Lecture I

Immune system

(overview of basic functions)

Nobel laureates

1901 Emil Adolf von Behring (1854-1917), "for his serum therapy to treat diphtheria" (First ever Nobel Prize in Physiology or Medicine)

1908 Eli Metchnikoff (1845-1916) and Paul Ehrlich (1854-1915), "for study of the immune system,,

1919 Jules Bordet (1870-1961), "for discovery of the complement system in the immune system,,

1930 Karl Landsteiner (1868-1943), "for discovery of human blood types,,

1960 Peter B. Medawar (1915-1987) and Frank Macfarlane Burnet (1899-1985), "for the discovery that the immune system of the fetus learns how to distinguish between self and non-self,,

1972 Gerald Maurice Edelman (1929-) and Rodney Robert Porter (1917-1985), "for discovering the chemical structure of antibodies,,

1980 Baruj Benacerraf (1920-2011), Jean Dausset (1916-2009) and George Davis Snell (1903-1996), "for discovery of the Major histocompatibility complex genes which encode cell surface molecules important for the immune system's distinction between self and non-self,,

1984 Niels Jerne (1911-1994), Georges J. F. Köhler (1946-1995) and César Milstein (1927-2002) "for work on the immune system and the production of monoclonal antibodies,,

1987 Susumu Tonegawa (1939-), "for discovering how the large diversity of antibodies is produced genetically"

1989 J. Michael Bishop (1936-) and Harold E. Varmus (1939-), "for discovering the cellular origins of retroviral oncogenes"

1996 Peter C. Doherty (1940-) and Rolf M. Zinkernagel (1944-) "for describing how MHC molecules are used by white blood cells to detect and kill virus-infected cells."

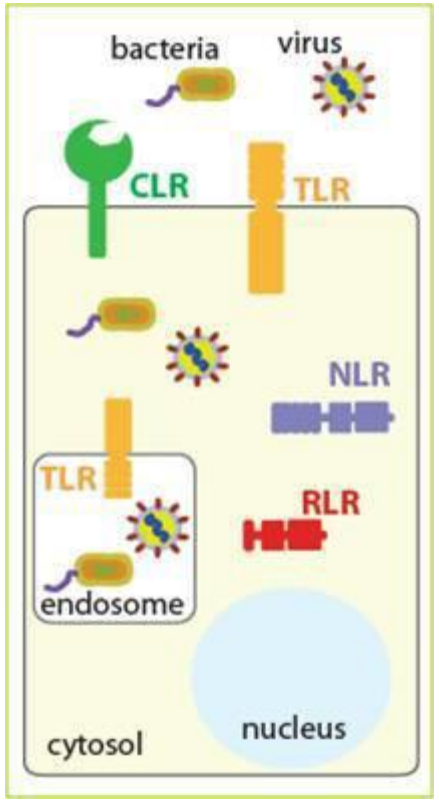
2011 Bruce Beutler(1957-), Jules A. Hoffmann (1941-) "for their discoveries concerning the activation of innate immunity" and Ralph Marvin Steinman (1943-2011)"for his discovery of the dendritic cell and its role in adaptive immunity"

2018 James P. Allison (1948-) and Tasuku Honjo (1942-) "for their discovery of cancer therapy by inhibition of negative immune regulation."

TABLE 1–2

SUMMARY OF NONSPECIFIC HOST DEFENSES

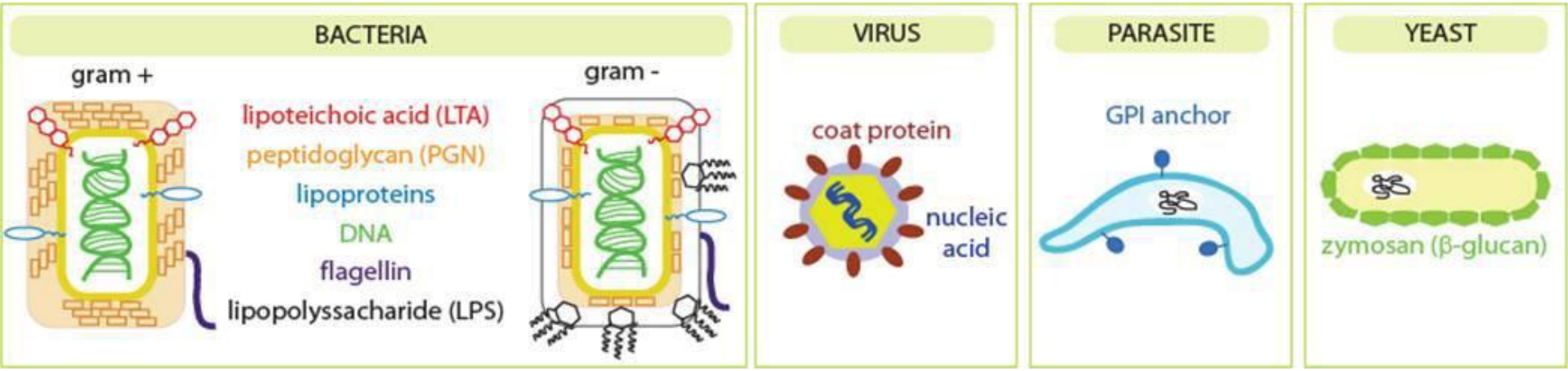
TYPE	MECHANISM
Atomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidic pH of stomach kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.



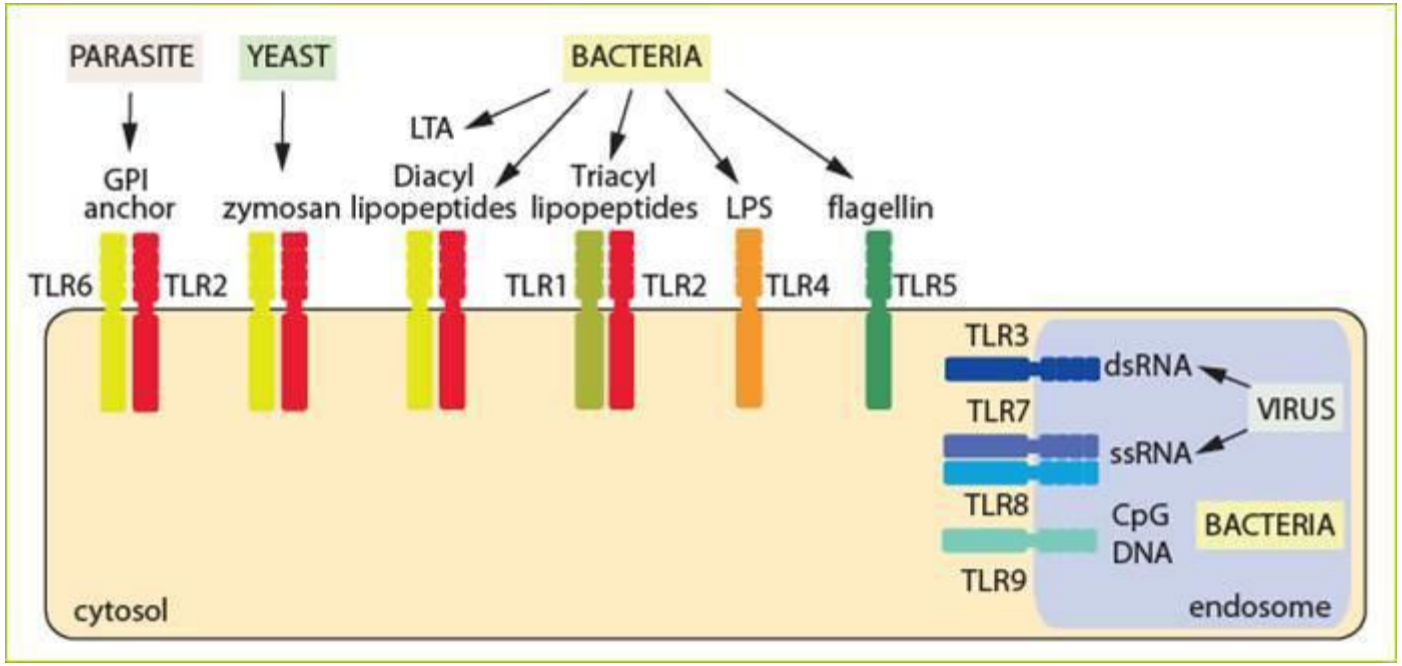
Pattern Recognition Receptors (PRR)

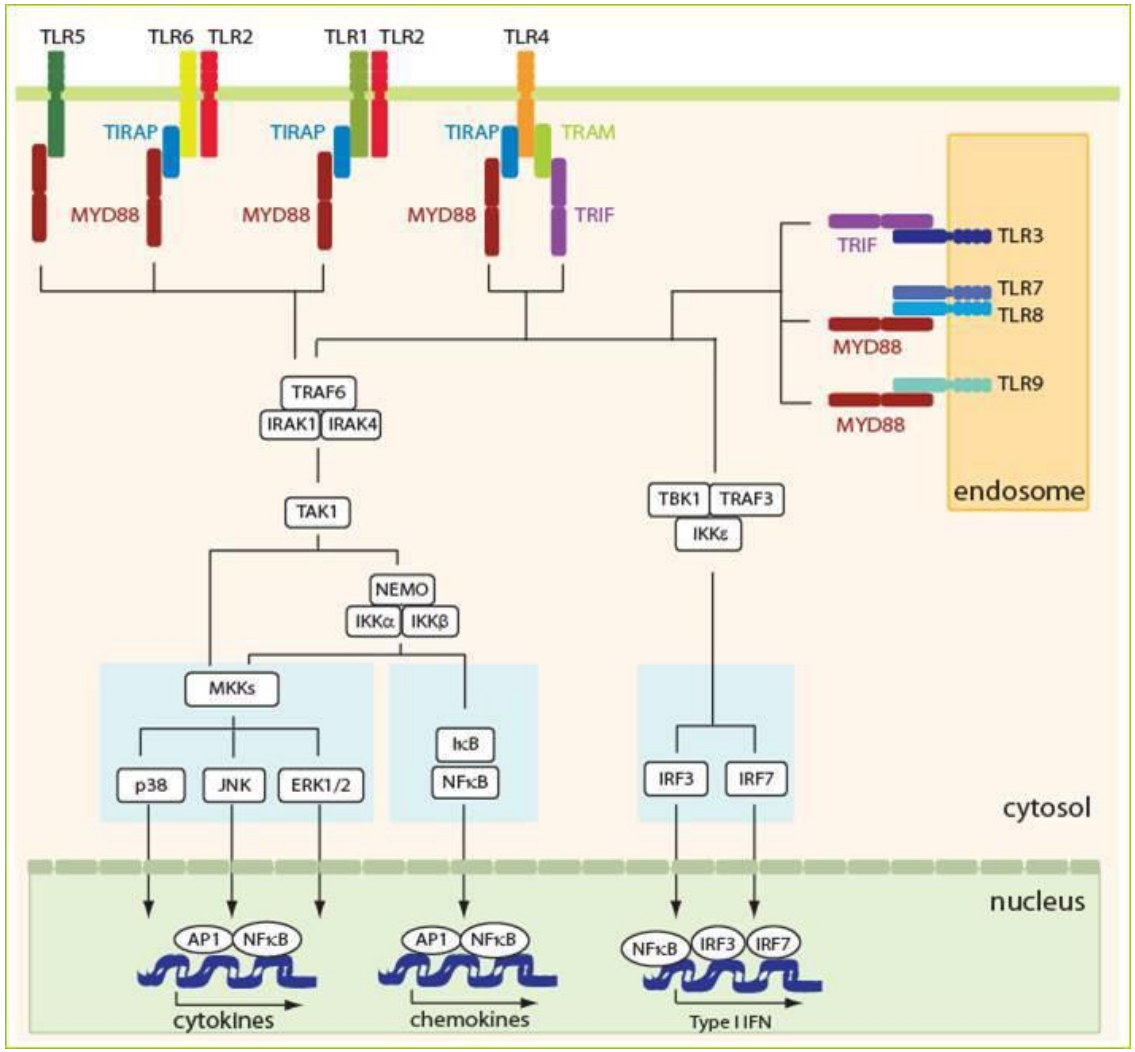
Toll-like receptors (**TLR**)
Nucleotide oligomerisation receptors (**NLR**)
C-type lectin receptors (**CLR**)
RIG-1 like receptors (**RLR**)

Pathogen associated molecular patterns (PAMPs) are specific to the microorganism and essential for its viability.



Toll-like Receptors





Three main pathways are activated by TLRs:

MAP kinase pathway (ERK, p38 and JNK)

NFkB pathway

IRF pathway

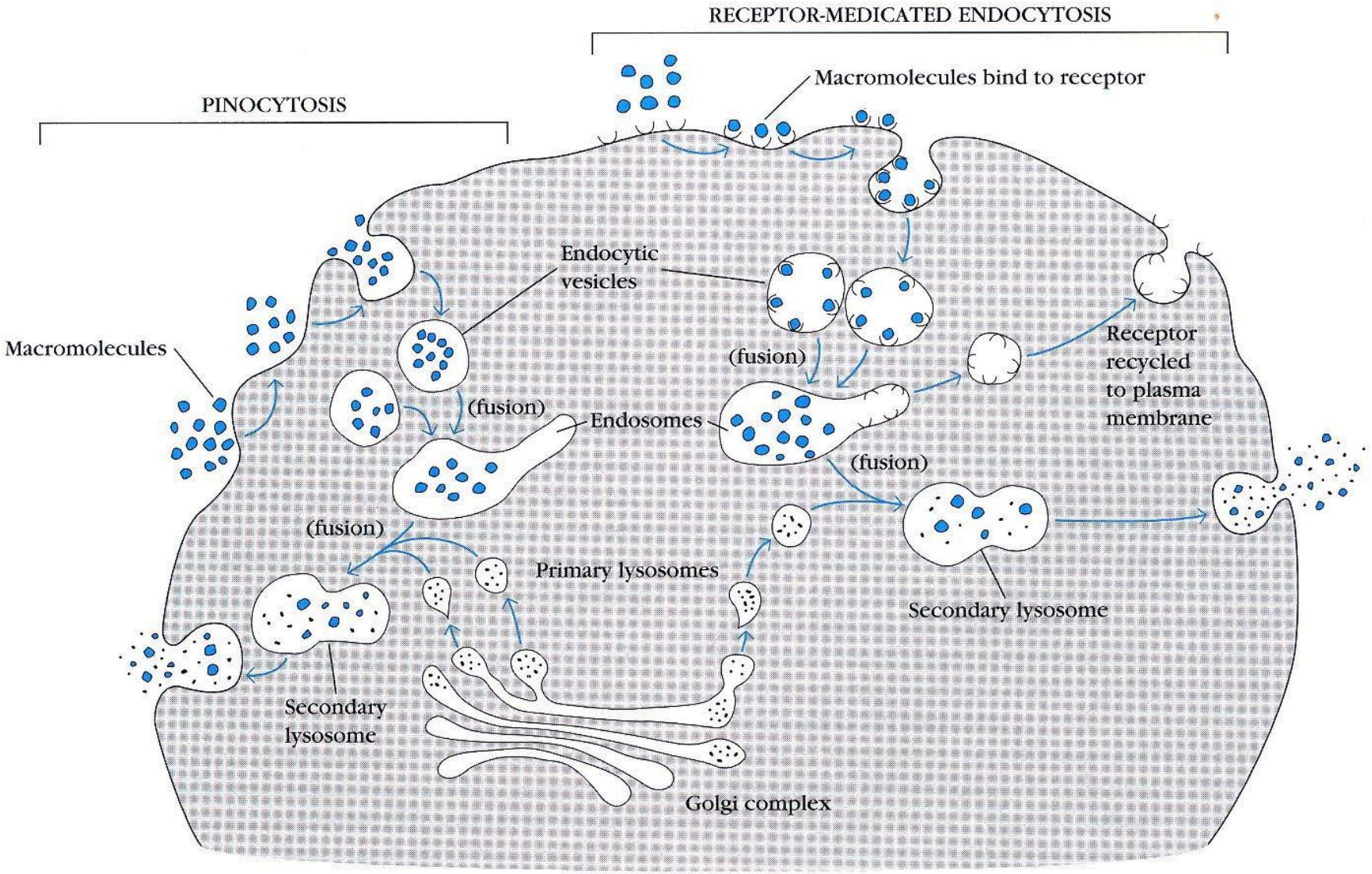
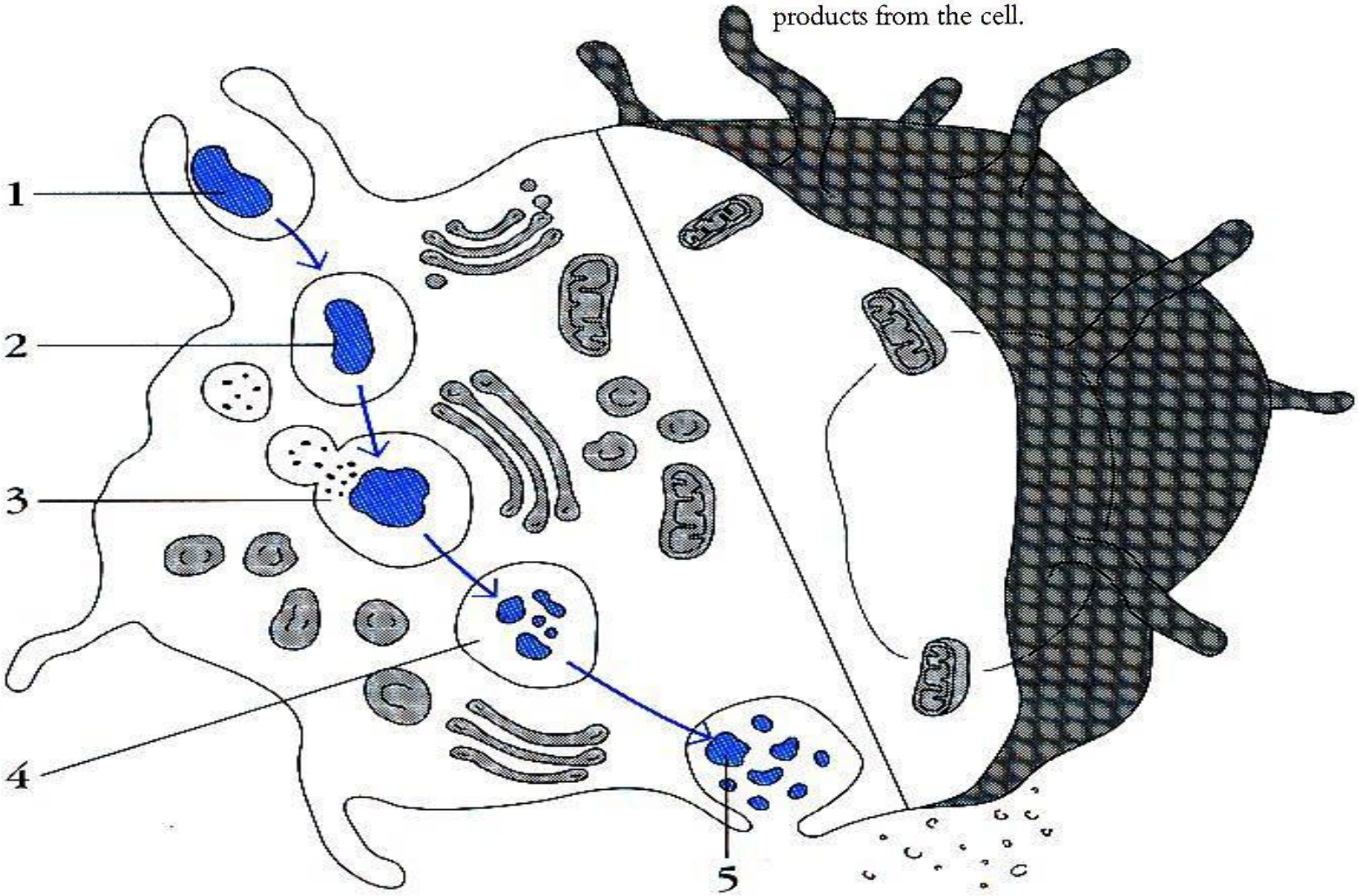


FIGURE 1-3

Endocytosis—the internalization of macromolecules within the extracellular fluid—occurs by pinocytosis or receptor-mediated endocytosis. In both processes, the ingested material is degraded via the endocytic processing pathway.

FIGURE 1-4

Phagocytosis of bacteria. Schematic diagram of the steps in phagocytosis: (1) attachment of a bacterium (blue) to long membrane evaginations, called pseudopodia; (2) ingestion of bacterium forming a phagosome, which moves toward a lysosome; (3) fusion of the lysosome and phagosome, releasing lysosomal enzymes into the phagosome; (4) digestion of ingested material; and (5) release of digestion products from the cell.



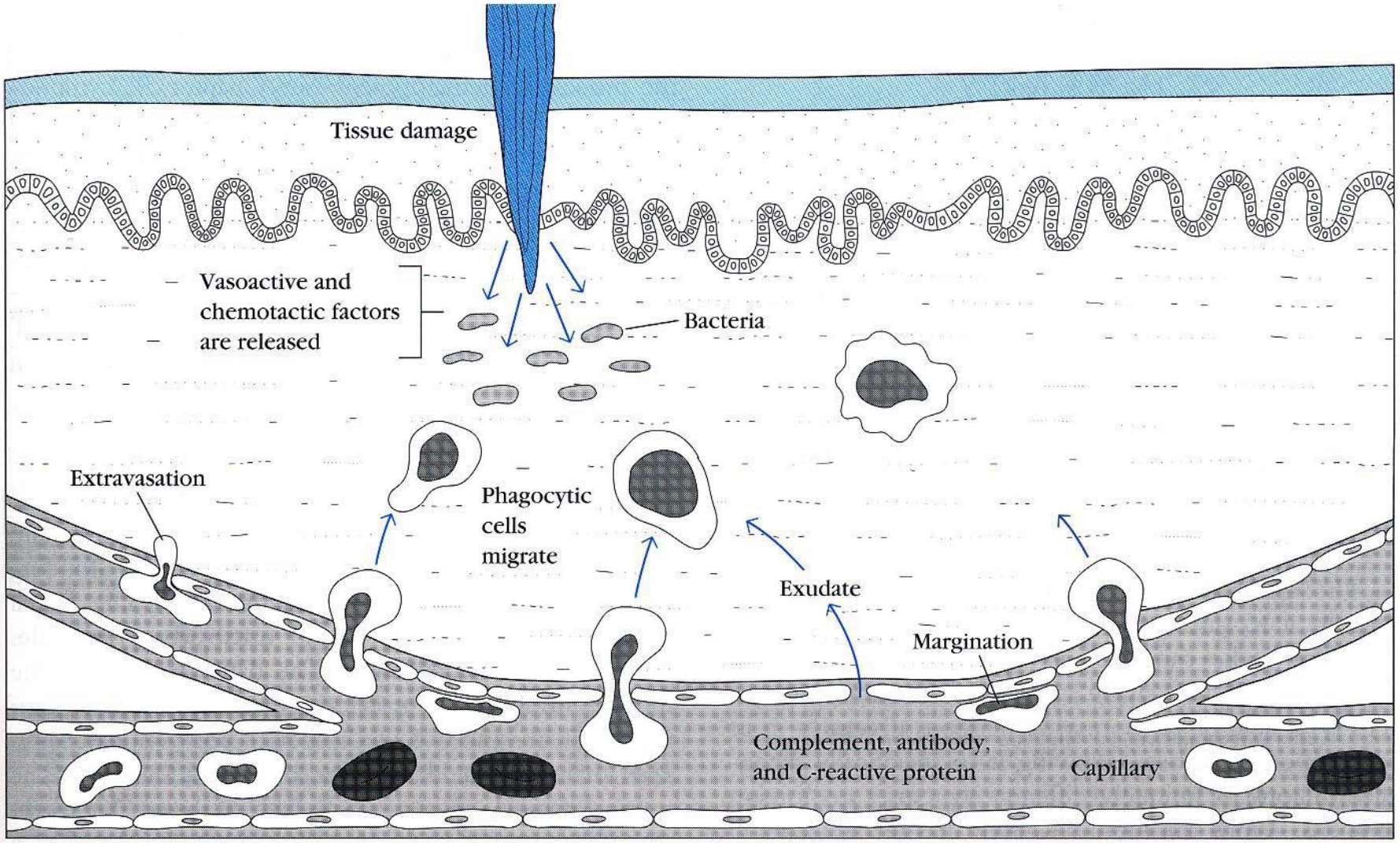


FIGURE 1-5

Major events in the inflammatory response. A bacterial infection causes tissue damage with release of various vasoactive and chemotactic factors. These factors induce increased blood flow to the area, increased capillary permeability, and an influx of white blood cells, including phagocytes and lymphocytes, from the blood into the tissues. The serum proteins contained in the exudate have antibacterial properties, and the phagocytes begin to engulf the bacteria, as illustrated in Figure 1-4.

NK cells – how they kill

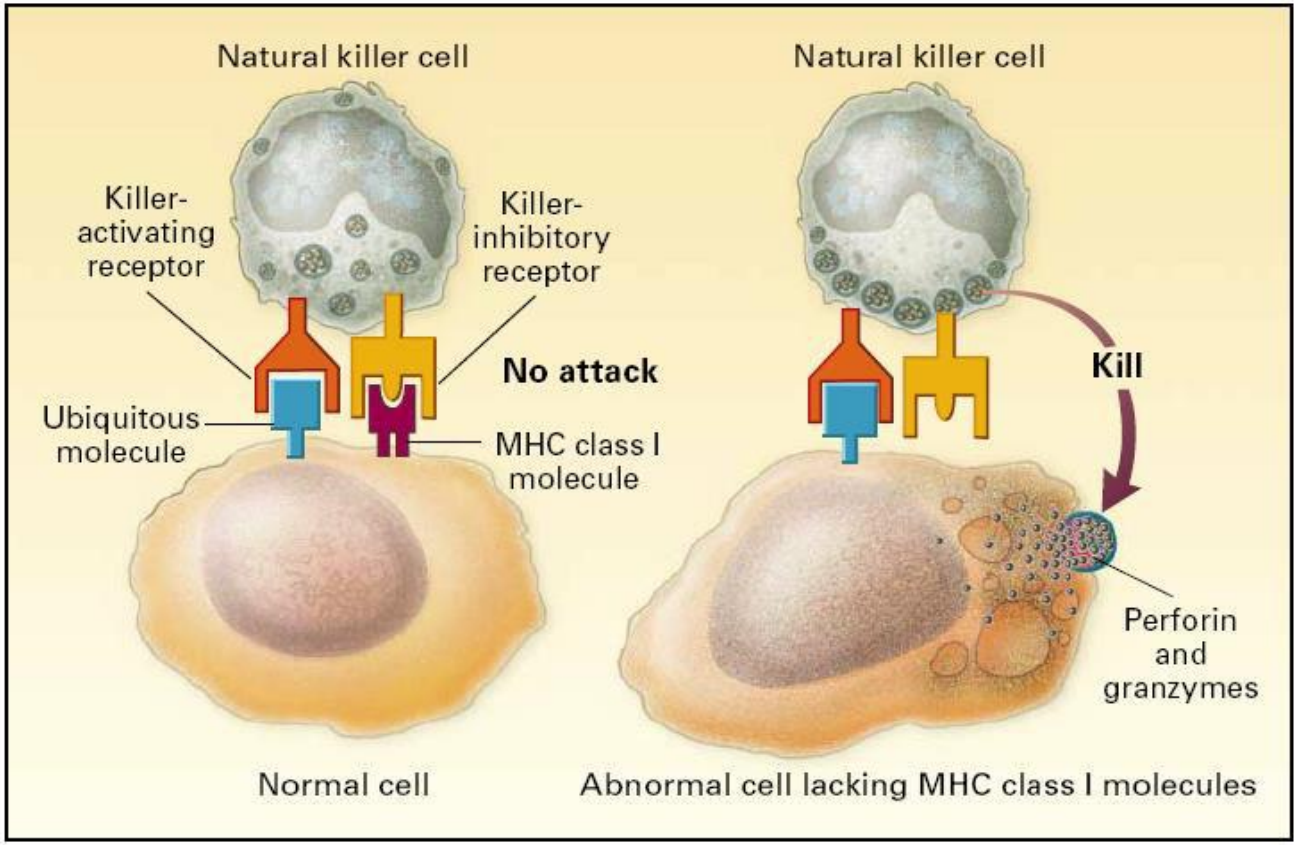


Figure 2. A System Used by Natural Killer Cells to Recognize Normal Cells and Cells That Lack Major-Histocompatibility-Complex Class I Surface Molecules.

Killer-activating receptors recognize a number of molecules present on the surface of normal, nucleated cells, and in the absence of an inhibitory signal from killer-inhibitory receptors, which recognize major-histocompatibility-complex (MHC) class I molecules, the receptors issue an order to the natural killer cells to attack and kill the other cell. The cytotoxic granules of the natural killer cells, which contain perforin and granzymes, become polarized at the interface with the target cell and are then released into the cell.

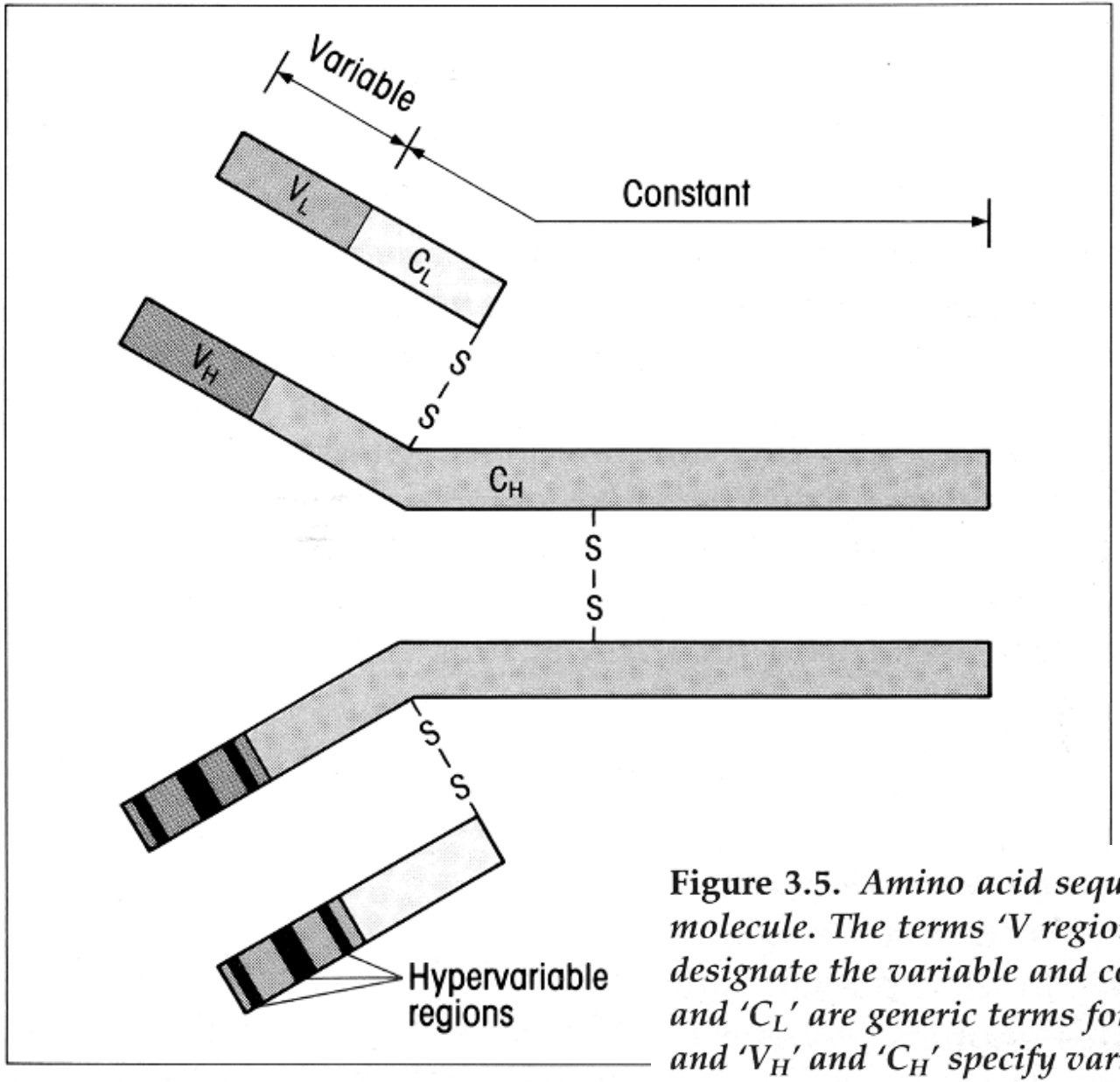


Figure 3.5. *Amino acid sequence variability in the antibody molecule. The terms 'V region' and 'C region' are used to designate the variable and constant regions respectively, 'V_L' and 'C_L' are generic terms for these regions on the light chain and 'V_H' and 'C_H' specify variable and constant regions on the heavy chain. As stressed previously, each pair of heavy chains are identical, as are each pair of light chains.*

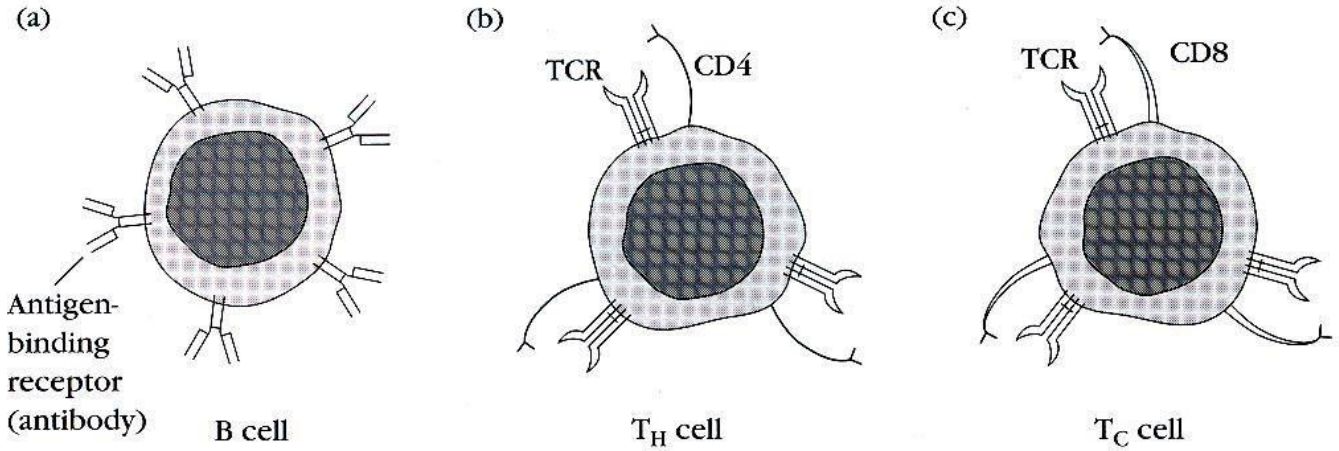


FIGURE 1-6

Distinctive membrane molecules on lymphocytes. (a) B cells have about 10^5 molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell exhibit the same antigenic specificity and can interact directly with antigen. (b) T cells bearing CD4 only recognize antigen associated with class II MHC molecules. (c) T cells bearing CD8 only recognize antigen associated with class I MHC molecules. In general, $CD4^+$ T cells function as helper cells and $CD8^+$ cells function as cytotoxic cells. Both types of T cells express about 10^5 identical molecules of the antigen-binding T-cell receptor (TCR) per cell, each with the same antigenic specificity.

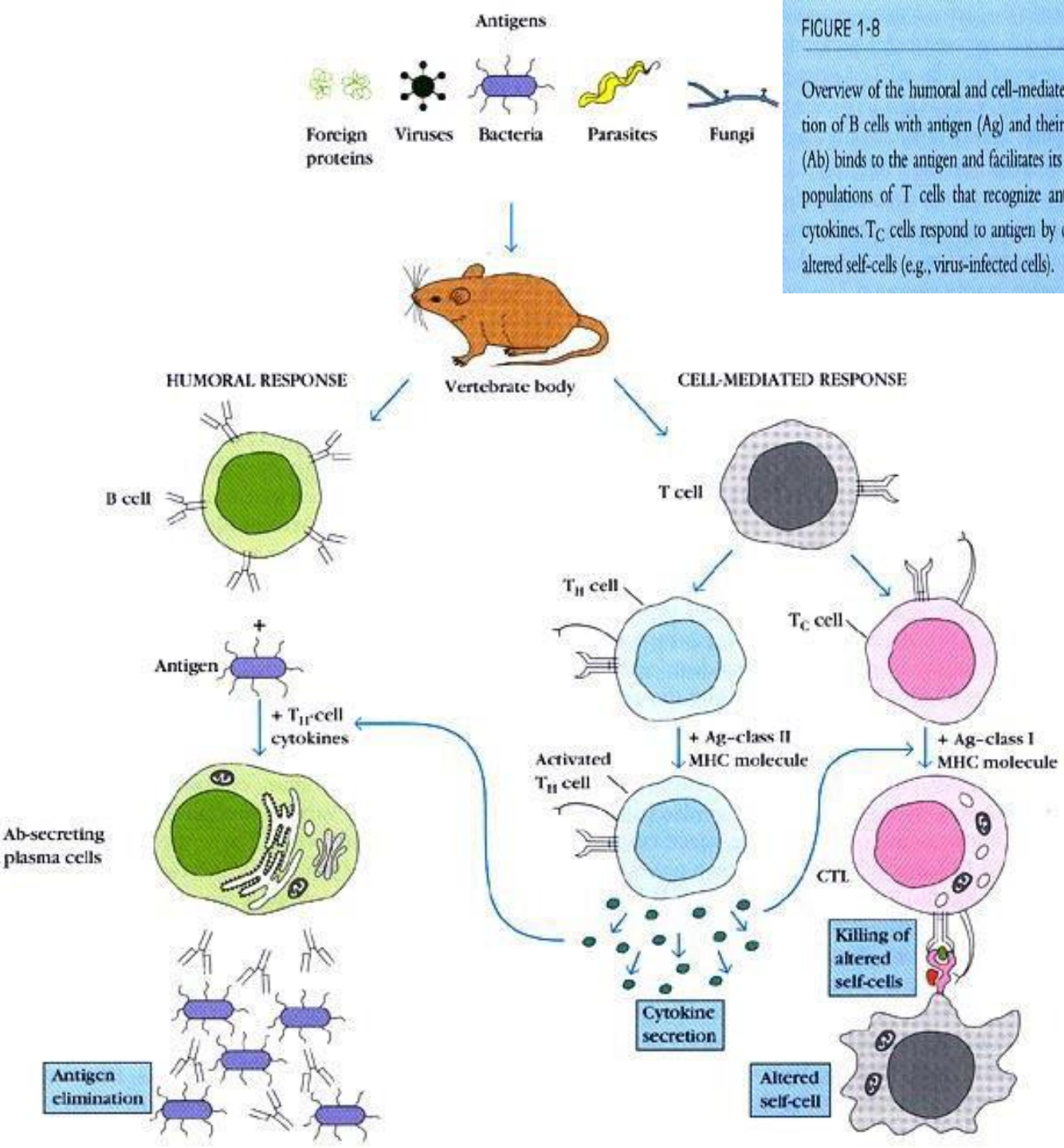


FIGURE 1-8

Overview of the humoral and cell-mediated branches of the immune system. The humoral response involves interaction of B cells with antigen (Ag) and their differentiation into antibody-secreting plasma cells. The secreted antibody (Ab) binds to the antigen and facilitates its clearance from the body. The cell-mediated response involves various subpopulations of T cells that recognize antigen presented on self-cells. T_H cells respond to antigen by producing cytokines. T_C cells respond to antigen by developing into cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).

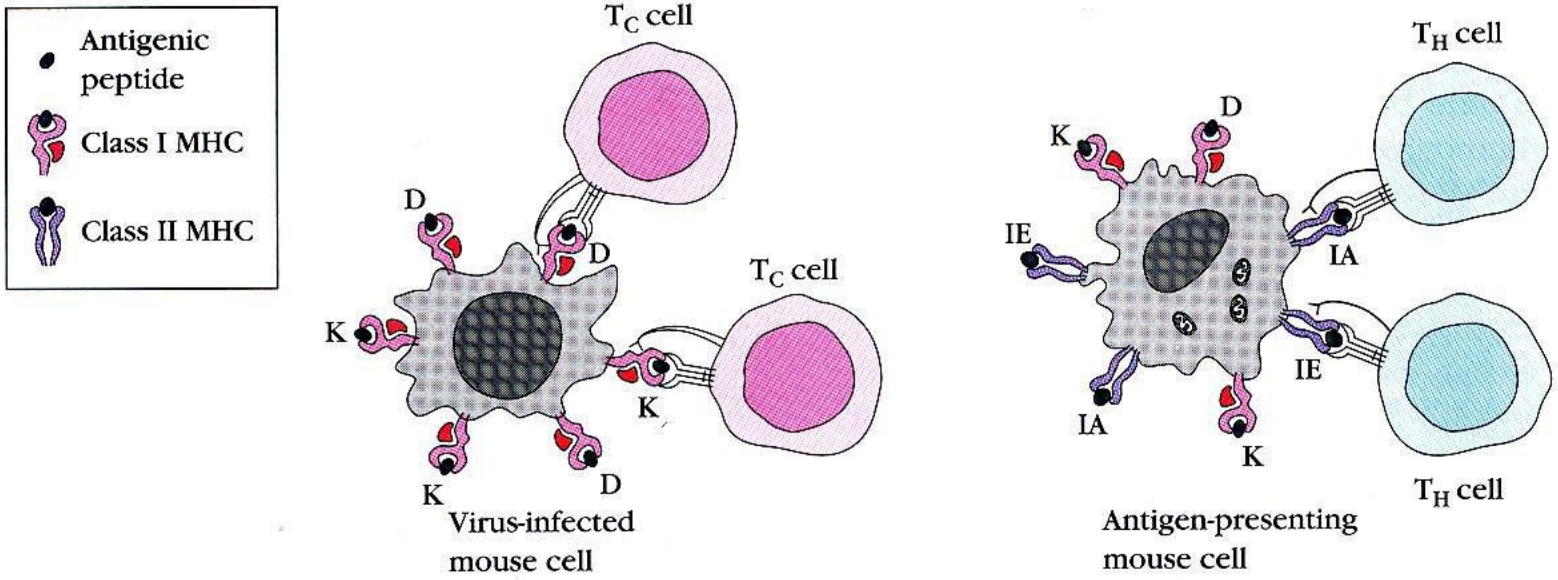


FIGURE 1-9

Role of MHC molecules in antigen recognition by T cells. Class I MHC molecules are encoded by the *K* and *D* loci in mice (*A*, *B*, and *C* loci in humans) and are expressed on nearly all nucleated cells. Class II MHC molecules are encoded by the *IA* and *IE* loci in mice (*DP*, *DQ*, and *DR* loci in humans) and are expressed only on antigen-presenting cells. $CD4^+$ T cells only recognize antigenic peptides displayed with a class II MHC molecule; they generally function as T helper (T_H) cells. $CD8^+$ T cells only recognize antigenic peptides displayed with a class I MHC molecule; they generally function as T cytotoxic (T_C) cells.

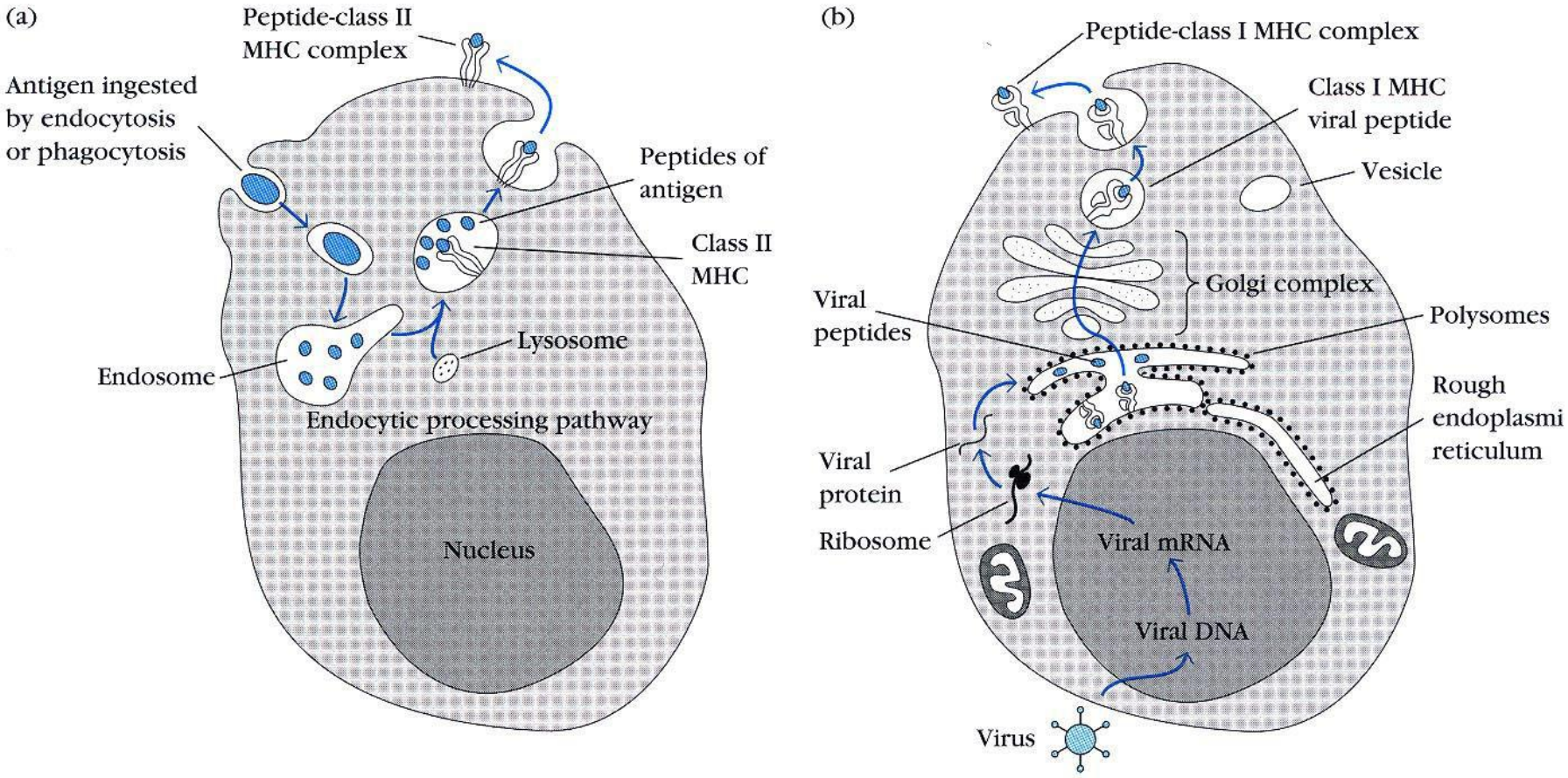


FIGURE 1-10

Processing and presentation of exogenous and endogenous antigens. (a) Exogenous antigen is ingested by endocytosis or phagocytosis and then enters the endocytic processing pathway. Here, within an acidic environment, the antigen is degraded into small peptides, which then are presented with class II MHC molecules on the membrane of the antigen-presenting cell. (b) Endogenous antigen, which is produce within the cell itself (e.g., in a virus-infected cell), is degraded withi the cytoplasm into peptides, which move into the endoplasmic reticu lum where they bind to class I MHC molecules. The peptide–class MHC complexes then move via the Golgi complex to the cell surface

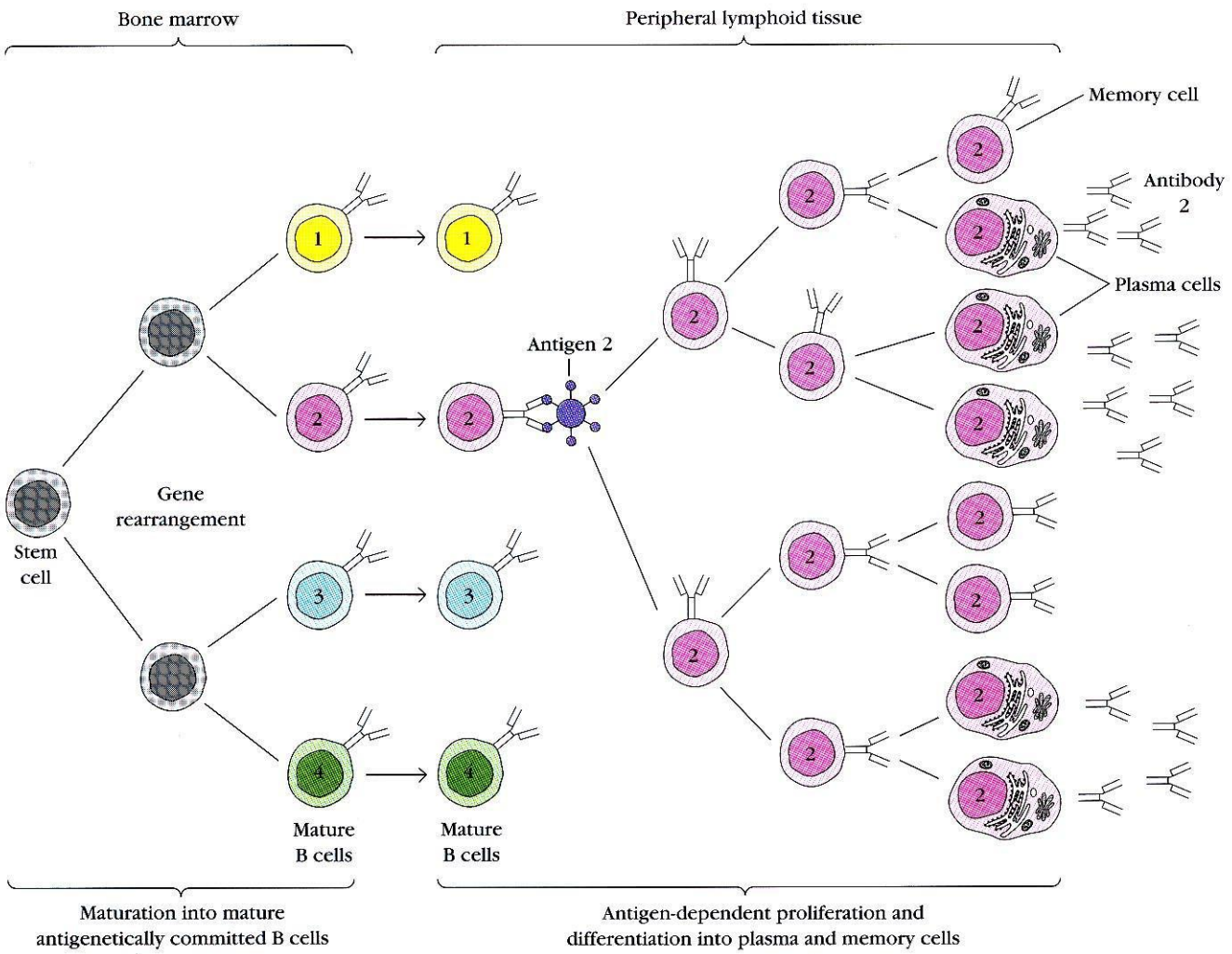


FIGURE 1-11

Maturation and clonal selection of B lymphocytes. Maturation, which occurs in the absence of antigen, produces antigenically committed B cells, each of which expresses antibody with a single antigenic specificity (indicated by 1, 2, 3, and 4). Clonal selection occurs when a given antigen binds to a B cell whose membrane-bound antibody molecules are specific for epitopes on that antigen. Clonal expansion of an antigen-activated B cell (number 2 in this example) leads to a clone of memory B cells and effector B cells, called plasma cells; all cells in the expanded clone are specific for the original antigen. The plasma cells secrete antibody reactive with the activating antigen. Similar processes occur in the T-lymphocyte population resulting in clones of memory T cells and effector T cells; the latter include activated T_H cells, which secrete cytokines, and cytotoxic T lymphocytes (CTLs).

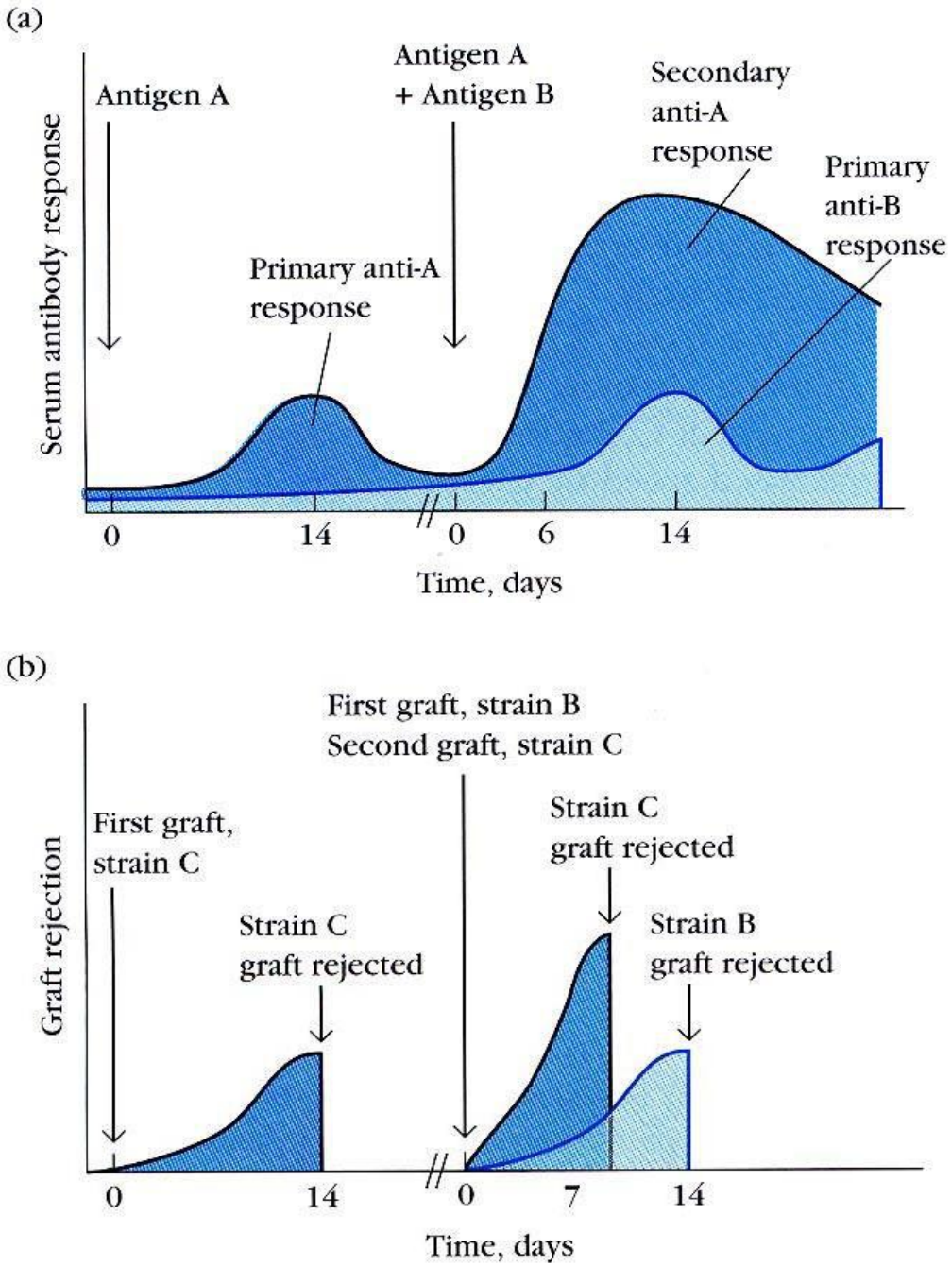


FIGURE 1-12

Differences in the primary and secondary response to injected antigen (humoral response) and to a skin graft (cell-mediated response) reflect the phenomenon of immunologic memory. (a) When an animal is injected with an antigen, it produces a primary serum antibody response of low magnitude and relatively short duration, peaking at about 10–17 days. A second immunization with the same antigen results in a secondary response that is greater in magnitude, peaks in less time (2–7 days), and lasts longer (months to years) than the primary response. (b) When skin from a strain C mouse is grafted onto a strain A mouse, the graft is rejected in about 10–14 days. If a second strain C graft is grafted onto the same mouse, it is rejected much more vigorously and rapidly than the first graft.

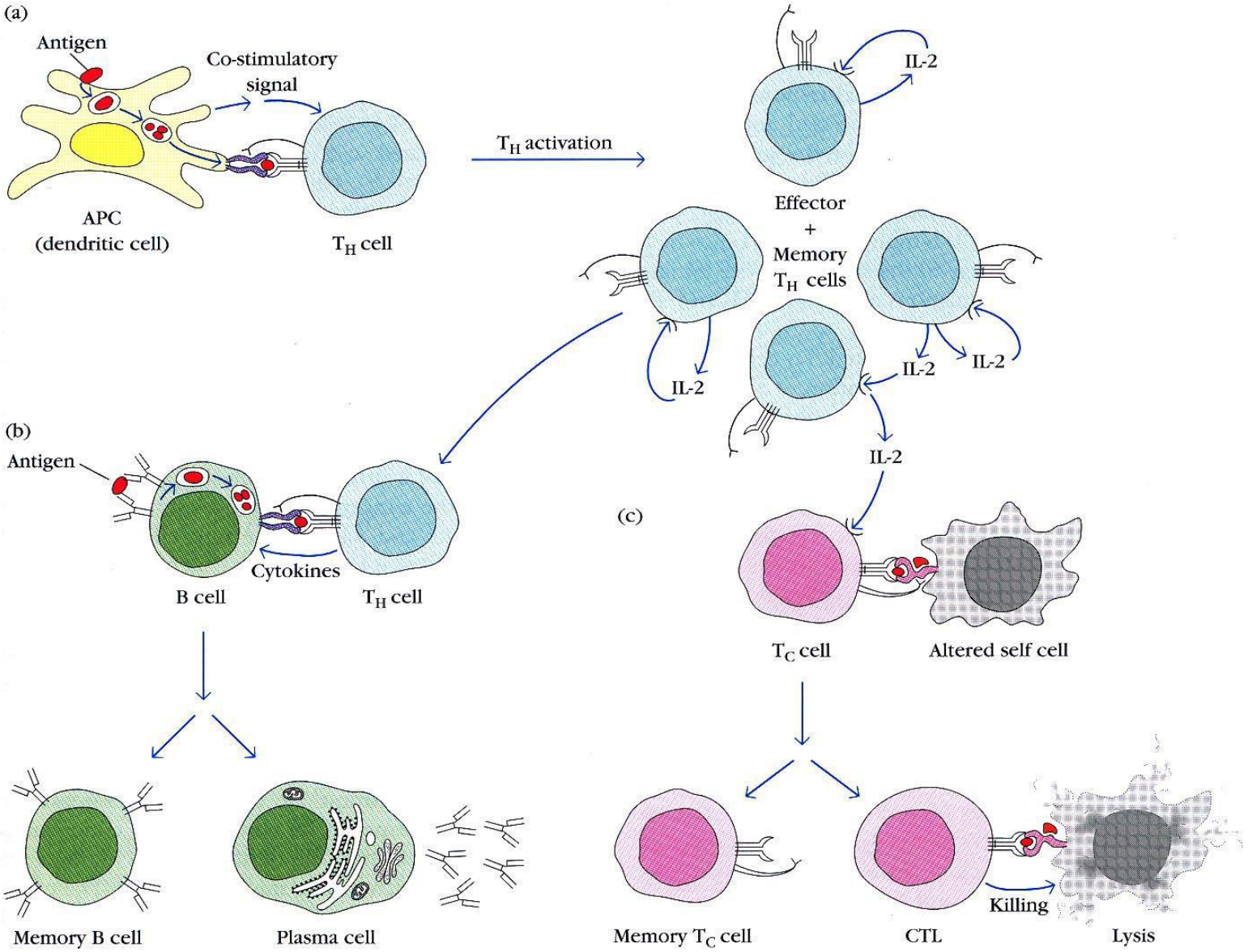


FIGURE 1-14

Cellular interactions involved in induction of immune responses. Activation and proliferation of T_H cells (a) is required for generation of a humoral response (b) and a cell-mediated response to altered self-cells (c). APC = antigen-presenting cell; Ag = antigen. See text for discussion.

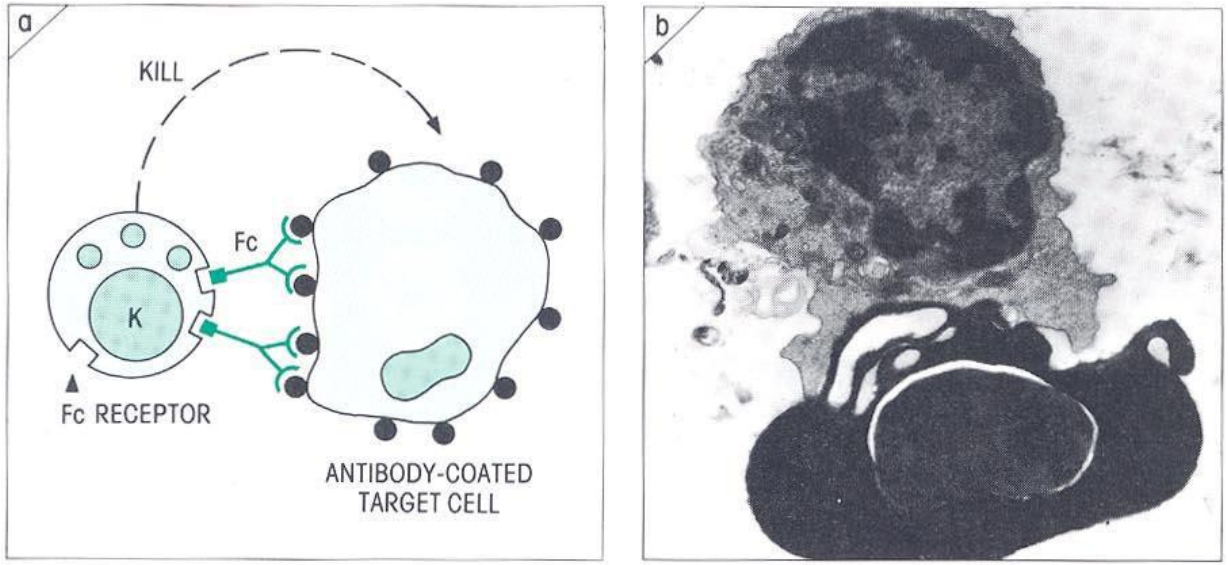


Figure 12.8. *Killing of antibody-coated target by antibody-dependent cell-mediated cytotoxicity (ADCC). The surface receptors for Ig Fc region bind the effector cell to the target which is then killed by an extracellular mechanism. Several different cell types may display ADCC activity: thus, human monocytes and IFNγ-activated neutrophils can kill antibody-coated tumour cells using their FcγRI and FcγRII receptors, and lymphocytes (NK cells) mediate killing of hybridoma targets through FcγRIII receptors. (a) Diagram of effector and target cells. (b) Electron micrograph of attack on antibody-coated chick red cell by a mouse large granular lymphocyte showing close apposition of effector and target and vacuolation in the cytoplasm of the latter (courtesy of P. Penfold).*