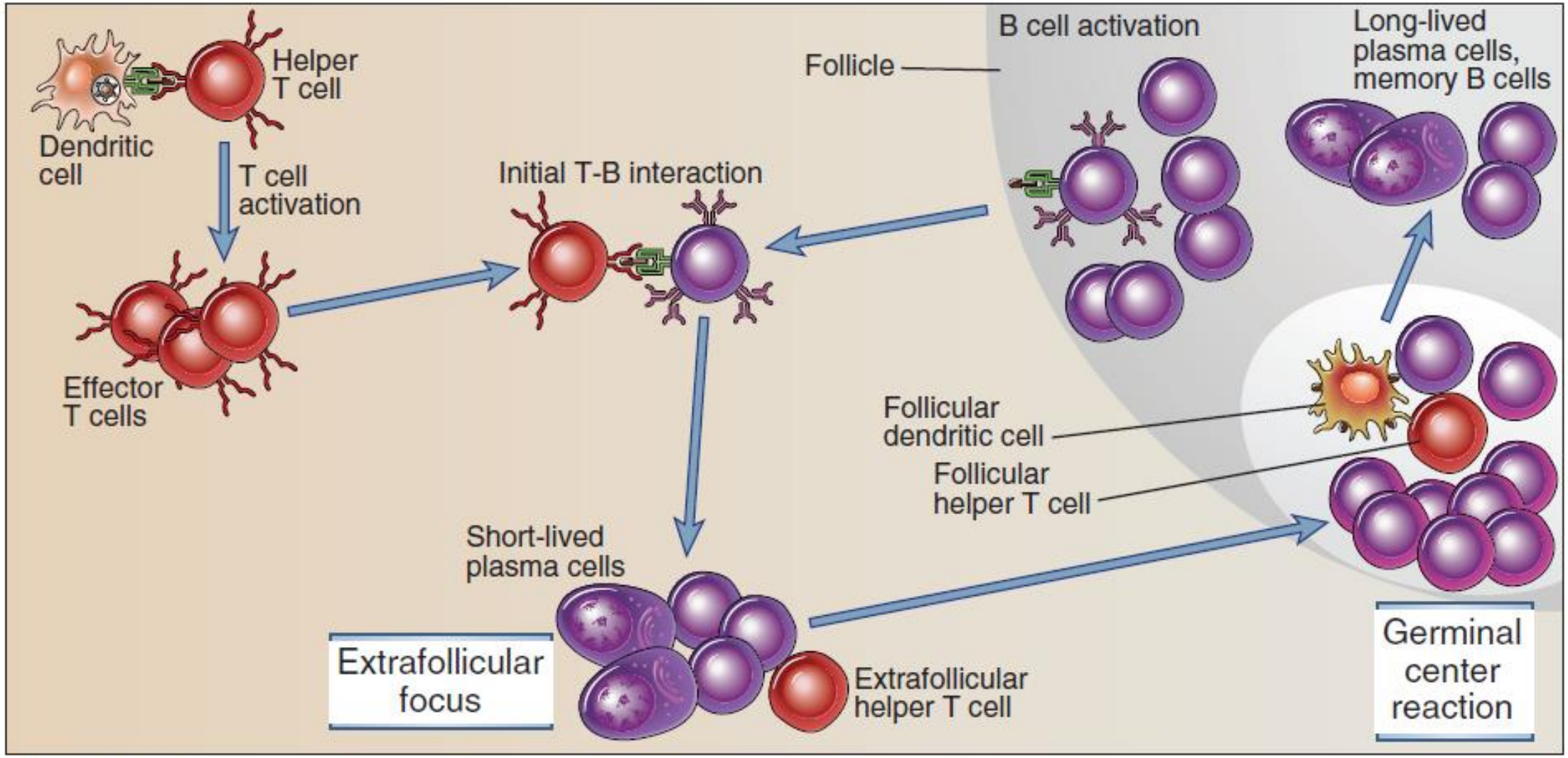
B cell response/ Affinity Maturation

- germinal center B cells that have undergone somatic mutation migrate into the FDC-rich light zone of the germinal center. In germinal center B cells, **IL-21 secreted by TFH cells induces the expression of proteins that induce apoptosis and reduces the expression of proteins that prevent apoptosis**. Therefore, these **B cells die by apoptosis unless they are rescued by recognition of antigen**. B cells with high-affinity receptors for the antigen are best able to bind the antigen when it is present at low concentrations, and these B cells survive preferentially because of several mechanisms

B cell response/ Affinity Maturation



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



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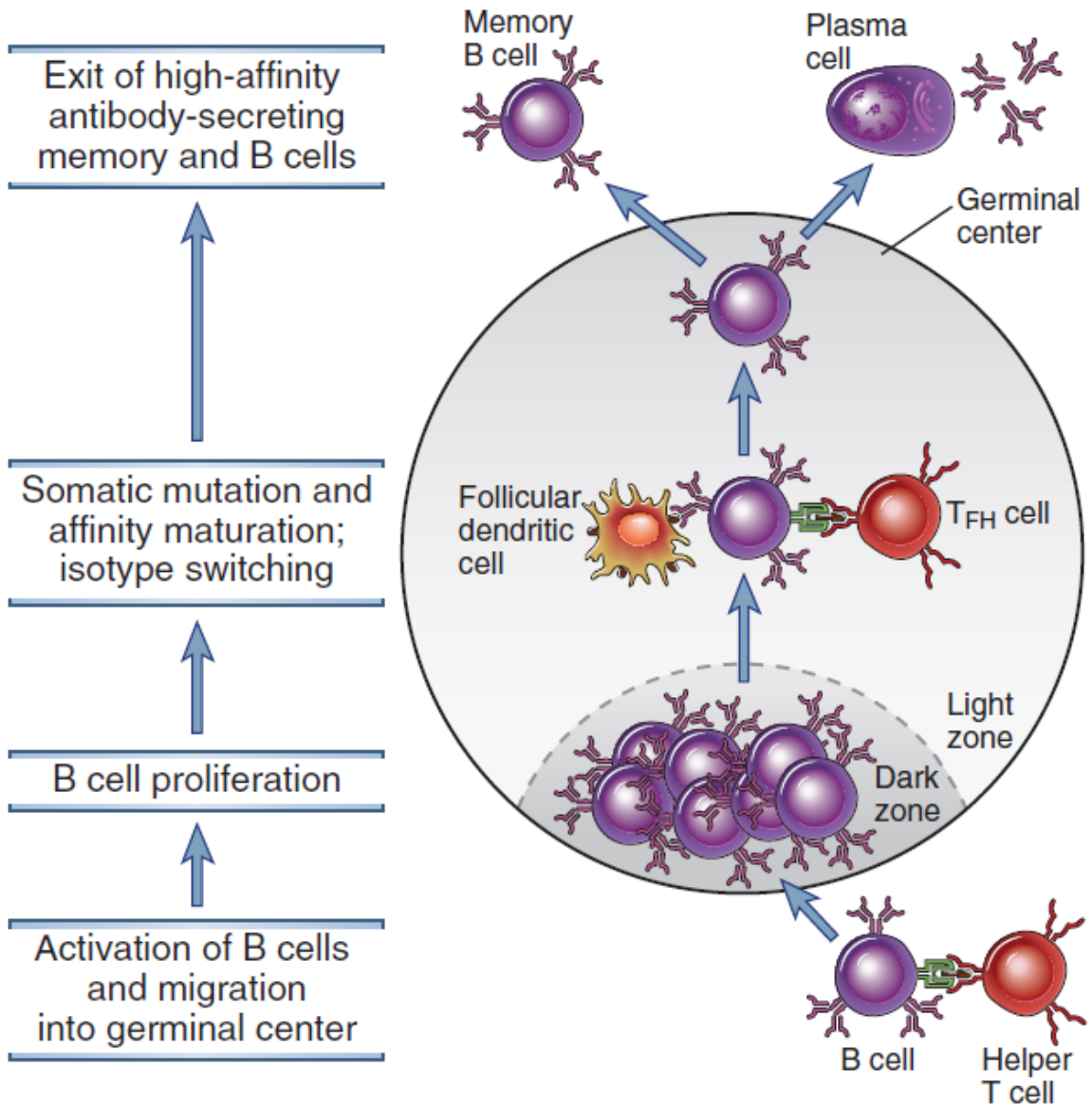

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B cell response/ B Cell Differentiation into Antibody-Secreting Plasma Cells

- Plasma cells are morphologically distinct, **terminally differentiated** B cells committed to abundant **antibody production**.

- They are generated after the activation of B cells through signals from the BCR, CD40, TLRs, and other receptors including cytokine receptors.

- There are 2 types of plasma cells:

➢ **Short-lived plasma cells** are generated during **T-independent** responses and early during T cell– dependent responses **in extrafollicular B cell foci**. These cells are generally found in **secondary lymphoid organs** and in **peripheral nonlymphoid** tissues

➢ **Long-lived plasma cells** are generated in **T-dependent** germinal center responses to protein antigens. Signals from the B cell antigen receptor and IL-21 cooperate in the generation of plasma cells, acquire the ability to home to the **bone marrow**, where they are maintained by cytokines of the BAFF family.

B cell response/ B Cell Differentiation into Antibody-Secreting Plasma Cells

- Plasma cells to survive for long periods, often **as long as the life span of the host.**

- Typically 2 to 3 weeks after immunization with a T cell–dependent antigen, the **bone marrow** becomes **a major site of antibody production.**

- Plasma cells in the bone marrow may continue to secrete antibodies for months or even years after the antigen is no longer present.

- It is estimated that almost **half the antibody in the blood of a healthy adult is produced by long-lived plasma cells** and is **specific** for antigens that were encountered in the past.

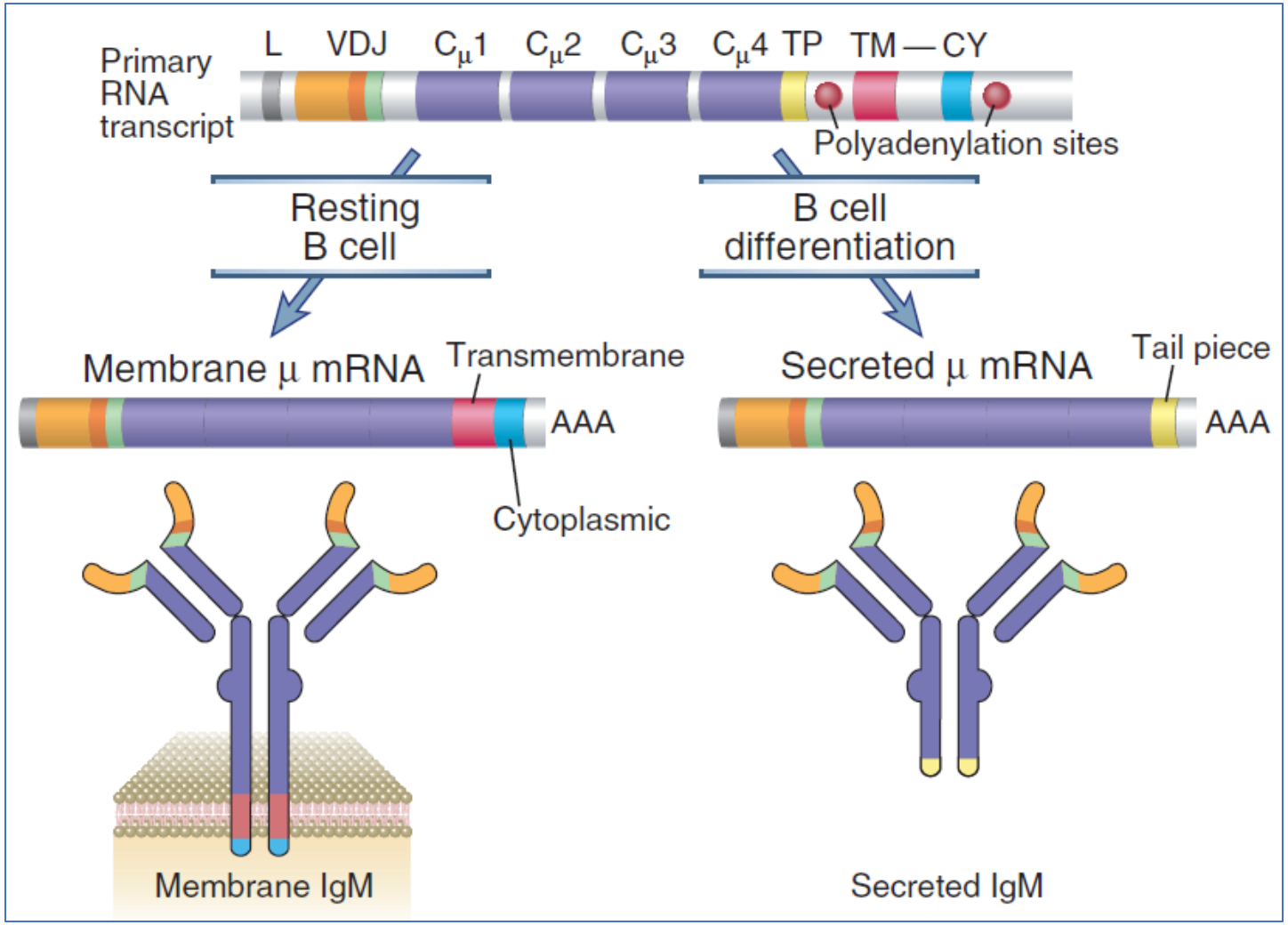
- Secreted antibodies enter the circulation and mucosal secretions, but mature plasma cells **do not recirculate.**

B cell response/ B Cell Differentiation into Antibody-Secreting Plasma Cells

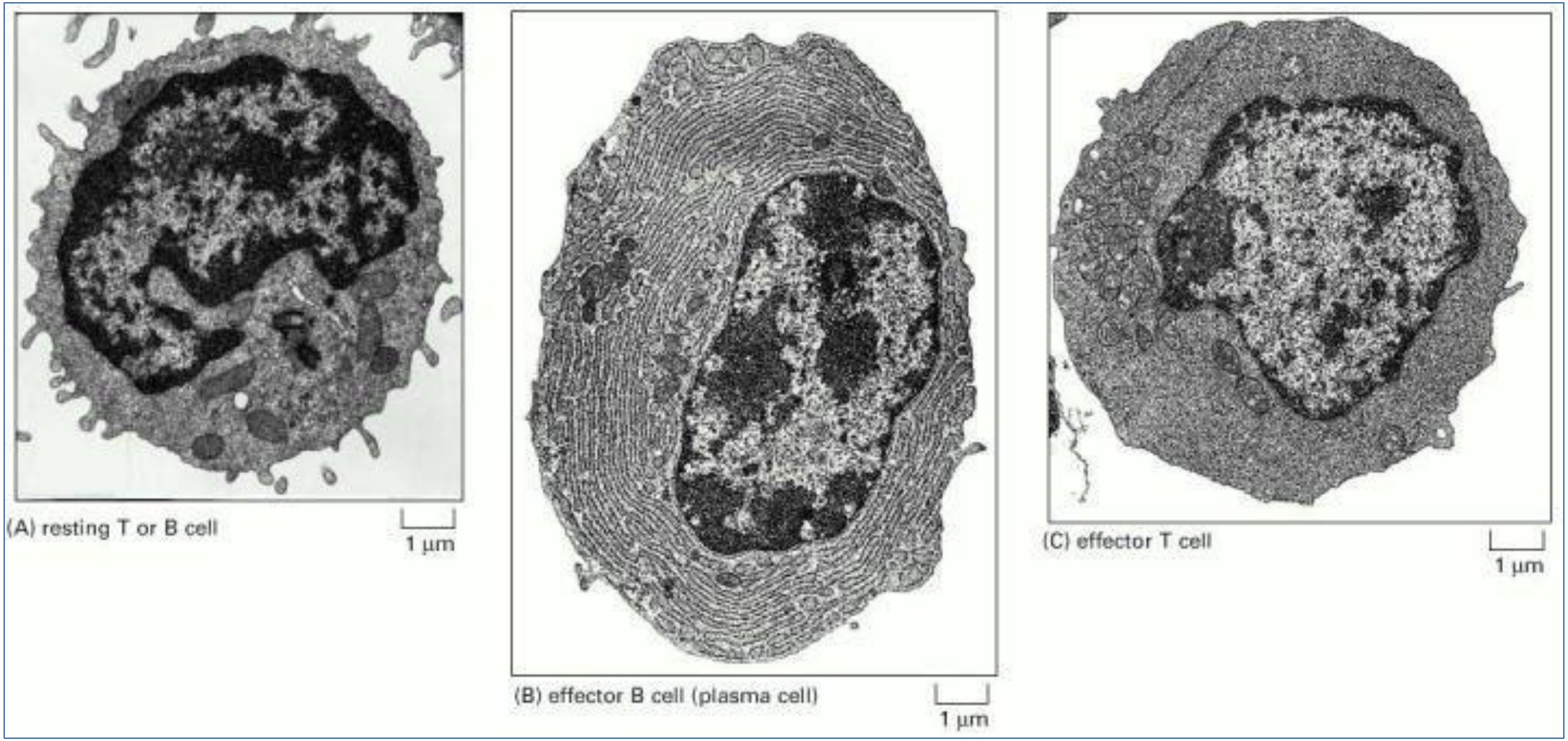
- Changes during differentiation of b cells include:

➢ the cell **enlarges dramatically**, and the ratio of cytoplasm to nucleus also undergoes a striking increase. The **endoplasmic reticulum becomes prominent**, and the cell is transformed into a **secretory cell** that bears little or no resemblance to a B cell.

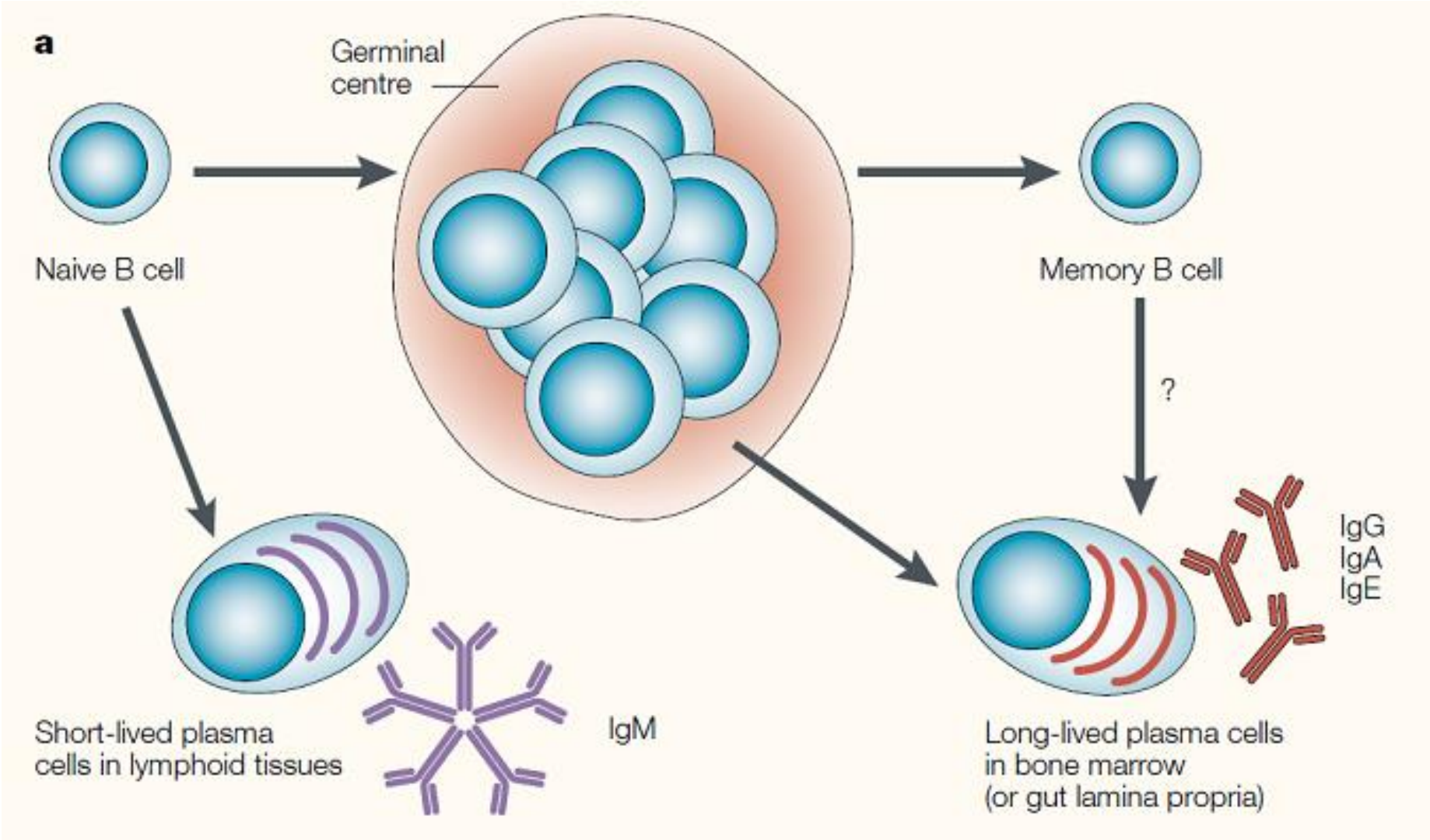
➢ The change in Ig production from the **membrane form** (characteristic of B cells) to the **secreted form** (in plasma cells)



B cell response/ B Cell Differentiation into Antibody-Secreting Plasma Cells



B cell response/ B Cell Differentiation into Antibody-Secreting Plasma Cells



B cell response/ Generation of Memory B Cells and Secondary Humoral Immune Responses

- Some of the antigen-activated B cells emerging from germinal centers acquire the ability to survive for long periods (by expressing high levels of the antiapoptotic protein Bcl-2), apparently without continuing antigenic stimulation, These are **memory cells**.

- Some memory B cells may **remain in the lymphoid organ** where they were generated, whereas **others exit germinal centers** and **recirculate** between the blood and lymphoid organs.

- They are produced in T cell dependent responses and usually emerge in parallel with **memory helper T cells**.

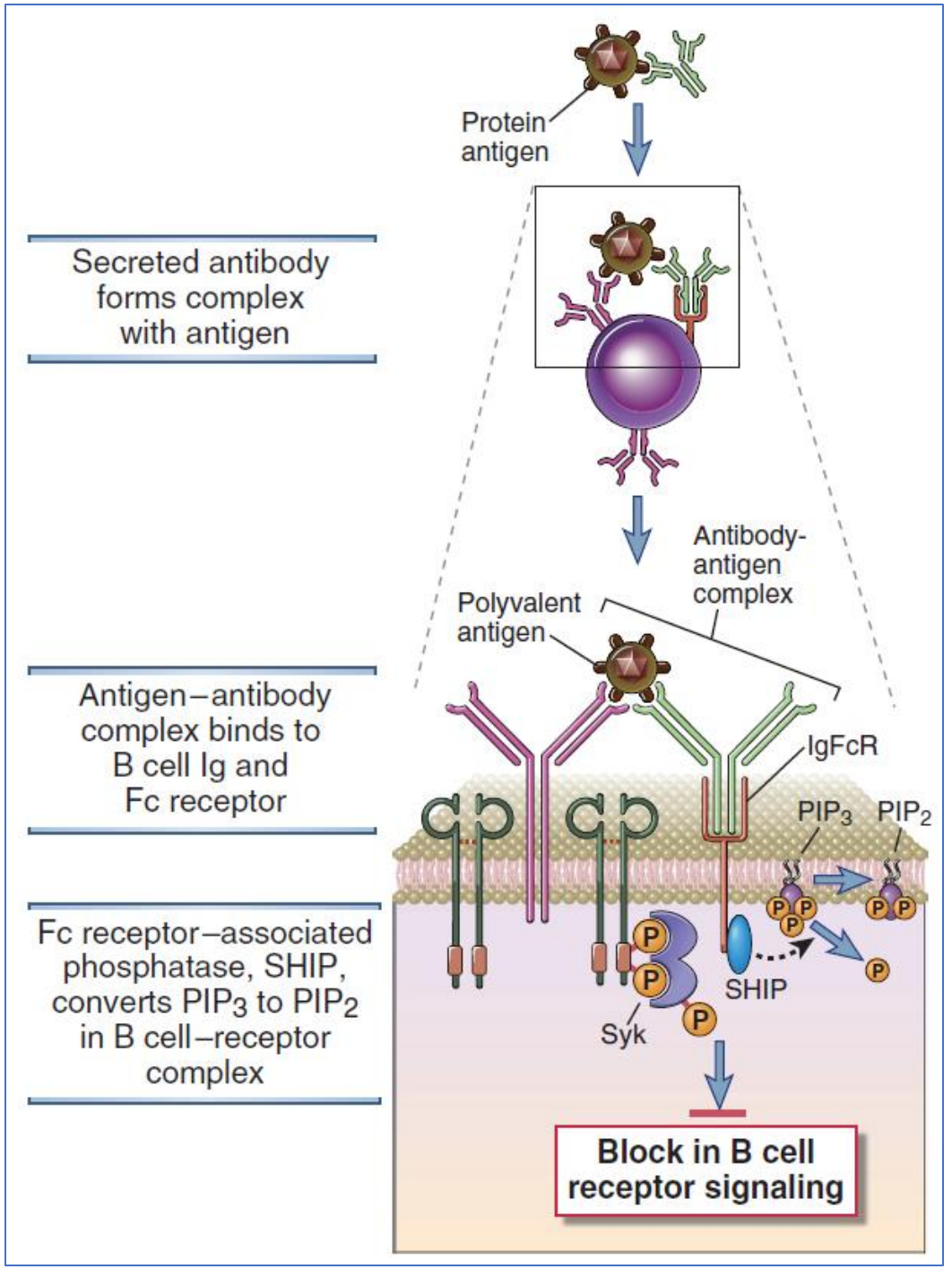
- The production of large quantities of **isotype-switched, high-affinity** antibodies is greatly accelerated **after secondary exposure** to antigens.

- After **re-encountering** the specific antigen they are able to **reactivate very quickly**, **propagate** themselves, create **plasma cells** and **reenter germinal centres** to **improve affinity** of their antibodies

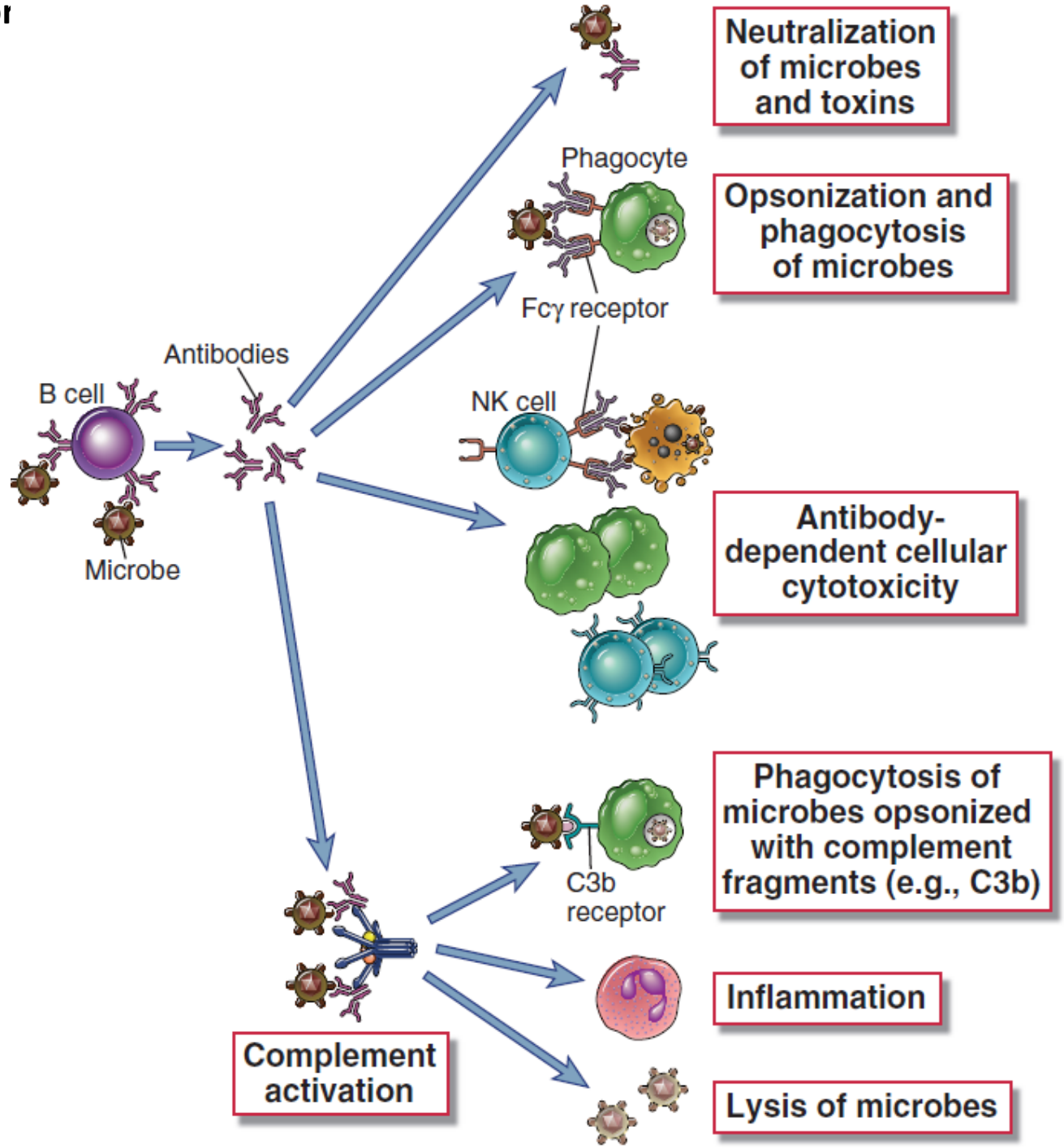
B cell response/ antibody feedback

- Secreted antibodies **inhibit continuing B cell activation** by forming antigen-antibody complexes that simultaneously bind to antigen receptors and inhibitory Fcγ receptors on antigen-specific B cells.

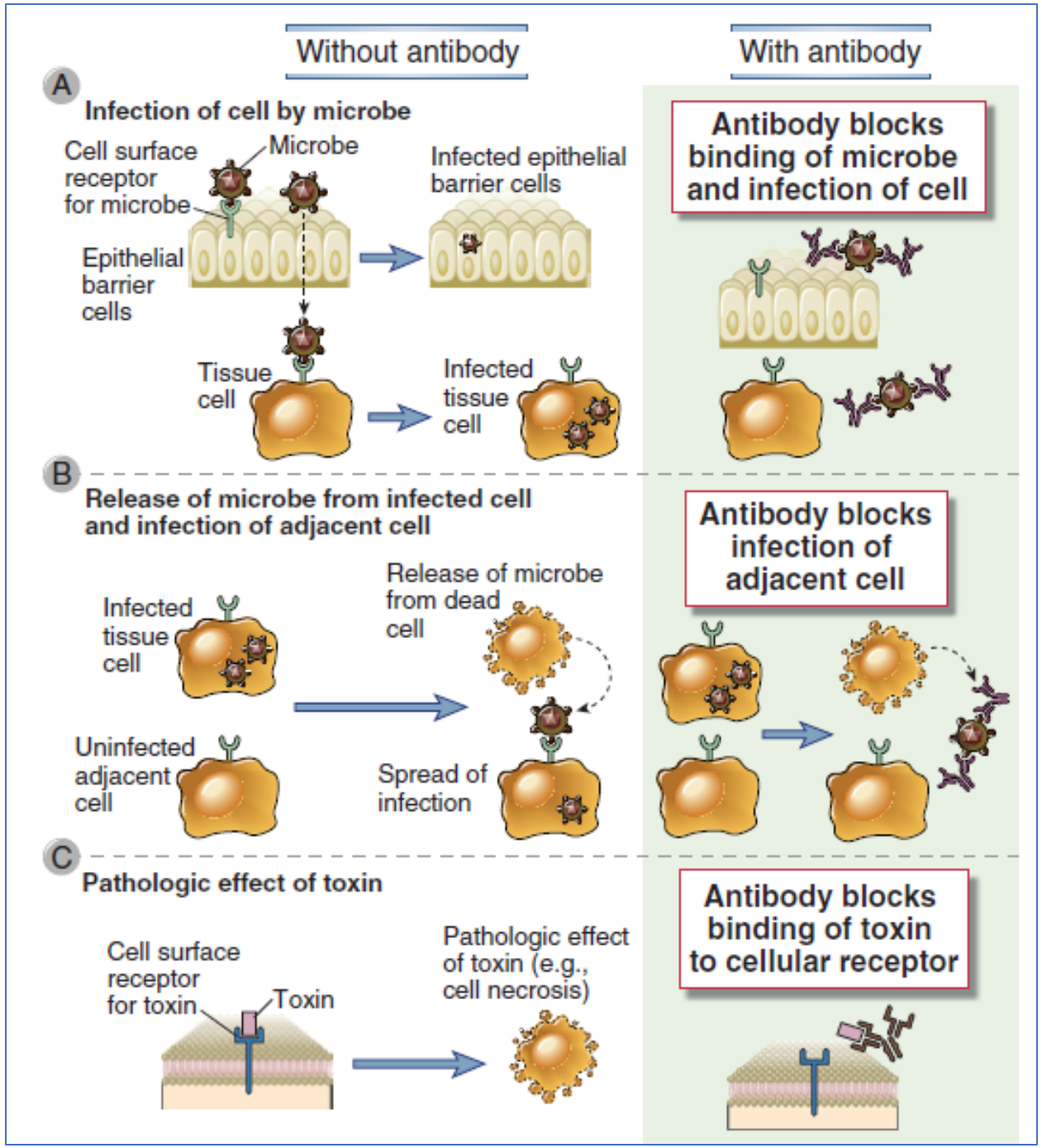
- The antigen-antibody complexes simultaneously interact with the antigen receptor (through the antigen) and with **FcγRIIB** (through the antibody), and this brings the inhibitory phosphatases close to the antigen receptors whose signaling is blocked.



Effector mechanisms of humor

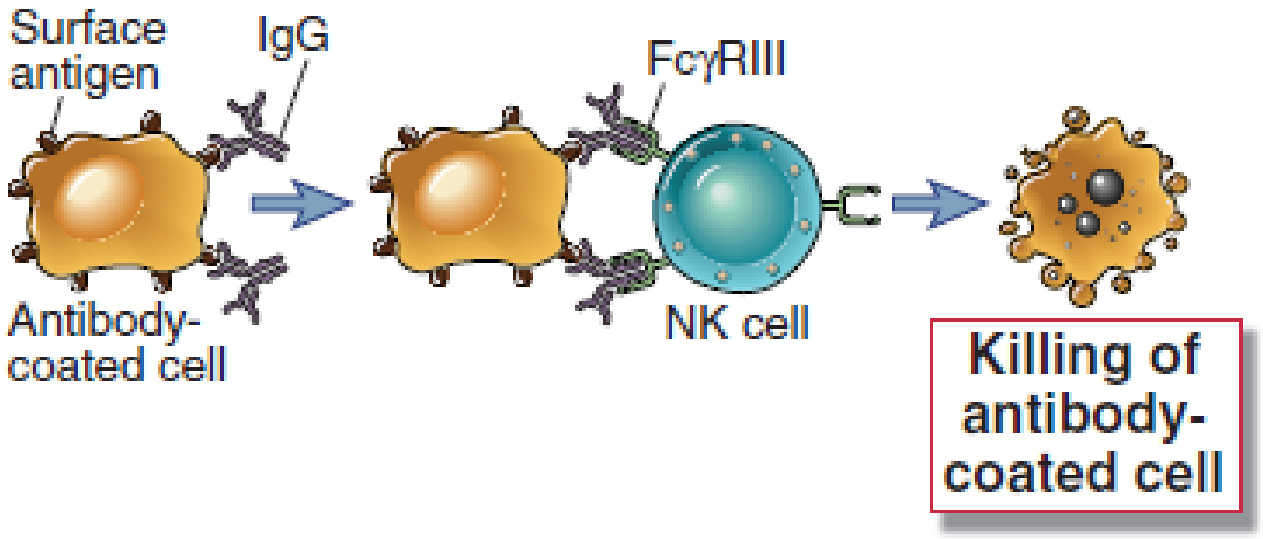


Effector mechanisms of humoral immunity



Effector mechanisms of humoral immunity/ antibody-dependent cellular cytotoxicity

FIGURE 12–5 Antibody-dependent cell-mediated cytotoxicity. Antibodies of certain IgG subclasses bind to cells (e.g., infected cells), and the Fc regions of the bound antibodies are recognized by an Fcγ receptor on NK cells. The NK cells are activated and kill the antibody-coated cells. Presumably, NK cells can lyse even class I MHC–expressing targets when these target cells are opsonized because the Fc receptor–mediated stimulation may overcome the inhibitory actions of class I MHC–recognizing NK cell inhibitory receptors (see Chapter 12).



- Natural killer (NK) cells and other leukocytes bind to antibody-coated cells by Fc receptors and destroy these cells. This process is called **antibody-dependent cellular cytotoxicity** (ADCC).
- Engagement of **FcγRIII** by antibody-coated target cells activates the NK cells to synthesize and secrete cytokines such as **IFN-γ** as well as to **discharge the contents of their granules**, which mediate the killing functions of this cell type

Effector mechanisms of humoral immunity

TABLE 12–3 Fc Receptors

FcR	Affinity for Immunoglobulin	Cell Distribution	Function
FcγRI (CD64)	High ($K_d < 10^{-9}$ M); binds IgG1 and IgG3, can bind monomeric IgG	Macrophages, neutrophils; also eosinophils	Phagocytosis; activation of phagocytes
FcγRIIA (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils; eosinophils, platelets	Phagocytosis; cell activation (inefficient)
FcγRIIB (CD32)	Low ($K_d > 10^{-7}$ M)	B lymphocytes	Feedback inhibition of B cells
FcγRIIC (CD32)	Low ($K_d > 10^{-7}$ M)	Macrophages, neutrophils, NK cells	Phagocytosis, cell activation
FcγRIIIA (CD16)	Low ($K_d > 10^{-6}$ M)	NK cells	Antibody-dependent cell-mediated cytotoxicity
FcγRIIIB (CD16)	Low ($K_d > 10^{-6}$ M); GPI-linked protein	Neutrophils	Phagocytosis (inefficient)
FcεRI	High ($K_d > 10^{-10}$ M); binds monomeric IgE	Mast cells, basophils, eosinophils	Cell activation (degranulation)
FcεRII (CD23)	Low ($K_d > 10^{-7}$ M)	B lymphocytes, eosinophils, Langerhans cells	Unknown
FcαR (CD89)	Low ($K_d > 10^{-6}$ M)	Neutrophils, eosinophils, monocytes	Cell activation?

GPI, glycophosphatidylinositol; NK, natural killer.

Effector mechanisms of humoral immunity

TABLE 12–1 Functions of Antibody Isotypes

Antibody Isotype	Isotype-Specific Effector Functions
IgG	Opsonization of antigens for phagocytosis by macrophages and neutrophils Activation of the classical pathway of complement Antibody-dependent cell-mediated cytotoxicity mediated by natural killer cells Neonatal immunity: transfer of maternal antibody across the placenta and gut Feedback inhibition of B cell activation
IgM	Activation of the classical pathway of complement Antigen receptor of naive B lymphocytes*
IgA	Mucosal immunity: secretion of IgA into the lumens of the gastrointestinal and respiratory tracts Activation of complement by the lectin pathway or by the alternative pathway
IgE	Mast cell degranulation (immediate hypersensitivity reactions)
IgD	Antigen receptor of naive B lymphocytes*

*These functions are mediated by membrane-bound and not secreted antibodies.

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 11. B Cell Activation and Antibody Production

Chapter 12. Effector Mechanisms of Humoral Immunity