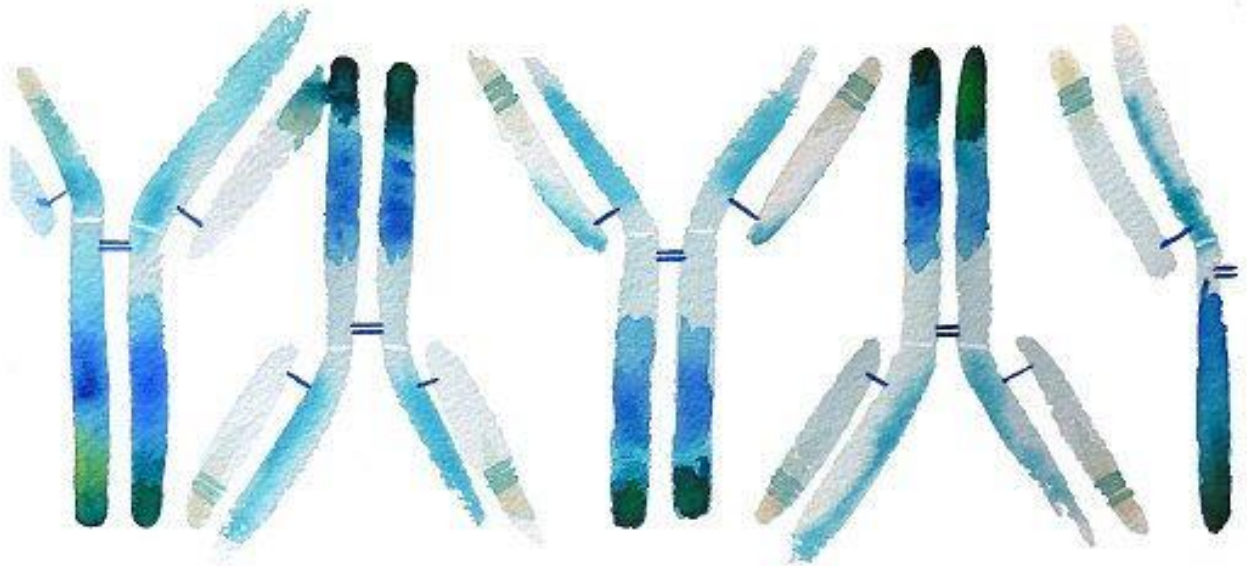
Medical Immunology



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

Lecture 16

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

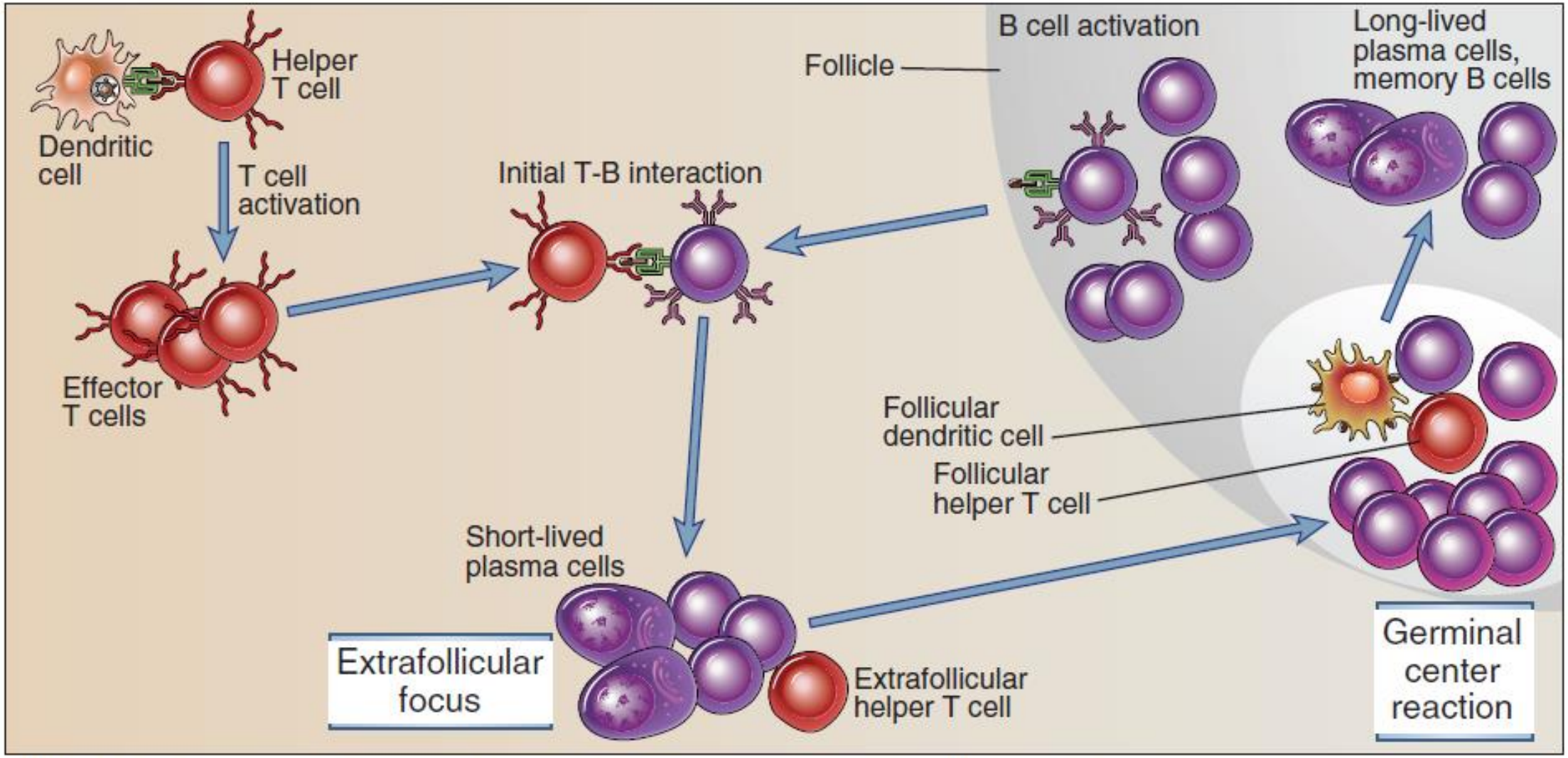


FIGURE 11–7 Sequence of events in humoral immune responses to T cell–dependent protein antigens. Immune responses are initiated by the recognition of antigens by B cells and helper T cells. The activated lymphocytes migrate toward one another and interact, resulting in B cell proliferation and differentiation.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

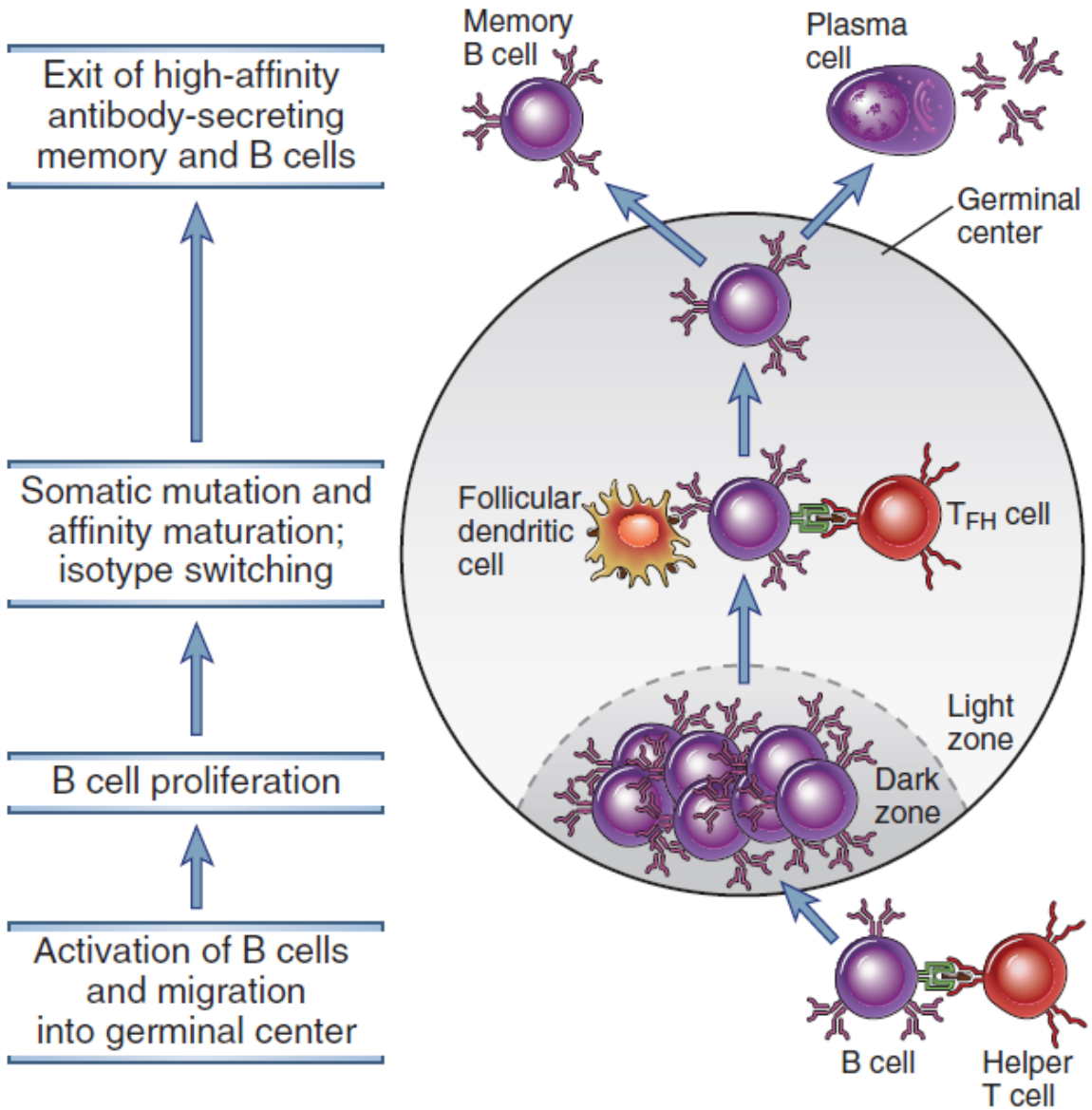


FIGURE 11–12 The germinal center reaction in a lymph node. B cells that have been activated by T helper cells at the edge of a primary follicle migrate into the follicle and proliferate, forming the dark zone of the germinal center. Germinal center B cells undergo extensive isotype switching. Somatic 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/ 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 which

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

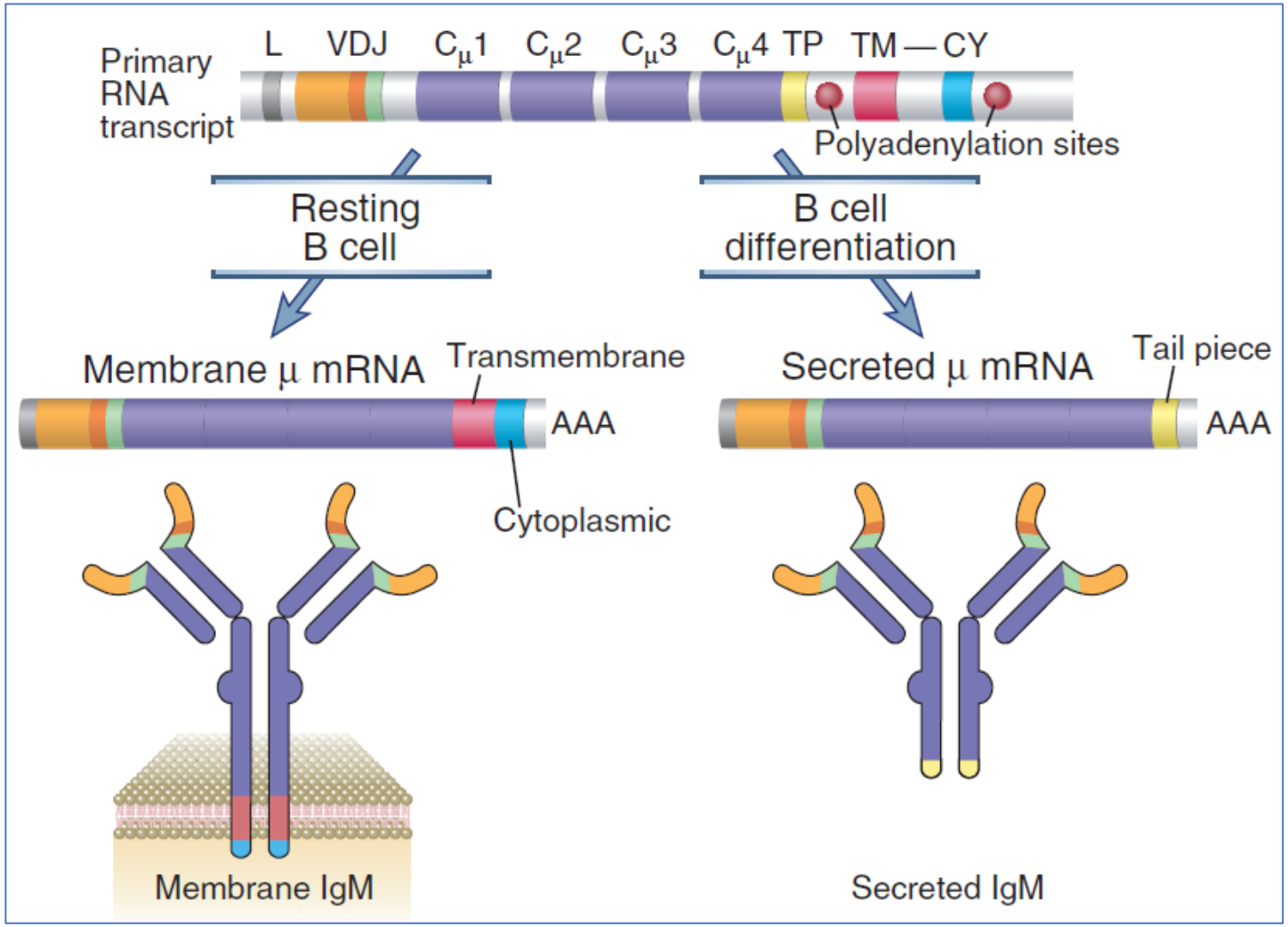
- Plasma cells to survive for long periods, often **as long as the life span of the host.**
- Typically 2 to 3 weeks after immunization with a T cell–dependent antigen, the **bone marrow** becomes **a major site of antibody production.**
- Plasma cells in the bone marrow may continue to secrete antibodies 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

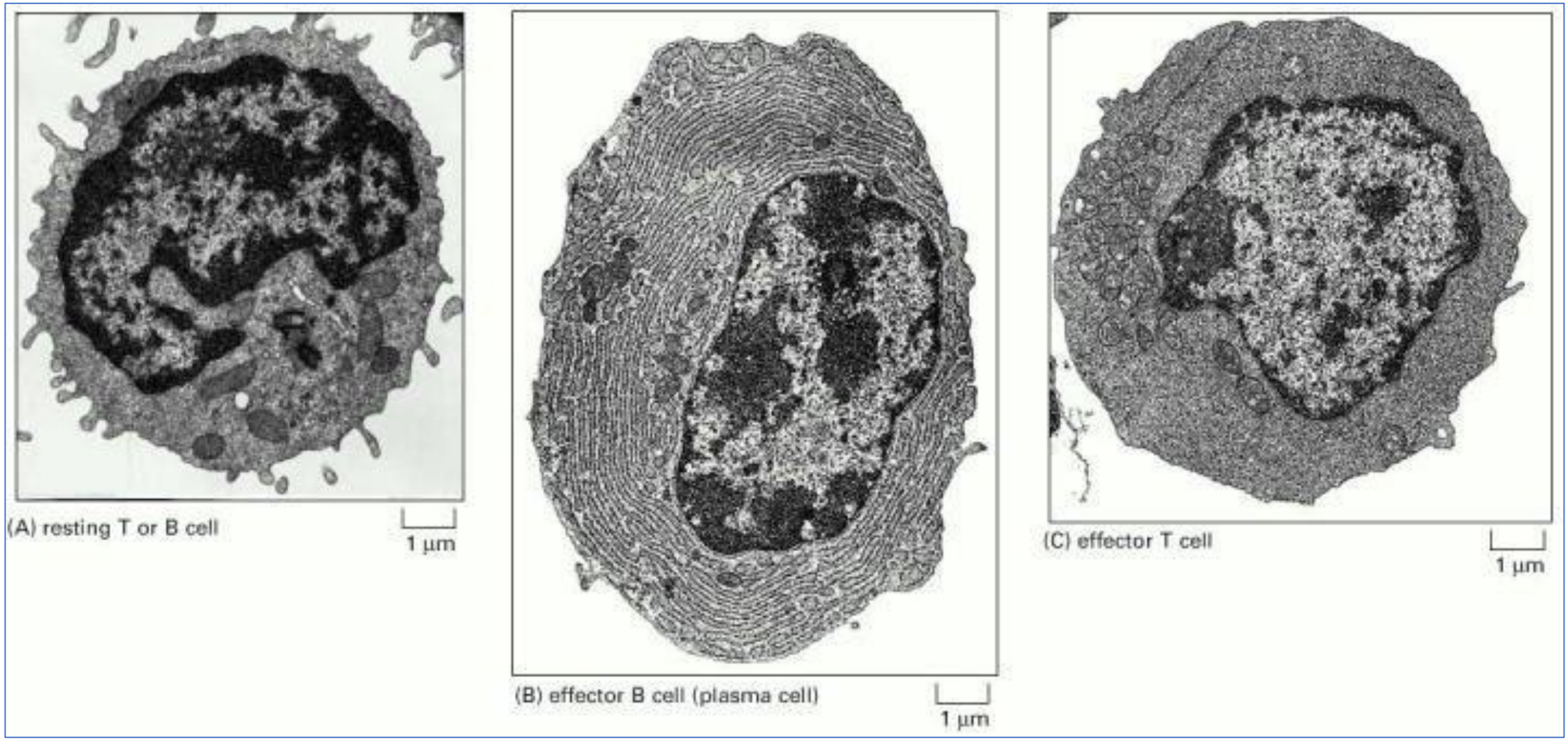
- Changes during differentiation of b cells include:

➢ 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.

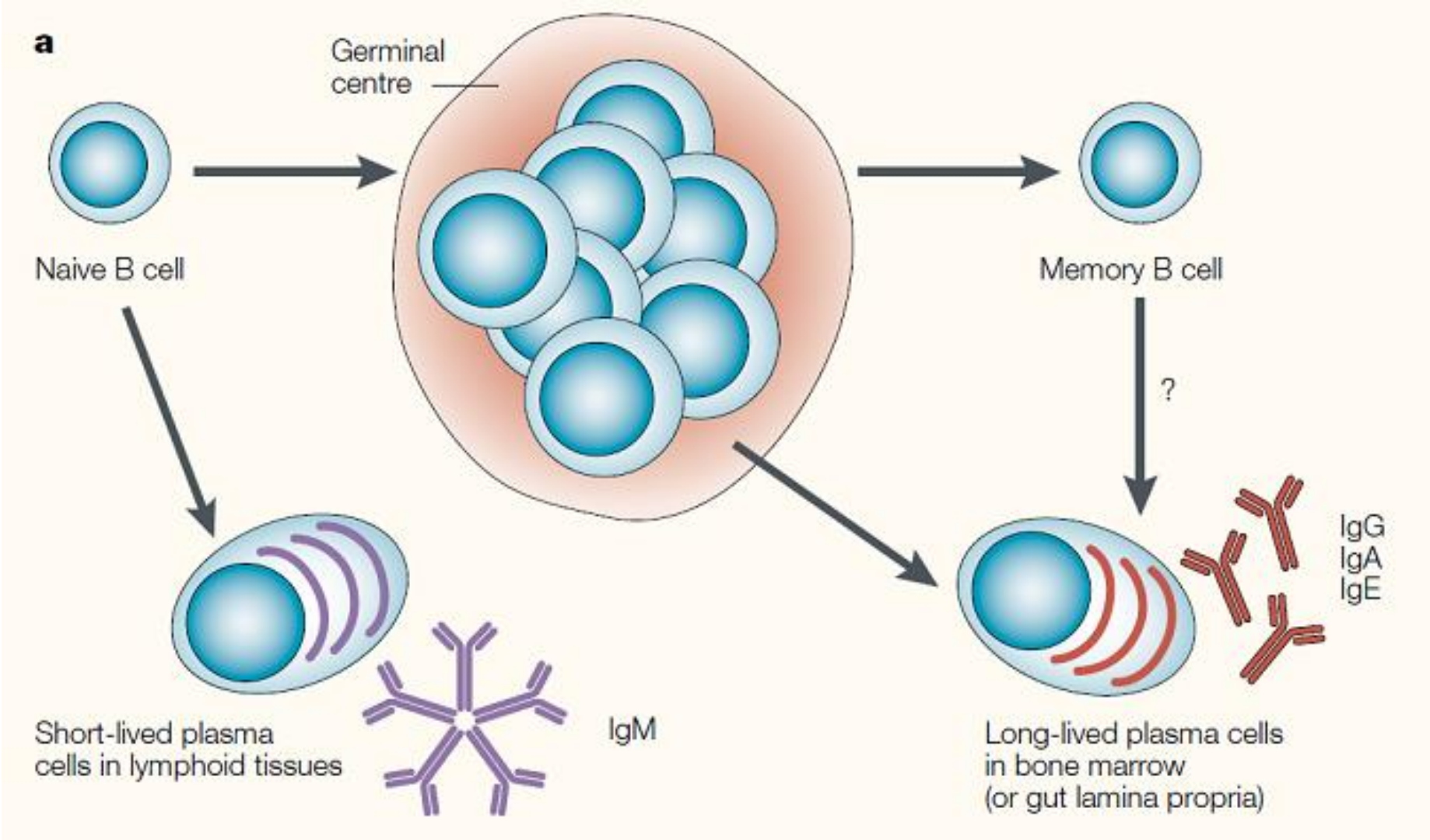
➢ The change in Ig production from the **membrane form** (characteristic of B cells) to the **secreted form** (in plasma cells)



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.

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

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- 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.

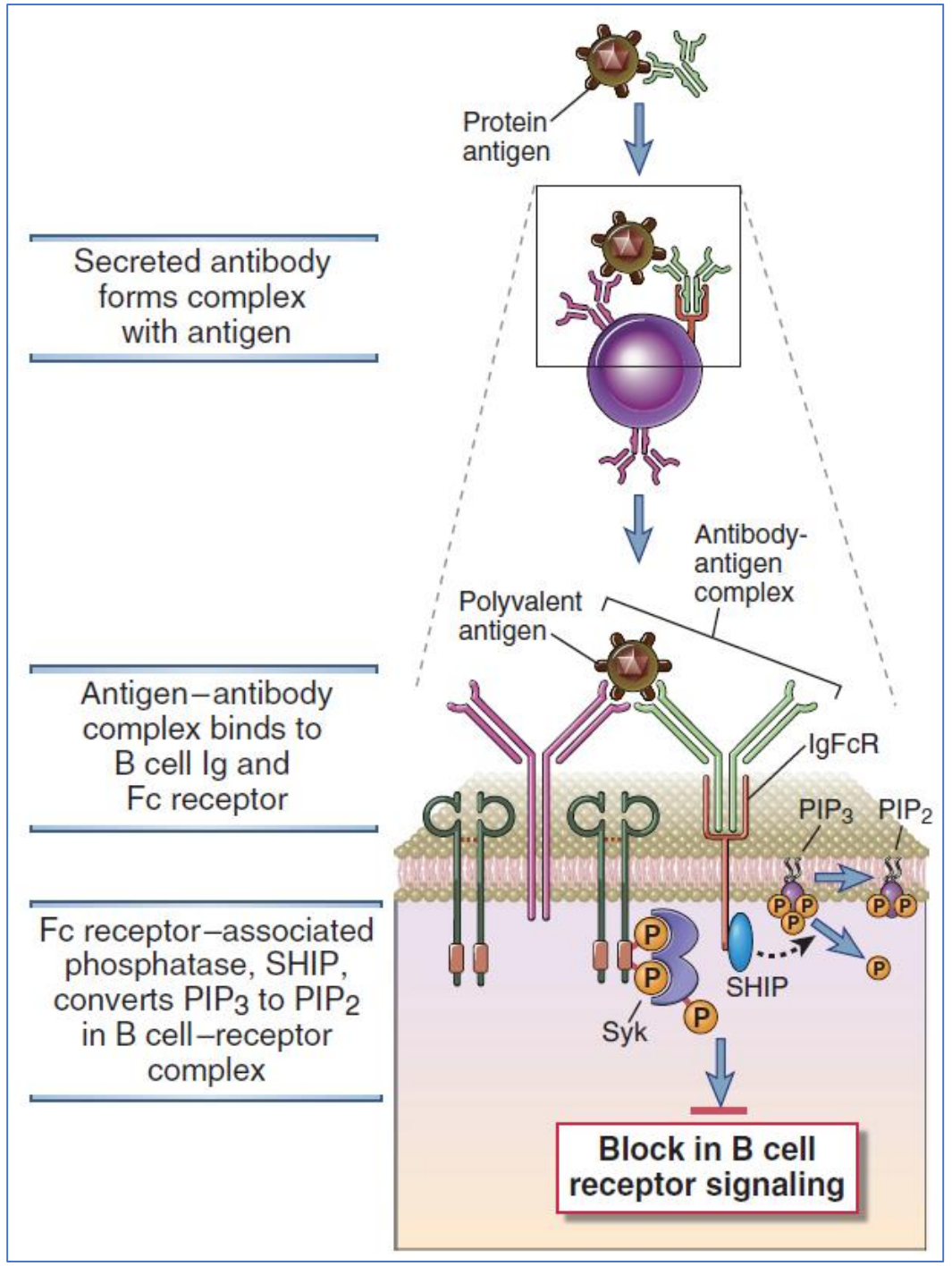
- They are produced in T cell dependent responses and usually emerge in parallel with **memory helper T cells**.

- 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

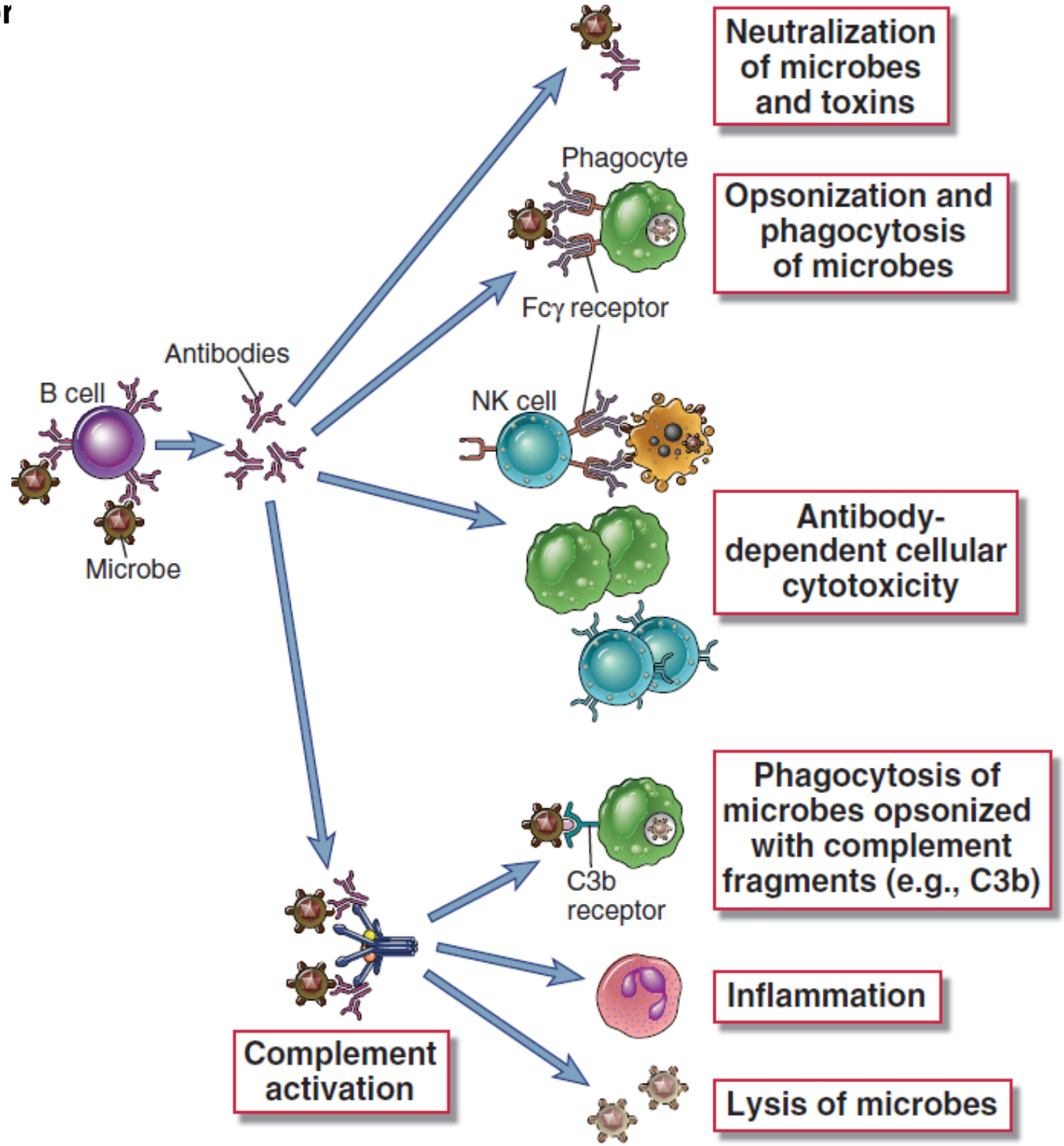
B cell response/ antibody feedback

- 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.

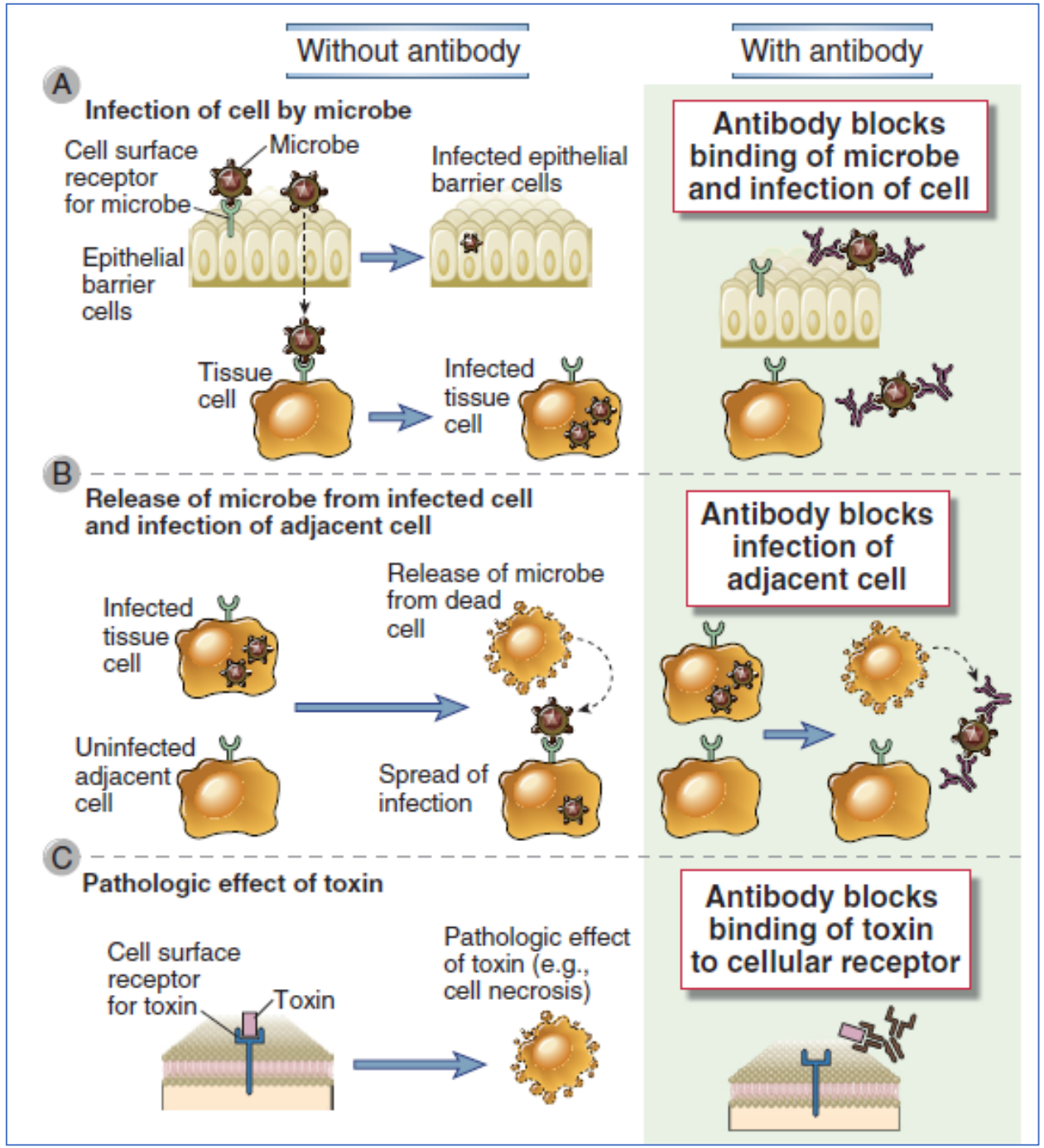
- The antigen-antibody complexes simultaneously interact with the antigen receptor (through the antigen) and with **FcγRIIB** (through the antibody), and this brings the inhibitory phosphatases close to the antigen receptors whose signaling is blocked.



Effector mechanisms of humor



Effector mechanisms of humoral immunity



Effector mechanisms of humoral immunity / Binding to Fc receptors

- IgG subtypes that bind best to Fc receptors (IgG1 and IgG3) are the most efficient opsonins for promoting phagocytosis. Binding of **FcγRI** receptors on phagocytes to multivalent antibody-coated particles leads to **engulfment** of the particles and the **activation** of phagocytes.

- Activation leads to:

➢ Production of the enzyme **phagocyte oxidase**, which catalyzes the intracellular generation of **reactive oxygen species** that are cytotoxic for phagocytosed microbes. This process is called the **respiratory burst**.

➢ Activation of an enzyme called **inducible nitric oxide synthase** (iNOS), which triggers the production of **nitric oxide** that also contributes to the killing of pathogens.

➢ Secretion of **hydrolytic enzymes** and reactive oxygen intermediates into the external milieu that are capable of killing extracellular microbes too large to be phagocytosed. The same toxic products may **damage tissues.**

Effector mechanisms of humoral immunity / Binding to Fc receptors

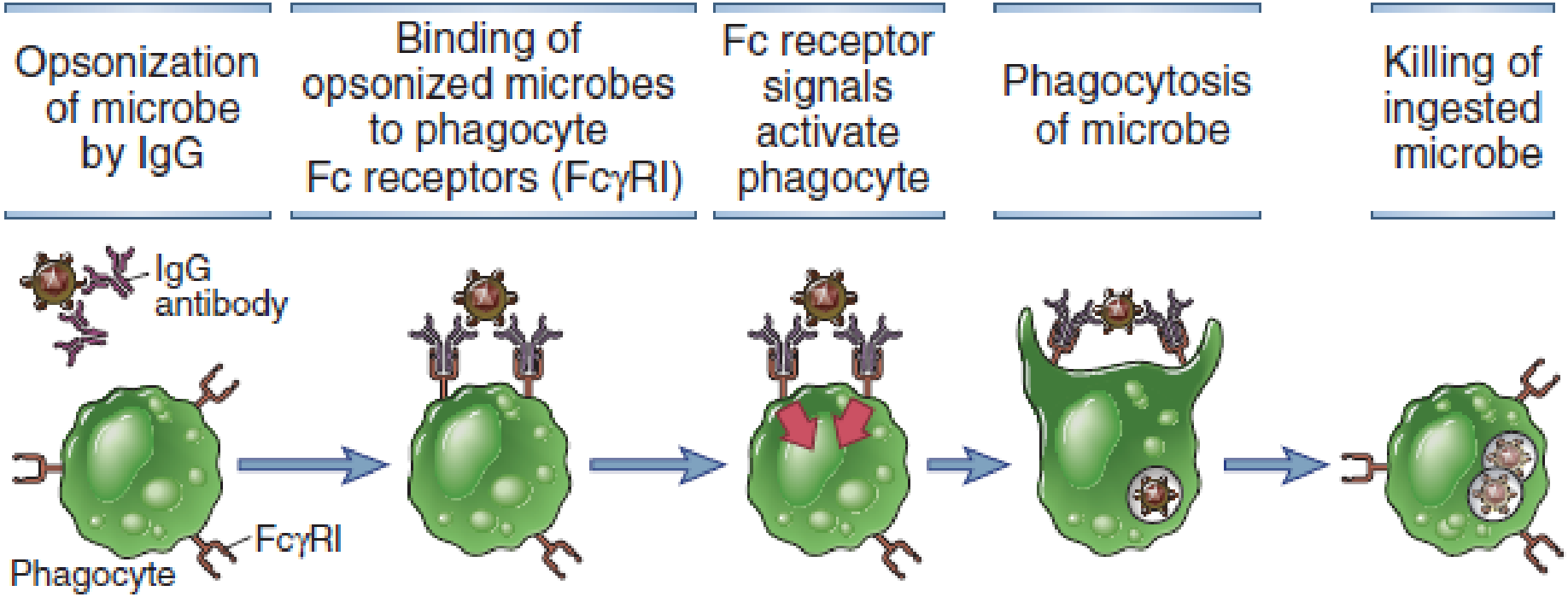
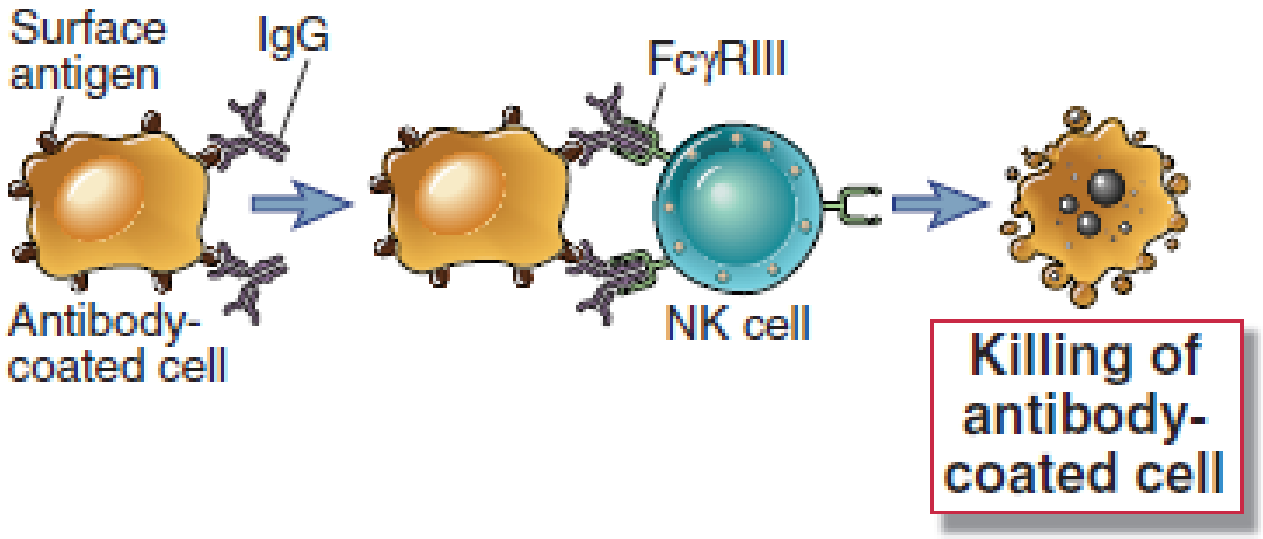


FIGURE 12–4 Antibody-mediated opsonization and phagocytosis of microbes. Antibodies of certain IgG subclasses bind to microbes and are then recognized by Fc receptors on phagocytes. Signals from the Fc receptors promote the phagocytosis of the opsonized microbes and activate the phagocytes to destroy these microbes. The microbicidal mechanisms of phagocytes are described in Chapters 4 (see Fig. 4-13) and 10 (see Fig. 10-7).

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

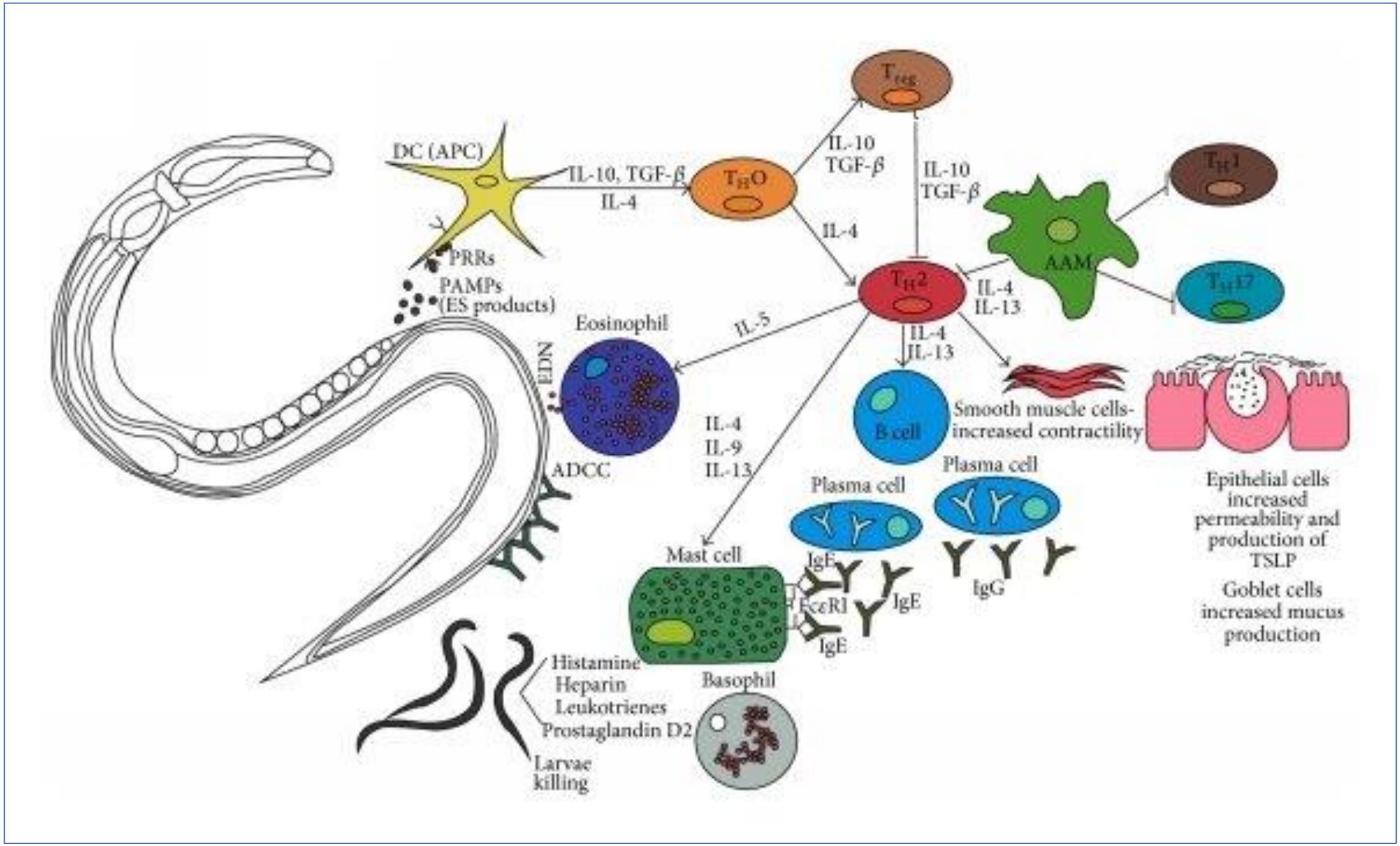
Effector mechanisms of humoral immunity/ Antibody-Mediated Clearance of Helminths

- **Antibodies**, **mast cells**, and **eosinophils** function with antibodies to mediate the expulsion and killing of some helminthic parasites. Helminths (worms) are too large to be engulfed by phagocytes, and their integuments are relatively resistant to the microbicidal products of neutrophils and macrophages.

- **IgE, IgG, and IgA** antibodies that coat helminths can bind to Fc receptors on eosinophils and cause the **degranulation of these cells**, releasing the **major basic protein**, a **toxic cationic protein**, present in the granules of eosinophils. Other eosinophil granule contents also aid in killing the parasites.

- **IgE antibodies** that recognize antigens on the surface of the helminths may initiate local **mast cell degranulation** through the **high-affinity IgE receptor**. Mast cell mediators may induce **bronchoconstriction and increased local motility**, contributing to the **expulsion** of worms.

Effector mechanisms of humoral immunity/ Antibody-Mediated Clearance of Helminths



Effector mechanisms of humoral immunity/ Antibody-Mediated Clearance of Helminths

Review Article

Harnessing the Helminth Secretome for Therapeutic Immunomodulators

Dana Ditgen,[1] Emmanuela M. Anandarajah,[1] Kamila A. Meissner,[2] Norbert Brattig,[3] Carsten Wrenger,[2] and Eva Liebau[1]

[1] *Department of Molecular Physiology, Westfälische Wilhelms-University Münster, Schlossplatz 8, 48143 Münster, Germany*
[2] *Unit for Drug Discovery, Department of Parasitology, Institute of Biomedical Science, University of São Paulo, 1374 Prof. Lineu Prestes Avenue, 05508-000 São Paulo, SP, Brazil*
[3] *Bernhard-Nocht-Institute, Bernhard-Nocht-Straße 74, 20259 Hamburg, Germany*

Correspondence should be addressed to Carsten Wrenger; cwrenger@icb.usp.br and Eva Liebau; liebaue@uni-muenster.de

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Helminths are the largest and most complex pathogens to invade and live within the human body. Since they are not able to outpace the immune system by rapid antigen variation or faster cell division or retreat into protective niches not accessible to immune effector mechanisms, their long-term survival depends on influencing and regulating the immune responses away from the mode of action most damaging to them. Immunologists have focused on the excretory and secretory products that are released by the helminths, since they can change the host environment by modulating the immune system. Here we give a brief overview of the helminth-associated immune response and the currently available helminth secretome data. We introduce some major secretome-derived immunomodulatory molecules and describe their potential mode of action. Finally, the applicability of helminth-derived therapeutic proteins in the treatment of allergic and autoimmune inflammatory disease is discussed.

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.

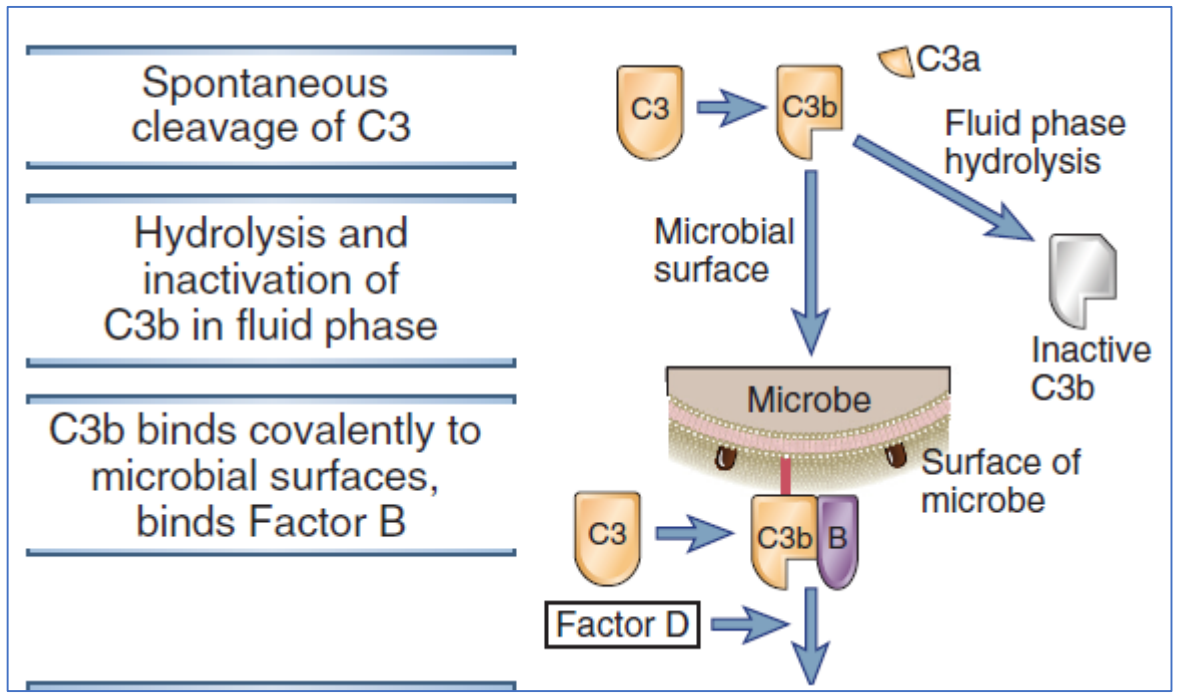
Effector mechanisms of humoral immunity

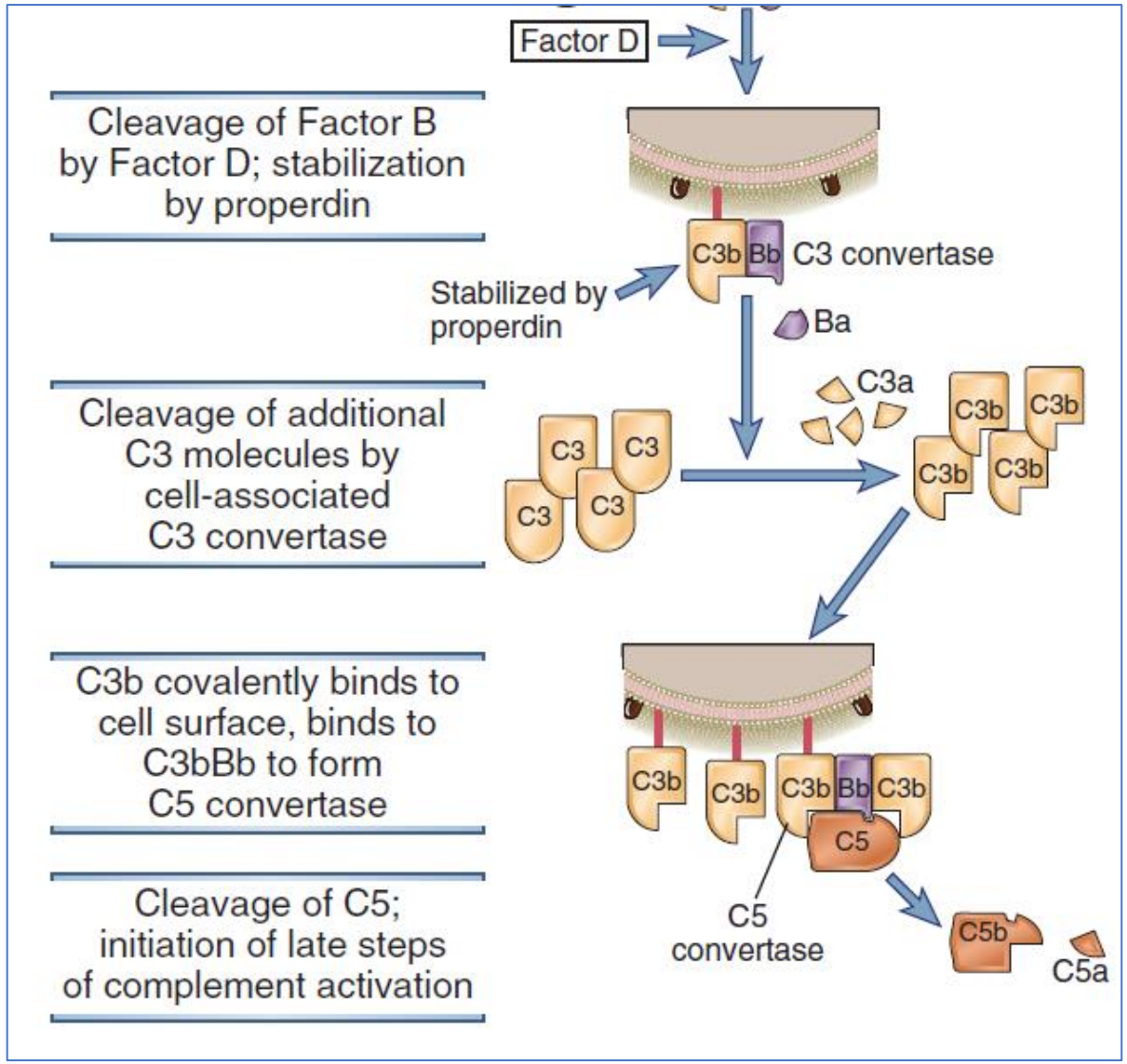
TABLE 12–1 Functions of Antibody Isotypes

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*

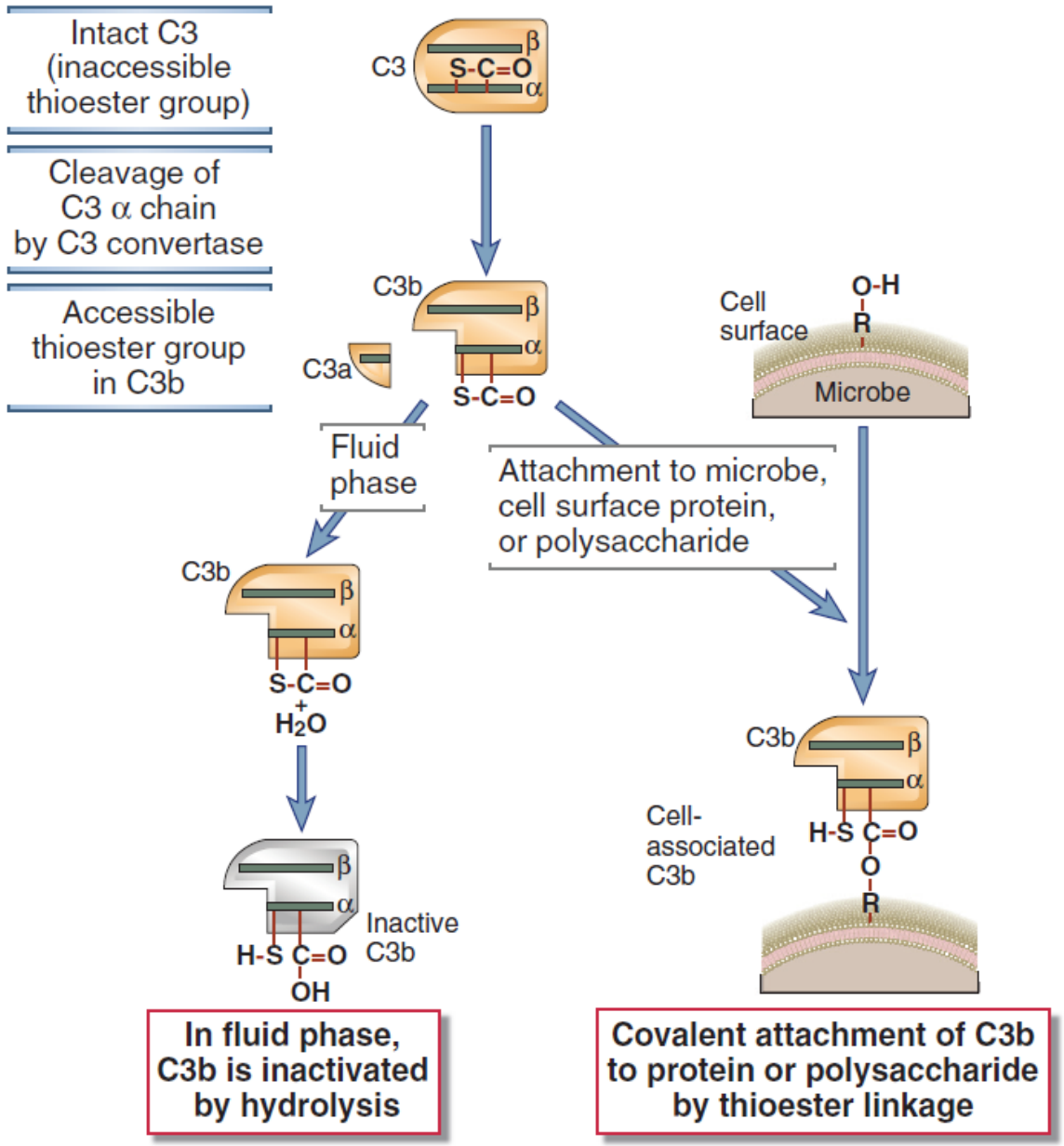
*These functions are mediated by membrane-bound and not secreted antibodies.

Effector mechanisms of humoral immunity





Effector mechanisms of humoral immunity



Effector mechanisms of humoral immunity

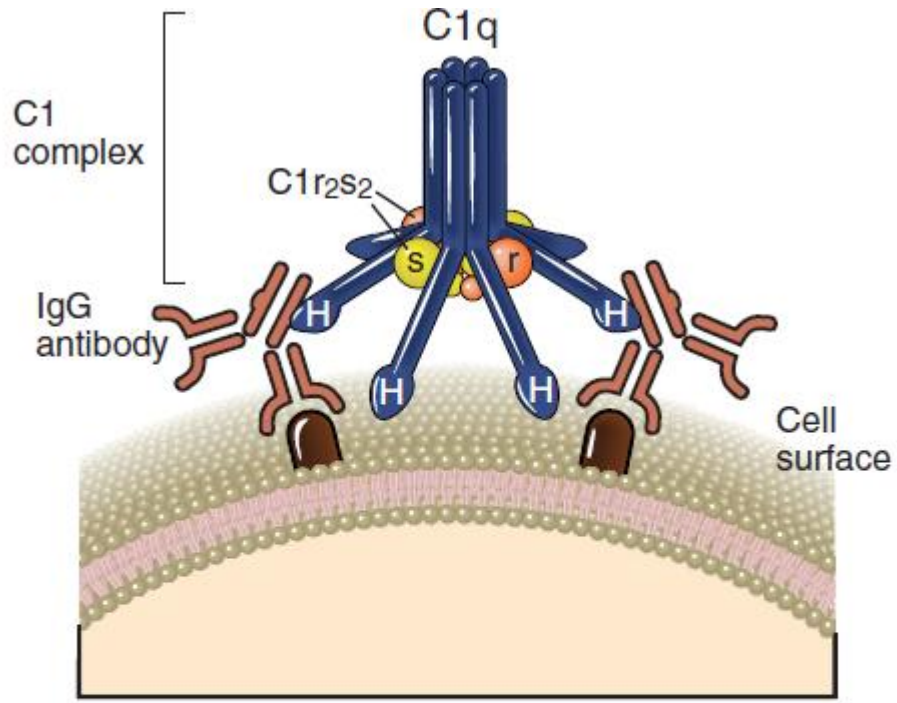


FIGURE 12–10 Structure of C1. C1q consists of six identical subunits arranged to form a central core and symmetrically projecting radial arms. The globular heads at the end of each arm, designated H, are the contact regions for immunoglobulin. C1r and C1s form a tetramer composed of two C1r and two C1s molecules. The ends of C1r and C1s contain the catalytic domains of these proteins. One $C1r_2s_2$ tetramer wraps around the radial arms of the C1q complex in a manner that juxtaposes the catalytic domains of C1r and C1s.

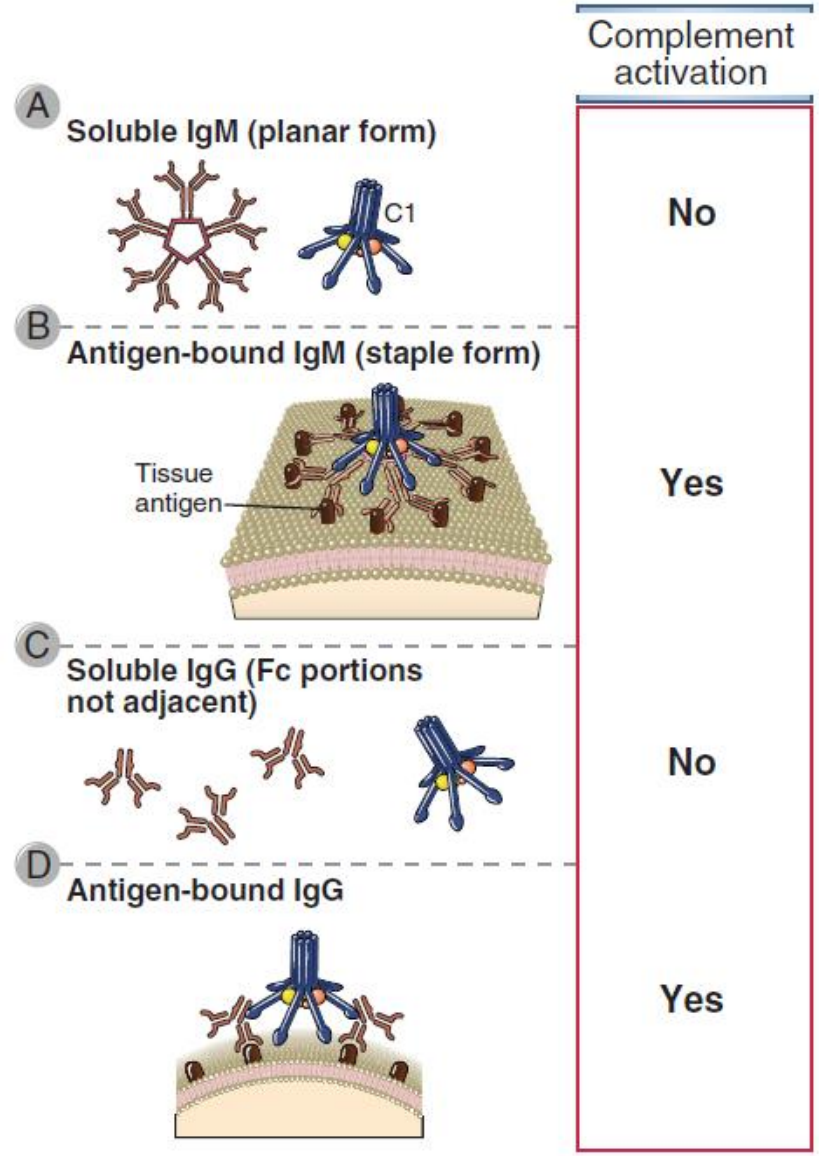
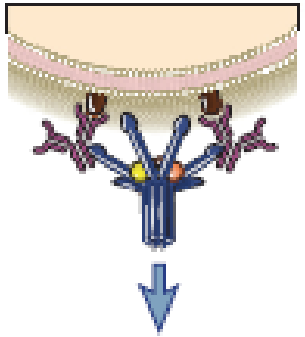


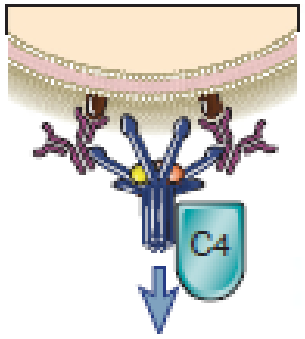
FIGURE 12–11 C1 binding to the Fc portions of IgM and IgG. C1 must bind to two or more Fc portions to initiate the complement cascade. The Fc portions of soluble pentameric IgM are not accessible to C1 **(A)**. After IgM binds to surface-bound antigens, it undergoes a shape change that permits C1 binding and activation **(B)**. Soluble IgG molecules will also not activate C1 because each IgG has only one Fc region **(C)**, but after binding to cell surface antigens, adjacent IgG Fc portions can bind and activate C1 **(D)**.

Effector mechanisms of humoral immunity

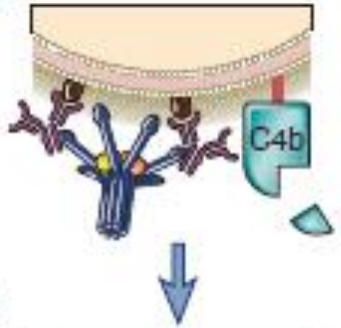
Binding of antibodies to multivalent antigen; binding of C1 to antibodies



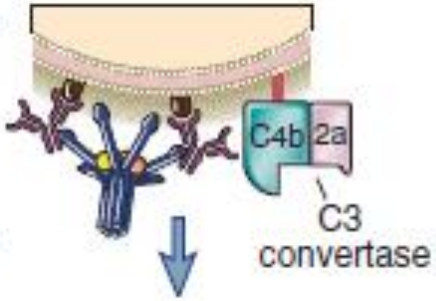
Binding of C4 to Ig-associated C1q



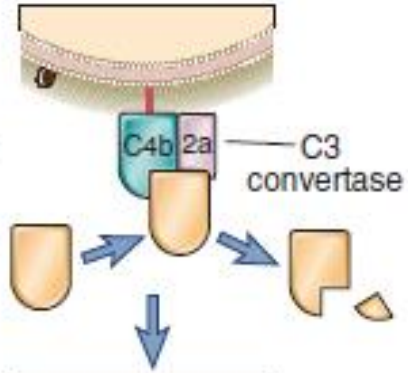
Cleavage of C4 by $C1r_2S_2$ enzyme; covalent attachment of C4b to antigenic surface and to antibodies



Binding of C2 to C4; cleavage of C2 to form C4b2b complex (C3 convertase)

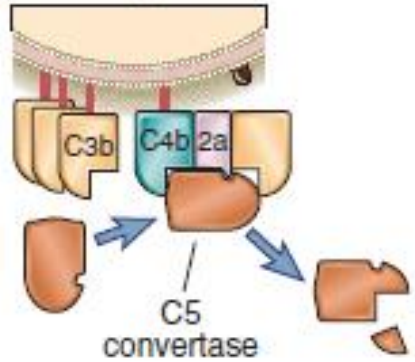


Cleavage of C3 by C3 convertase



Binding of C3b to antigenic surface and to C4b2b complex

Cleavage of C5; initiation of late steps of complement activation



Effector mechanisms of humoral immunity

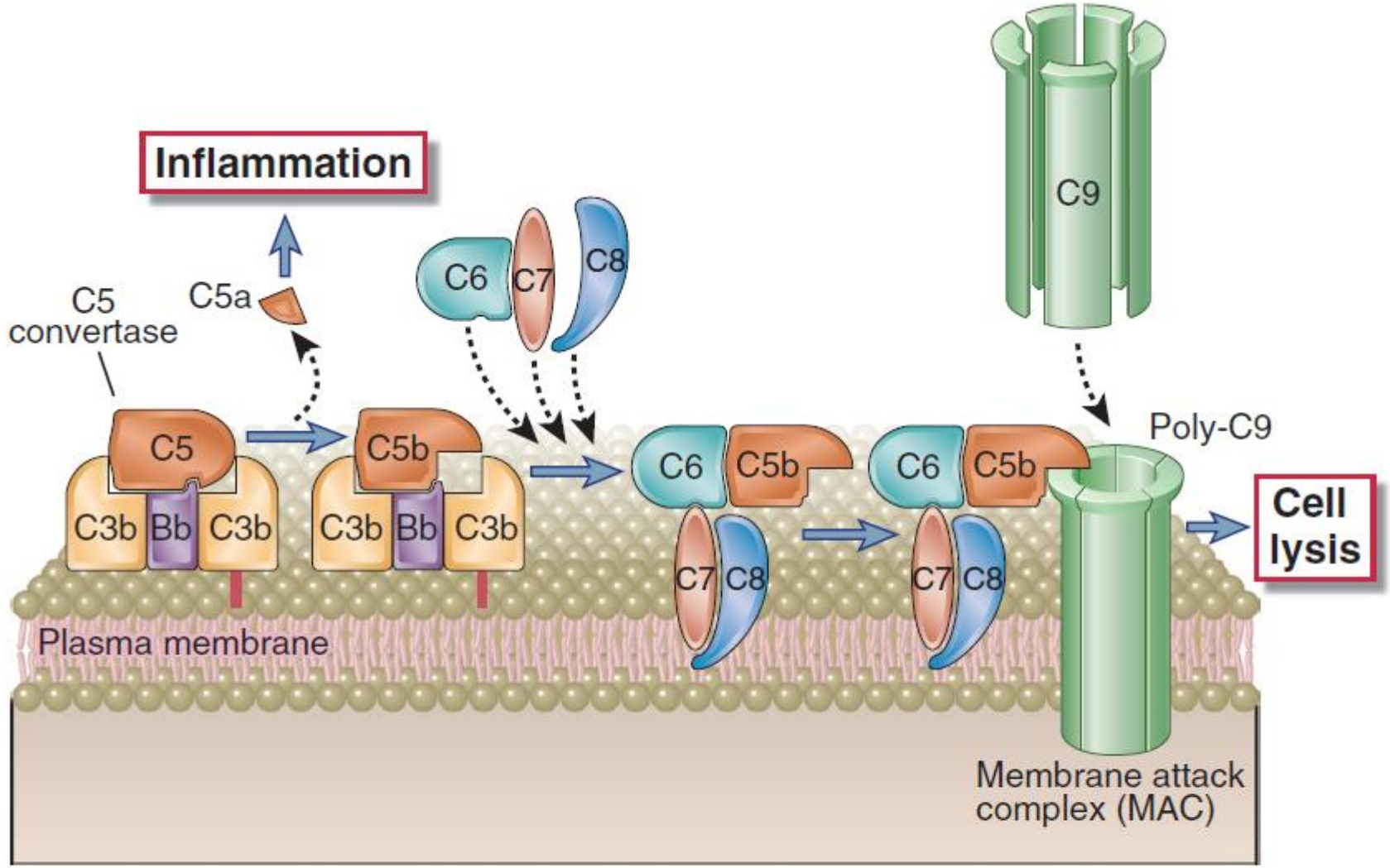


FIGURE 12–12 Late steps of complement activation and formation of the MAC. A schematic view of the cell surface events leading to formation of the MAC is shown. Cell-associated C5 convertase cleaves C5 and generates C5b, which becomes bound to the convertase. C6 and C7 bind sequentially, and the C5b,6,7 complex becomes directly inserted into the lipid bilayer of the plasma membrane, followed by stable insertion of C8. Up to 15 C9 molecules may then polymerize around the complex to form the MAC, which creates pores in the membrane and induces cell lysis. C5a released on proteolysis of C5 stimulates inflammation.

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 11. B Cell Activation and Antibody Production

Chapter 12. Effector Mechanisms of Humoral Immunity