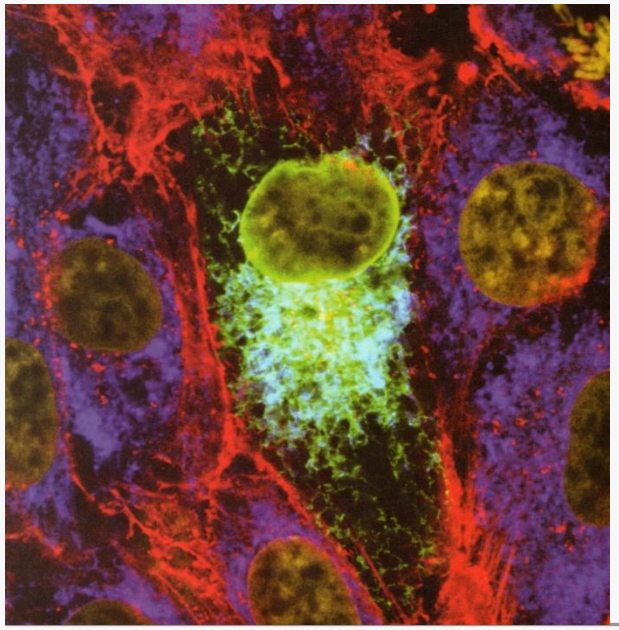
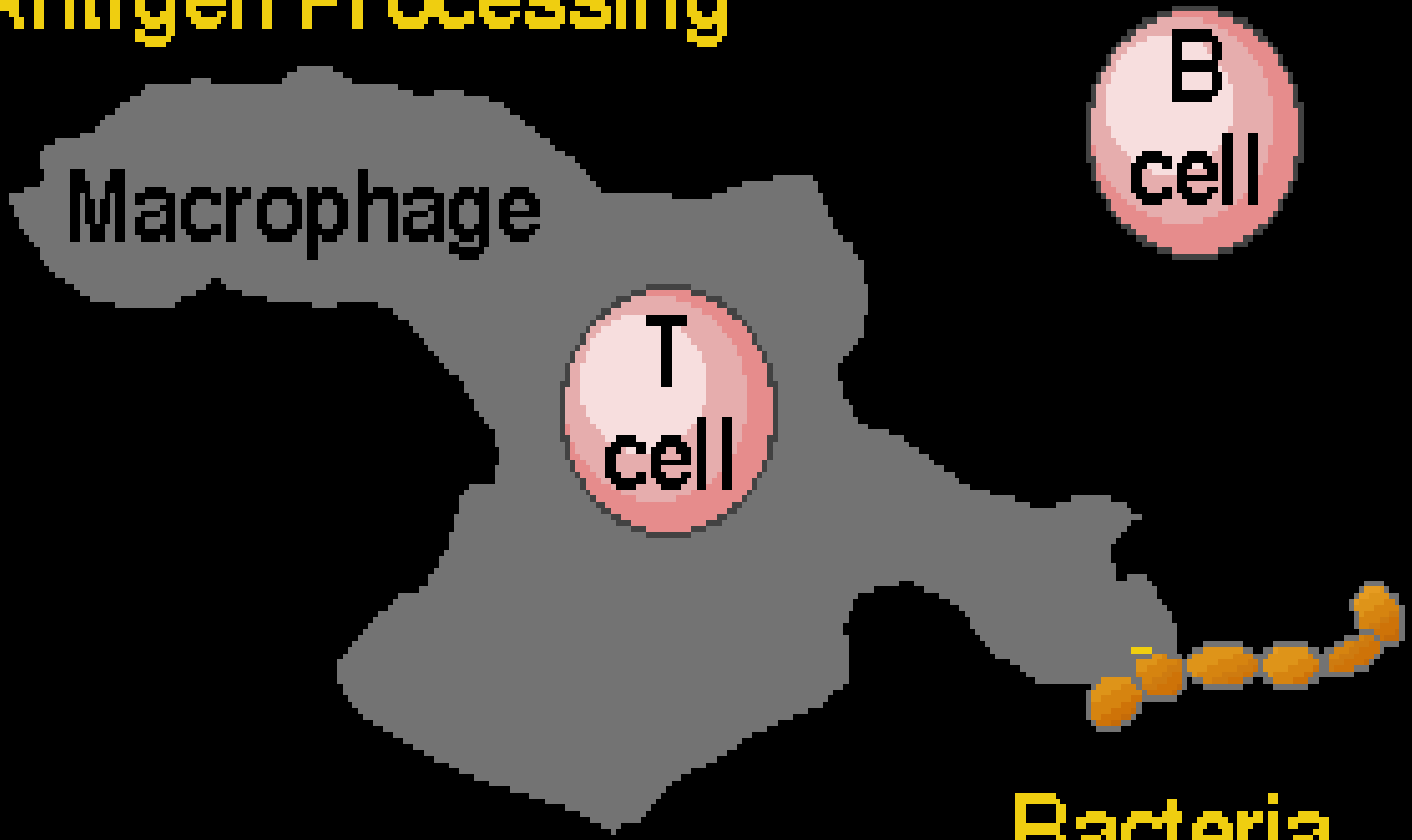


In cells infected with mumps virus the viral proteins are processed into peptides that enter the endoplasmic reticulum to be bound by MHC Class I molecules.

Chapter 5

Antigen Recognition by T Lymphocytes

Antigen Processing



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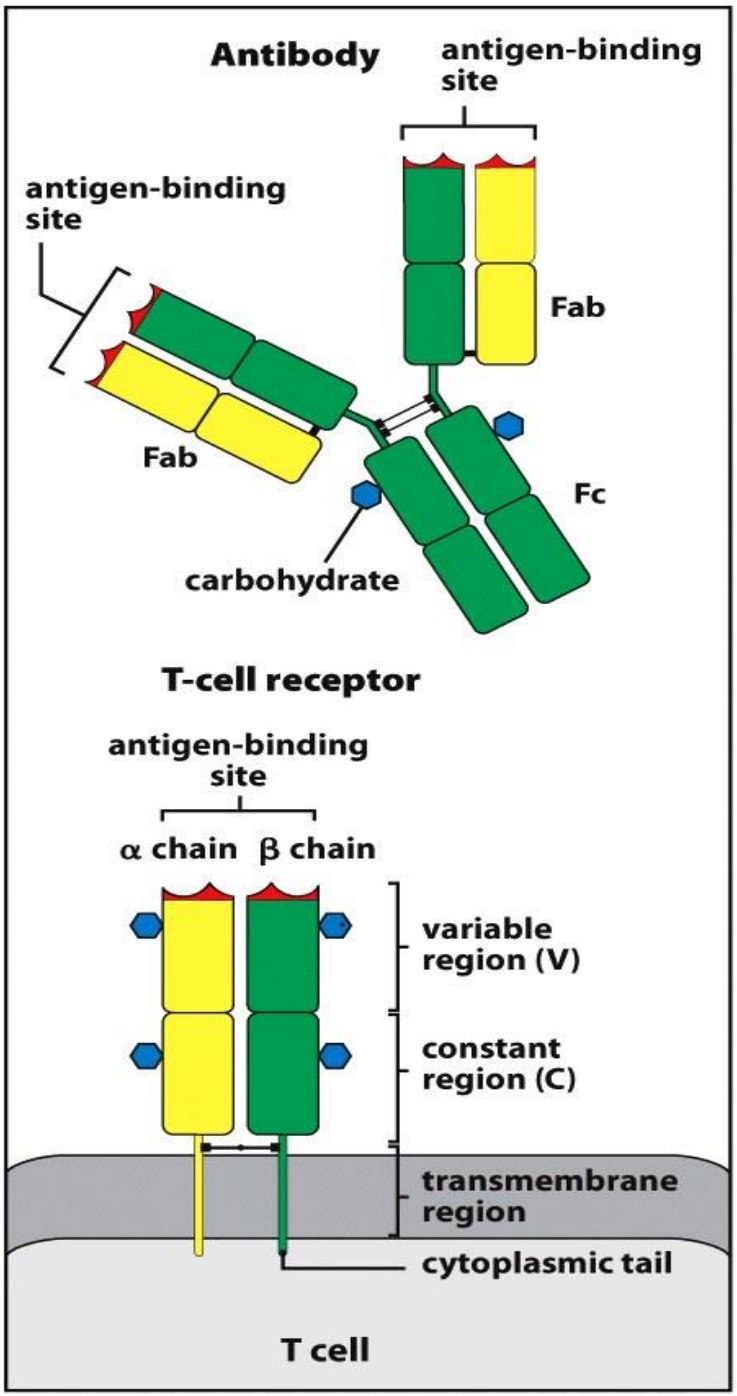


Figure 5.1 The T-cell receptor resembles a membrane-bound Fab fragment. Comparison of the T-cell receptor with an IgG antibody. The T-cell receptor is a membrane-bound heterodimer composed of an α chain of 40–50 kDa and a β chain of 35–46 kDa. The extracellular portion of each chain consists of two immunoglobulin-like domains: the one nearest to the membrane is a C domain and the domain farthest from the membrane is a V domain. The α and β chains both span the cell membrane and have very short cytoplasmic tails. The three-dimensional structure formed by the four immunoglobulin-like domains of the T-cell receptor resembles that of an antigen-binding Fab fragment of antibody.

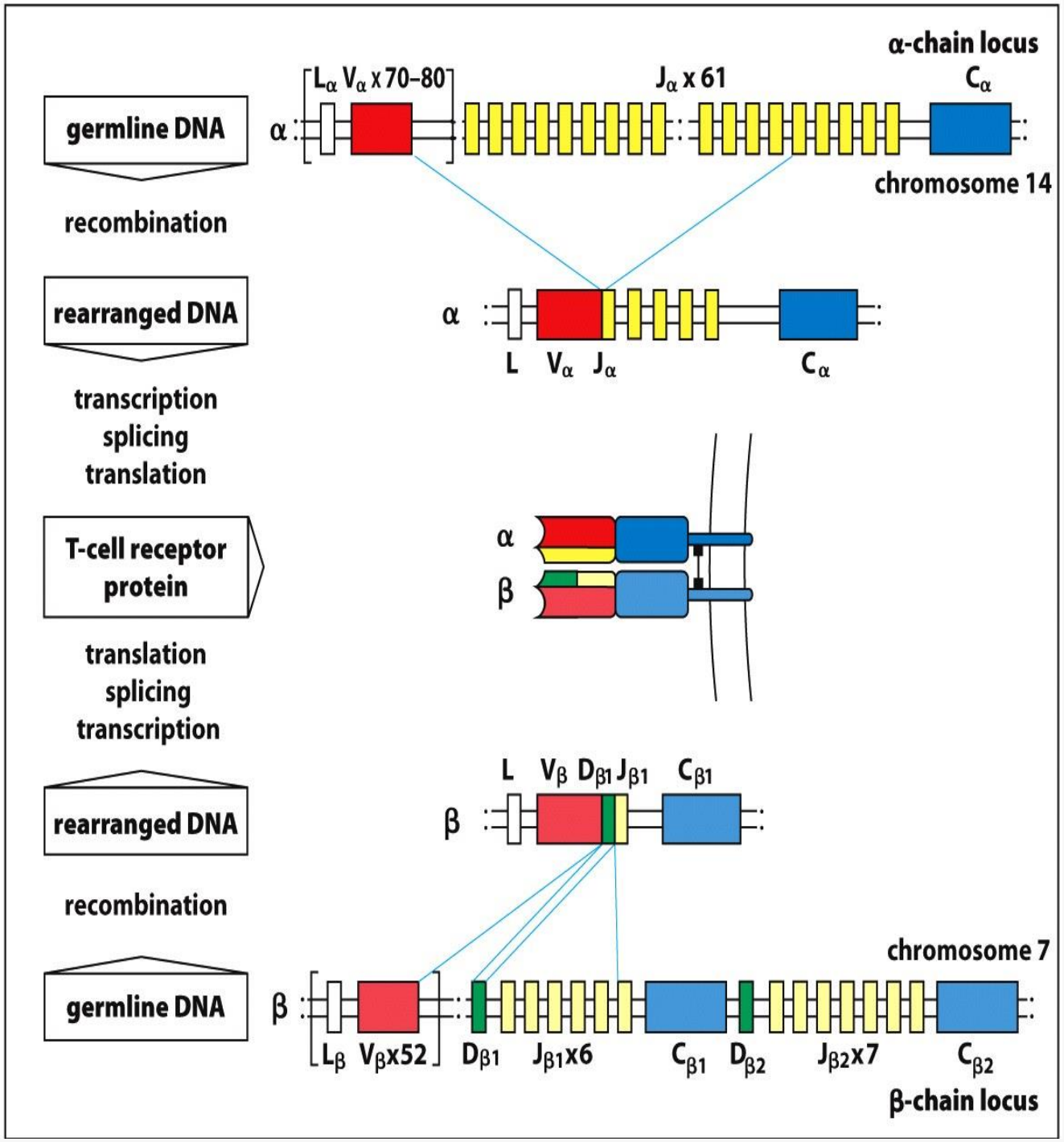


Figure 5.3 Organization and rearrangement of the T-cell receptor genes. The top and bottom rows of the figure show the germline arrangement of the variable (V), diversity (D), joining (J), and constant (C) gene segments at the T-cell receptor α-chain and β-chain loci. During T-cell development, a V-region sequence for each chain is assembled by DNA recombination. For the α chain (top), a V_α gene segment rearranges to a J_α gene segment to create a functional exon encoding the V domain. For the β chain (bottom), rearrangement of a V_β, a D_β, and a J_β gene segment creates the functional V-domain exon. The assembled genes are transcribed and spliced to produce mRNA (not shown) encoding the α and β chains. Exons encoding the membrane-spanning regions are not shown. L, leader sequence.

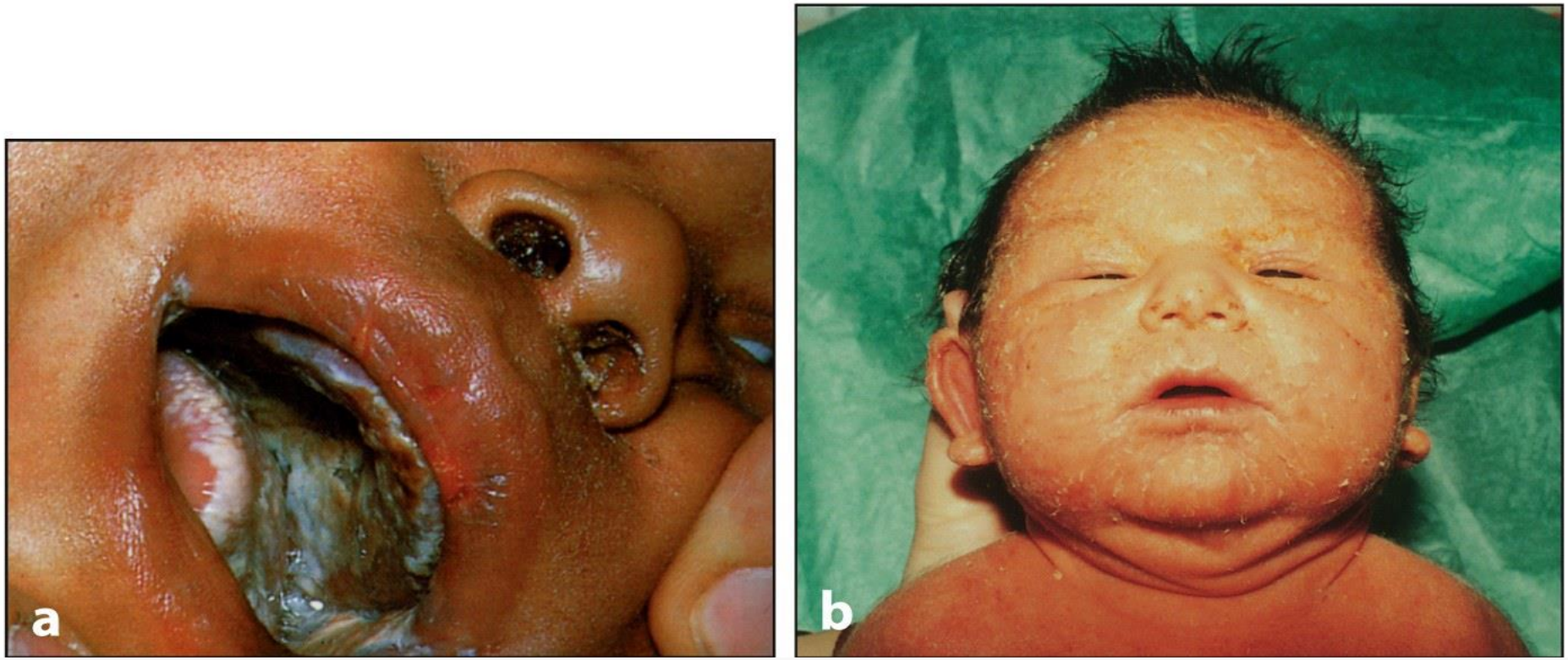


Figure 5.4 Severe combined immunodeficiency syndrome (SCID). SCID is characterized by a lack of functional T cells and B cells and the inability to make an adaptive immune response. Infants with SCID typically show infections with opportunistic pathogens. Panel a shows chronic *Candida albicans* infection in the mouth of an infant with SCID. SCID can be caused by various genetic defects, one of which is complete loss of RAG function. Panel b shows an infant with Omenn syndrome, a similar immunodeficiency which is due to a genetic defect that results in 80% loss of RAG activity. The bright red rash on the face and shoulders, which is due to chronic inflammation, is a characteristic of this condition. Unless an immune system can be reconstituted by bone marrow transplantation from a healthy donor, babies with SCID or Omenn syndrome die in infancy. Panel a courtesy of Fred Rosen; panel b courtesy of Luigi Notarangelo.

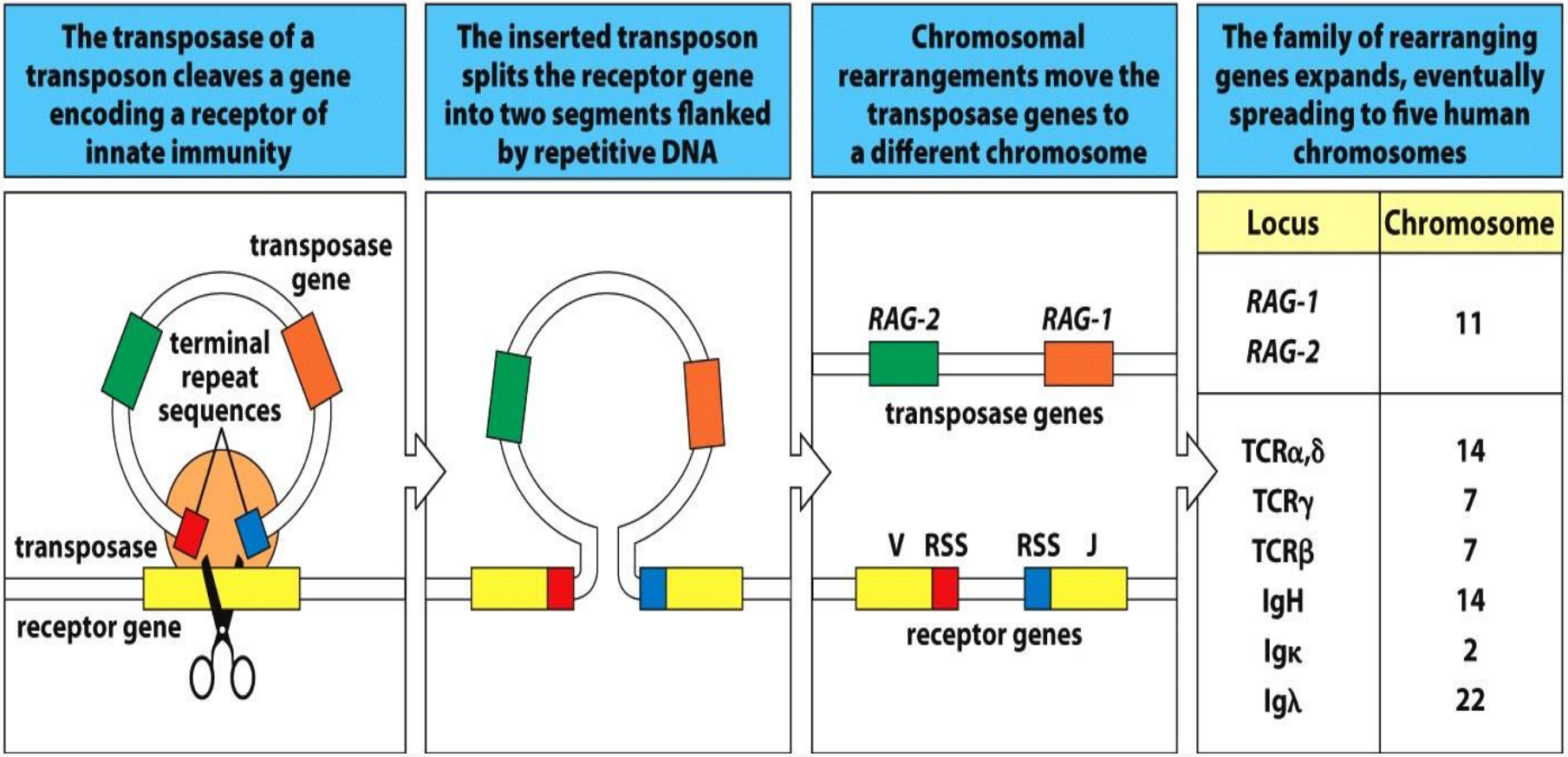


Figure 5.5 Components of a transposon could have evolved to become the *RAG* genes and the recombination signal sequences of immunoglobulin and T-cell receptor genes. The first event in the evolution of rearranging antigen-receptor genes is thought to have occurred more than 400 million years ago, when a transposon integrated into a gene encoding an innate immune receptor protein (first panel). The transposon separated the gene into two segments, each flanked by a piece of repetitive transposon DNA (second panel). Subsequently, chromosomal rearrangements placed the transposase gene (or genes) onto a different chromosome from the primordial rearranging gene. The repetitive DNAs became the RSSs of a primordial rearranging gene and the transposase genes became the ancestral *RAG-1* and *RAG-2* genes (third panel). Over 400 million years of evolution, the family of rearranging genes has expanded and is now spread over five different human chromosomes (fourth panel).

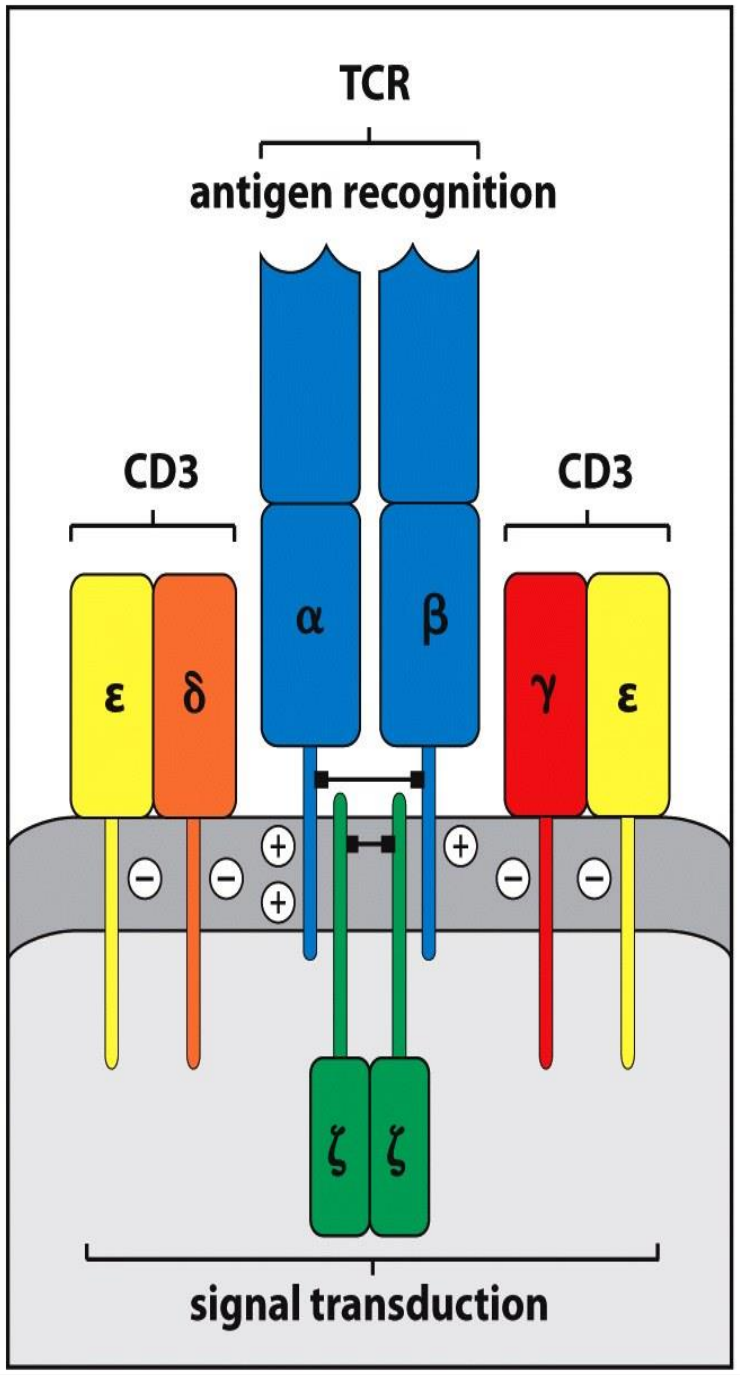


Figure 5.6 Polypeptide composition of the T-cell receptor complex. The functional antigen receptor on the surface of T cells is composed of eight polypeptides and is called the T-cell receptor complex. The α and β chains bind antigen and form the core T-cell receptor (TCR). They associate with one copy each of CD3γ and CD3δ and two copies each of CD3ε and the ζ chain. These associated invariant polypeptides are necessary for the transport of newly synthesized TCR to the cell surface and for the transduction of signals to the cell's interior after the TCR has bound antigen. The transmembrane domains of the α and β chains contain positively charged amino acids (+), which form strong electrostatic interactions with negatively charged amino acids (–) in the transmembrane regions of the CD3γ, δ, and ε chains.

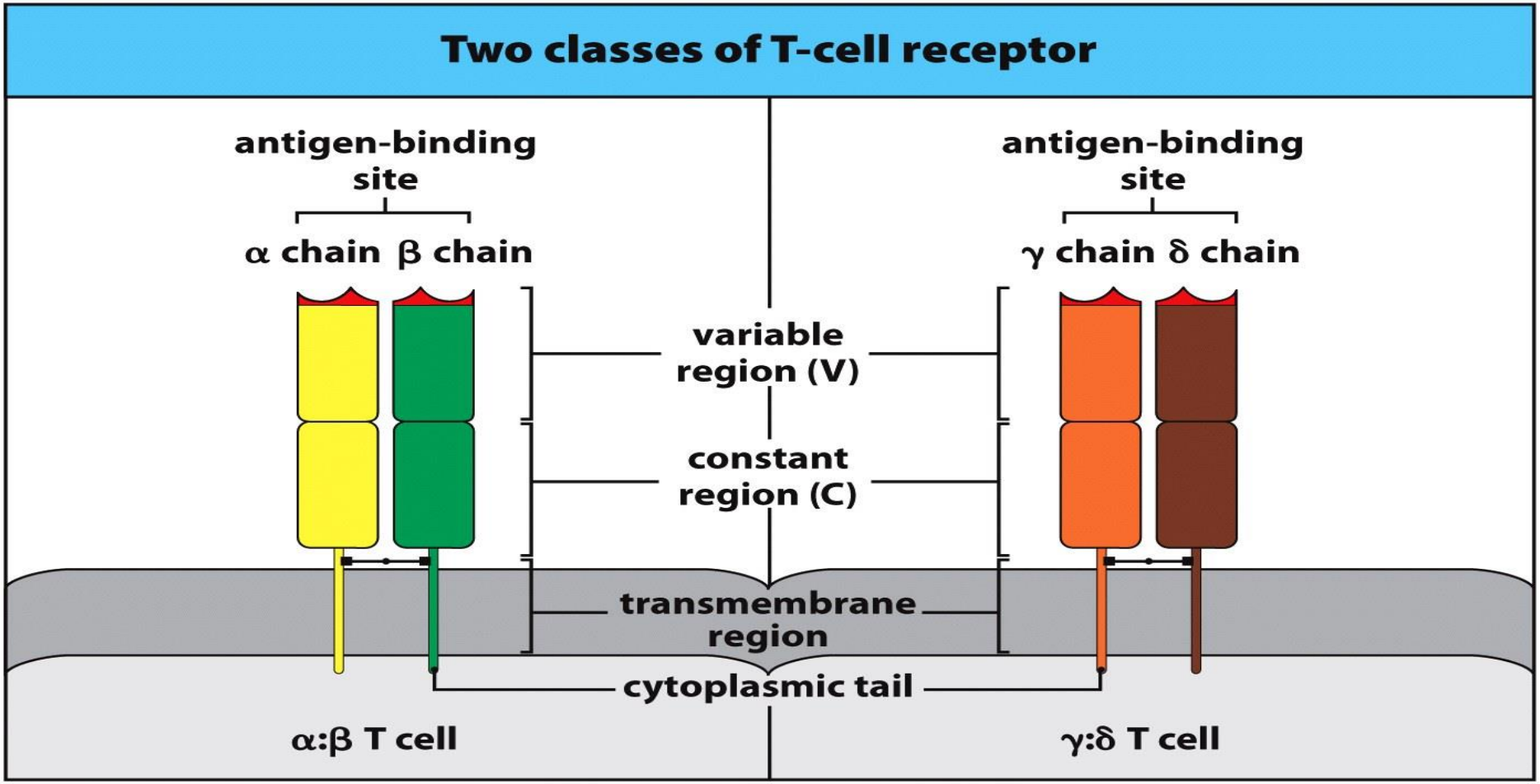
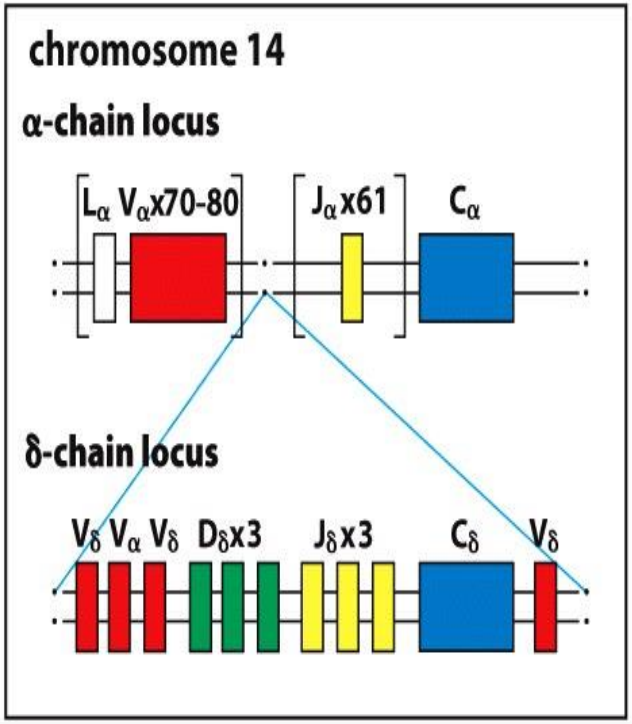


Figure 5.7 There are two classes of T-cell receptor. The α:β T-cell receptor (left panel) and the γ:δ T-cell receptor (right panel) have similar structures, but they are encoded by different sets of rearranging gene segments and have different functions.



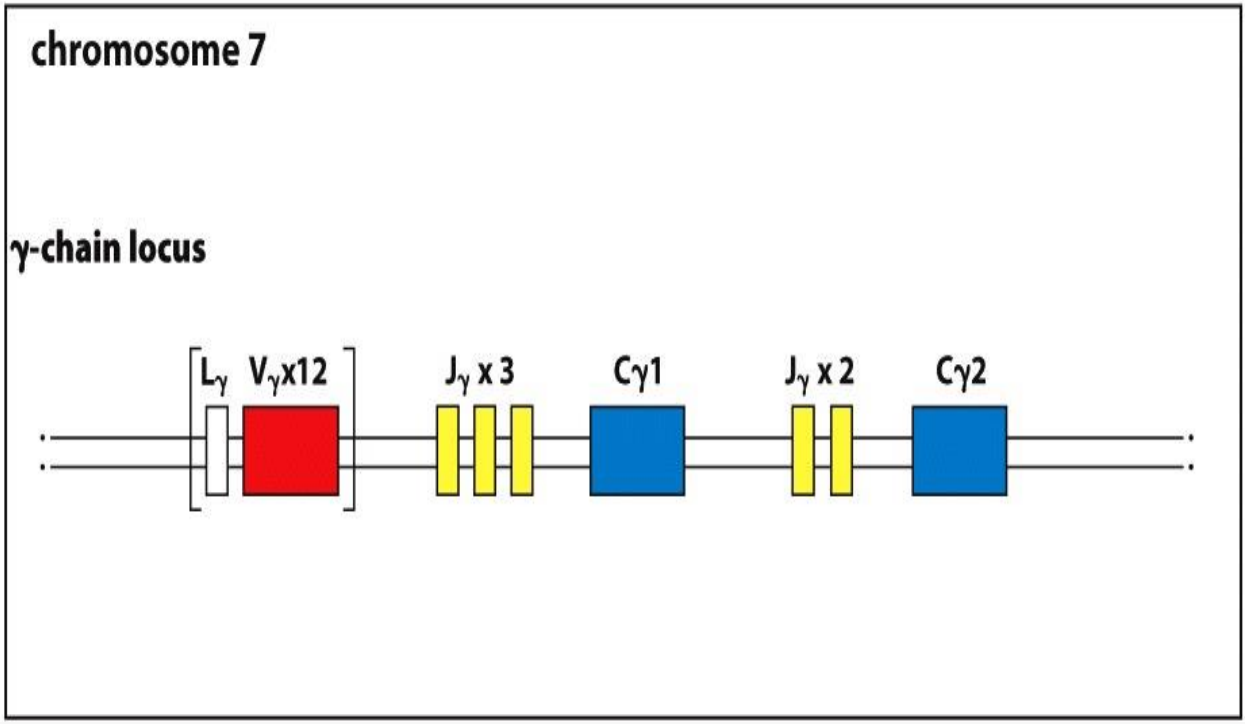


Figure 5.8 The organization of the human T-cell receptor γ-chain and δ-chain loci. The TCR γ and δ loci, like the α and β loci, contain sets of variable (V), diversity (D), joining (J), and constant (C) gene segments. The δ locus is located within the α-chain locus on chromosome 14, lying between the clusters of V_α and J_α gene segments. There are at least three V_δ gene segments, three D_δ gene segments, three J_δ gene segments, and a single C_δ gene segment. V_δ segments are interspersed among V_α and other gene segments. The γ locus, on chromosome 7, resembles the β locus, with a set of V segments and two C gene segments each with its own set of J segments.

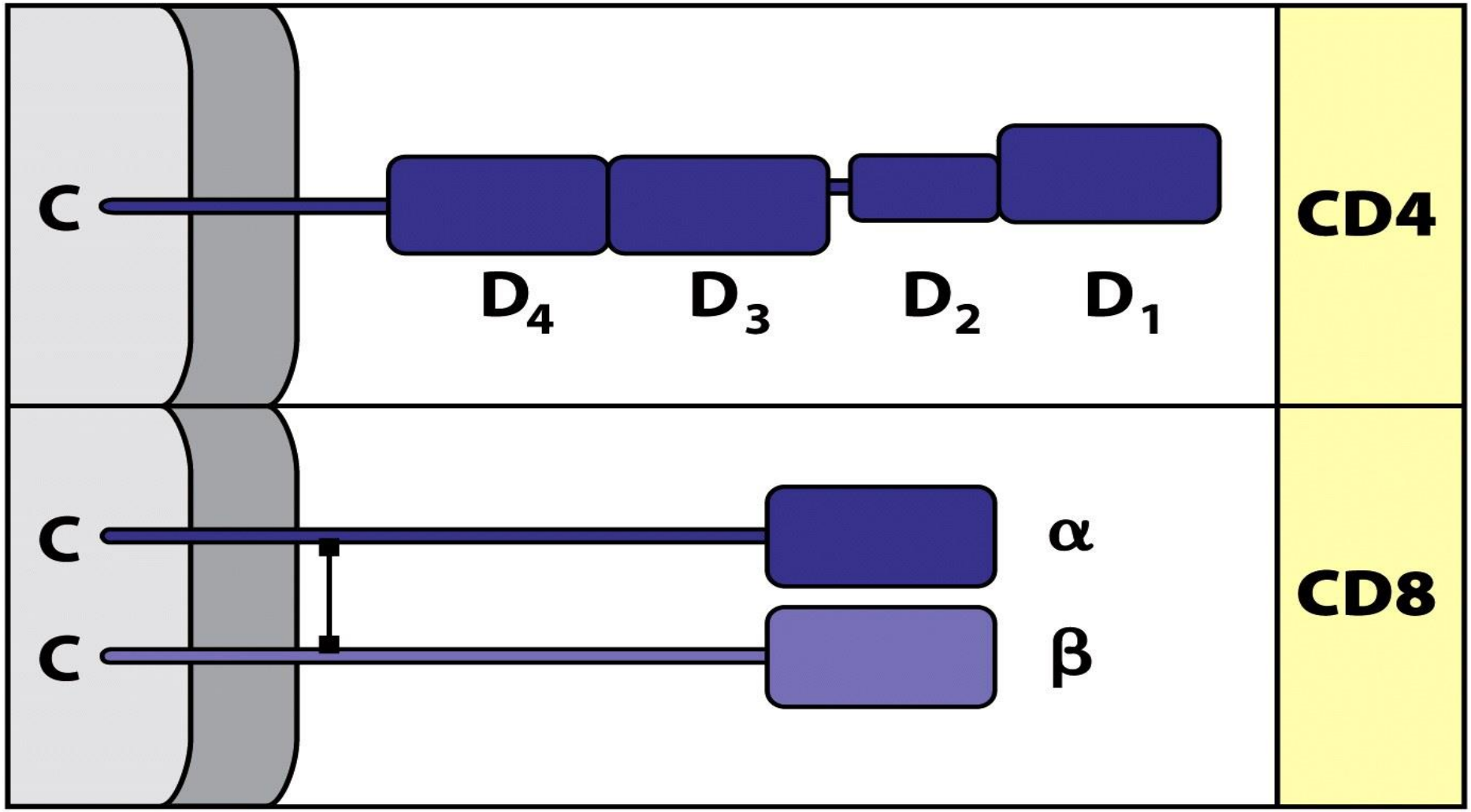


Figure 5.11 The structures of the CD4 and CD8 glycoproteins. CD4 and CD8 are members of the immunoglobulin superfamily of proteins. CD4 has four extracellular immunoglobulin-like domains (D_1–D_4) with a hinge between the D_2 and D_3 domains. CD8 consists of an α and a β chain, which both have an immunoglobulin-like domain that is connected to the membrane-spanning region by an extended stalk. C denotes the carboxy terminus.

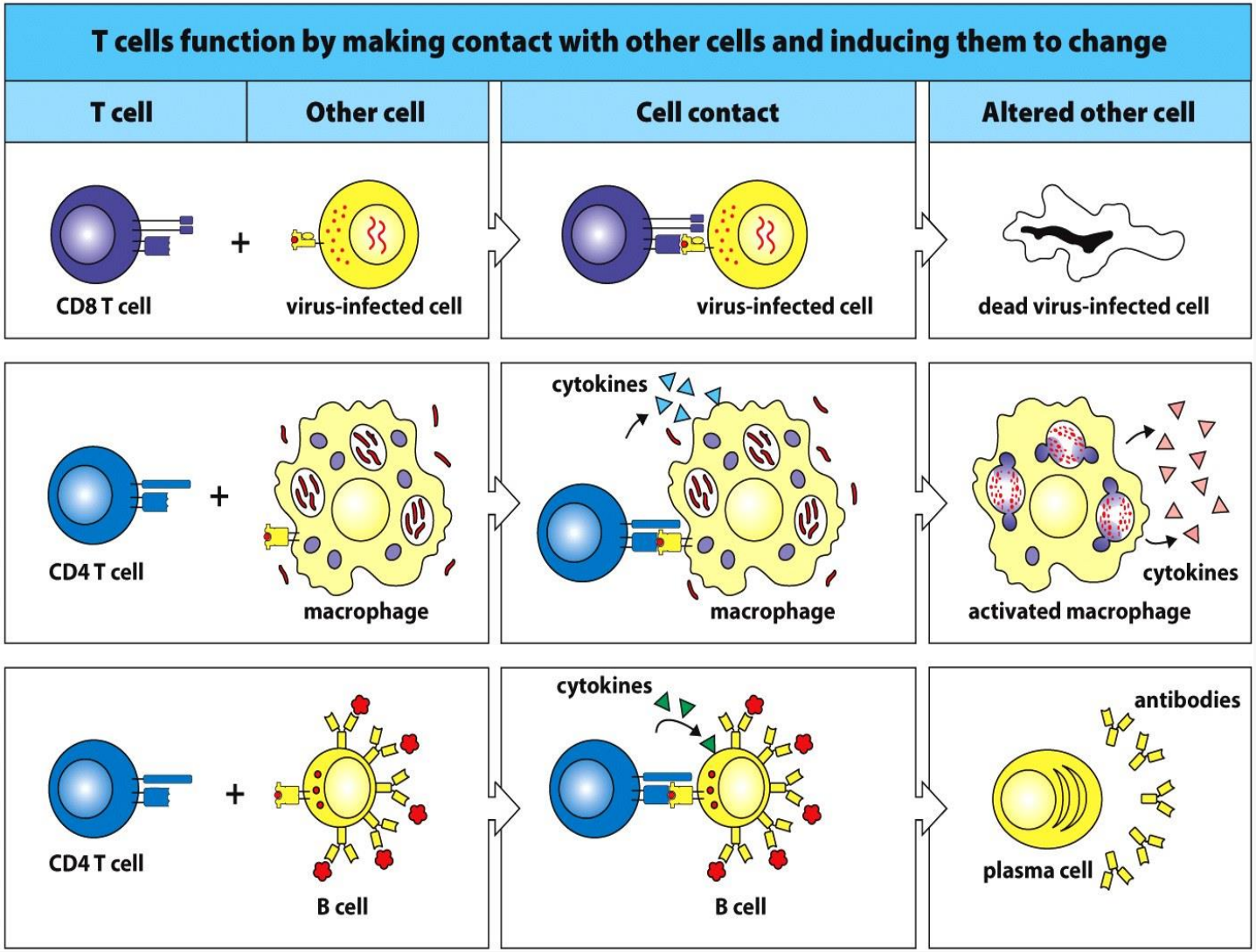
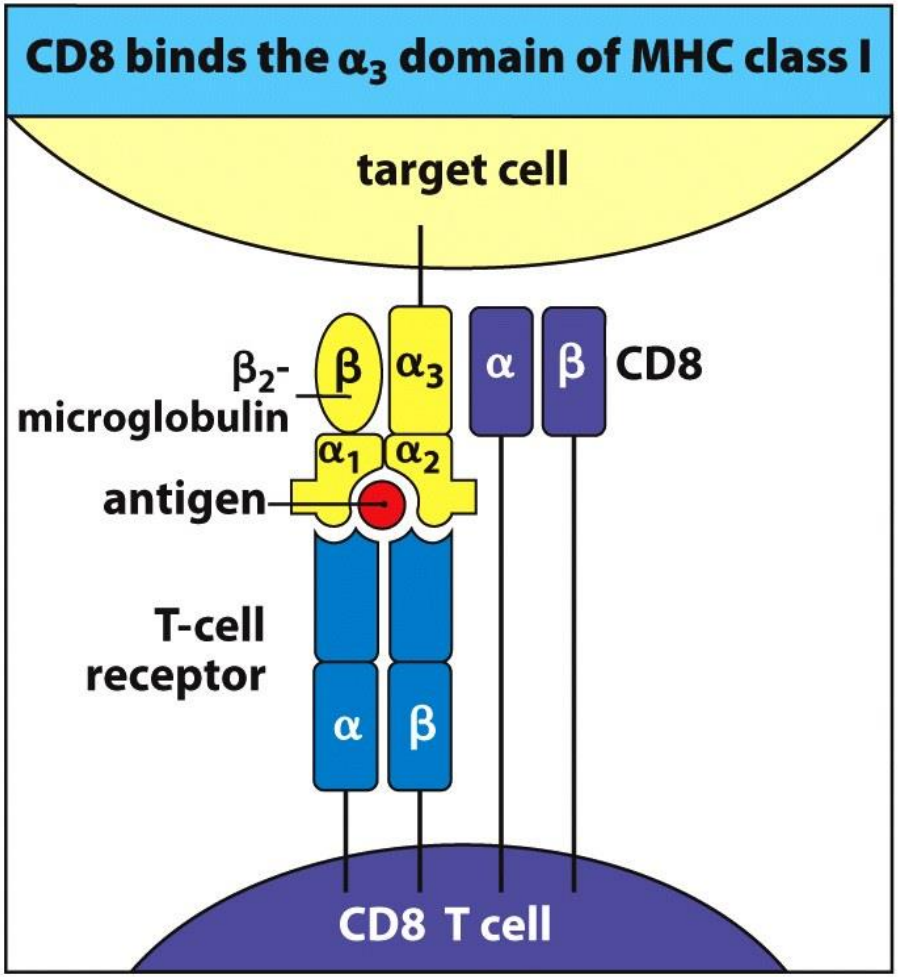


Figure 5.12 T cells function by making contact with other cells. Top panels: a cytotoxic CD8 T cell makes contact with a virus-infected cell, recognizes that it is infected, and kills it. Middle panels: a CD4 helper T cell contacts a macrophage that is engaged in the phagocytosis of bacteria and secretes cytokines that increase the microbicidal power of the macrophage and its secretion of inflammatory cytokines. Bottom panels: a CD4 helper T cell contacts a B cell that is binding its specific antigen and secretes cytokines that cause the B cell to differentiate into an antibody-secreting plasma cell.



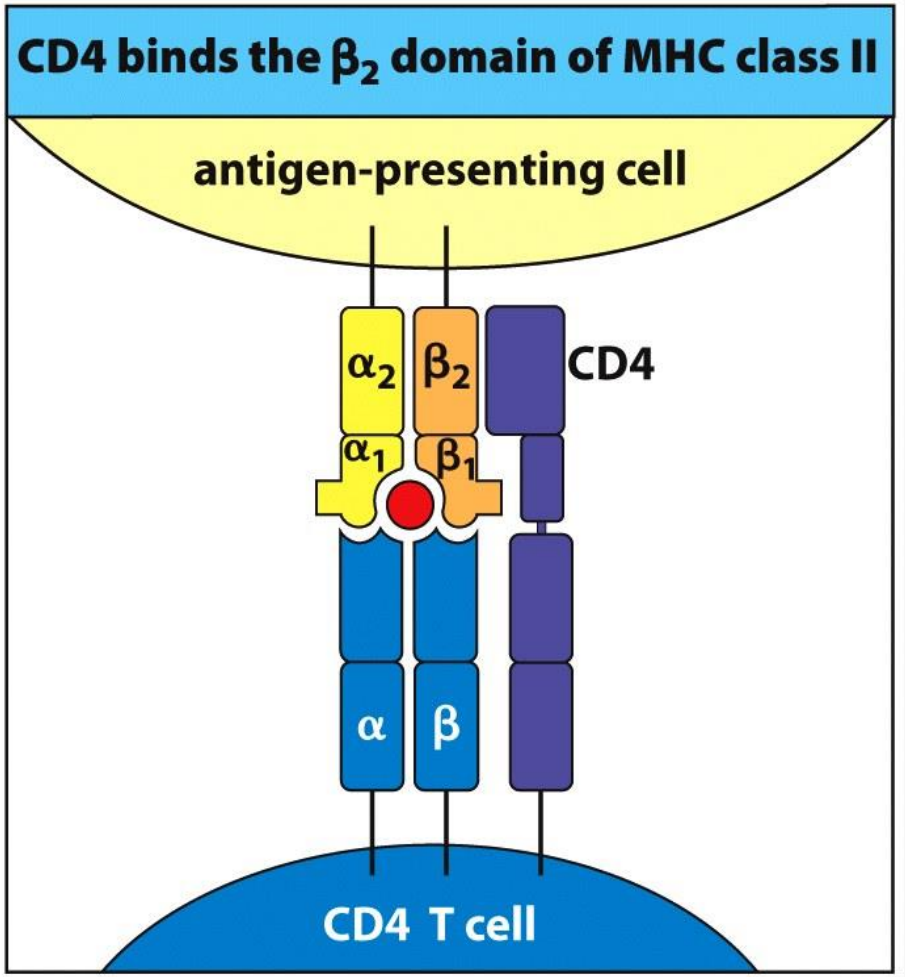


Figure 5.14 MHC class I molecules bind to CD8, and MHC class II molecules bind to CD4. The CD8 co-receptor binds to the α_3 domain of the MHC class I heavy chain, ensuring that MHC class I molecules present peptides only to CD8 T cells (left panel). In a complementary fashion, the CD4 co-receptor binds to the β_2 domain of MHC class II molecules, ensuring that peptides bound by MHC class II stimulate only CD4 T cells (right panel).

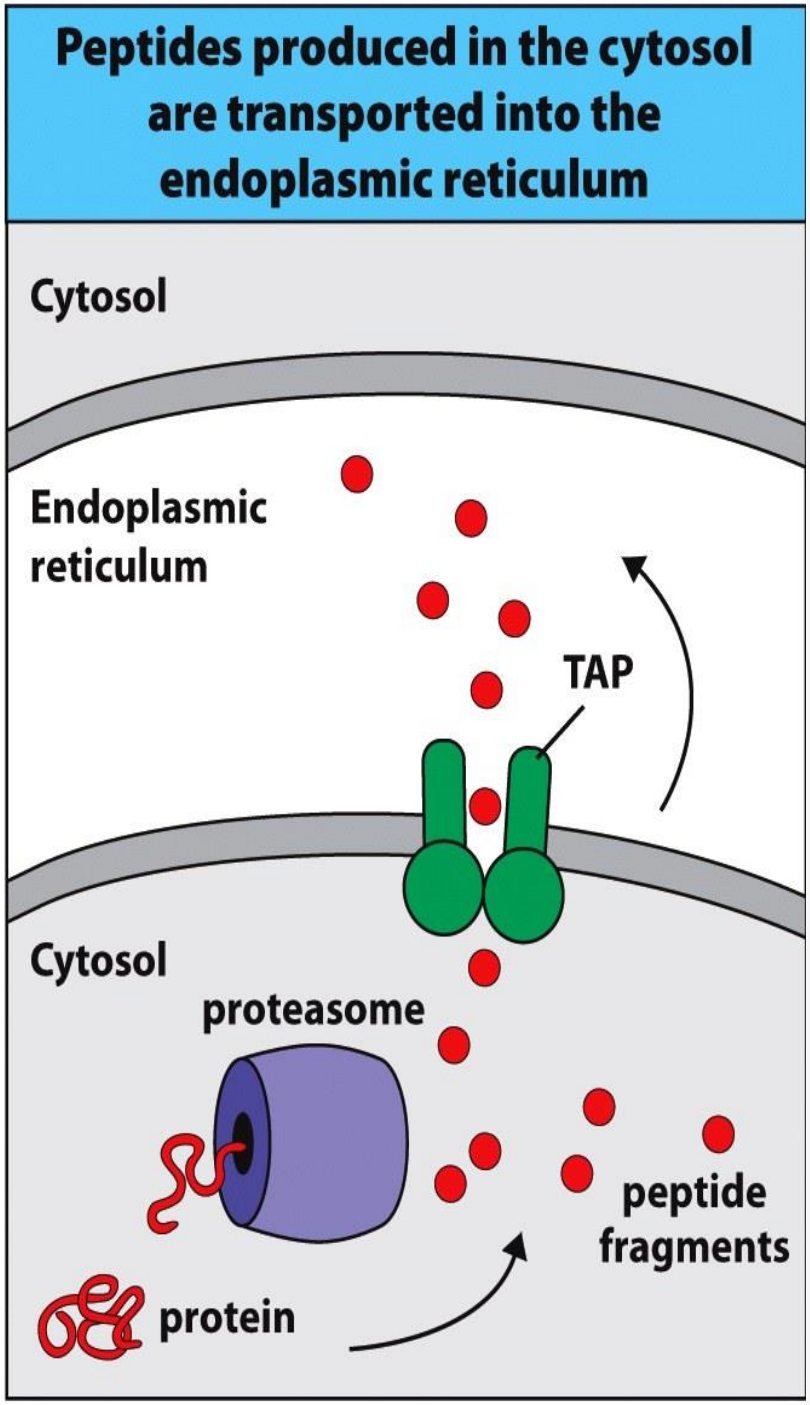


Figure 5.17 Formation and transport of peptides that bind to MHC class I molecules. In all cells, proteasomes degrade cellular proteins that are poorly folded, damaged, or unwanted. When a cell becomes infected, pathogen-derived proteins in the cytosol are also degraded by the proteasome. Peptides are transported from the cytosol into the lumen of the endoplasmic reticulum by the protein called transporter associated with antigen processing (TAP), which is embedded in the endoplasmic reticulum membrane.

Physics and Chemistry

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The Nobel Prize in 2004

"for the discovery of ubiquitin-mediated protein degradation"

Aaron Ciechanover

Avram Hershko

Irwin Rose

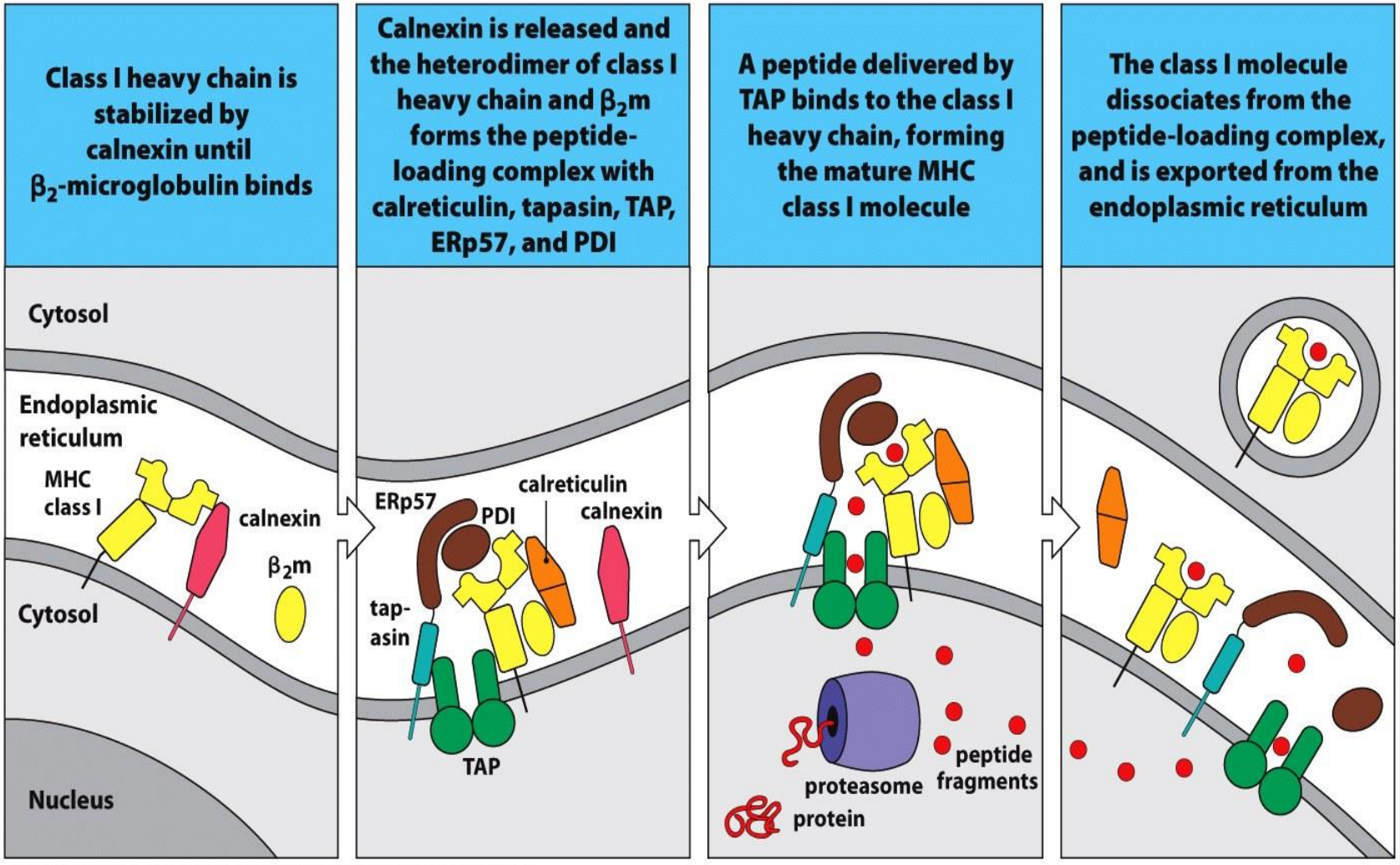


Figure 5.18 Proteins of the peptide-loading complex aid the assembly and peptide loading of MHC class I molecules in the endoplasmic reticulum. MHC class I heavy chains assemble in the endoplasmic reticulum with the membrane-bound protein calnexin. When this complex binds β_2-microglobulin (β_2m) the partly folded MHC class I molecule is released from calnexin and then associates with the TAP, tapasin, calreticulin, ERp57, and protein disulfide isomerase (PDI) to form the peptide-loading complex. The MHC class I molecule is retained in the endoplasmic reticulum until it binds a peptide, which completes the folding of the molecule. The peptide:MHC class I molecule is then released from the other proteins and leaves the endoplasmic reticulum for transport to the cell surface.

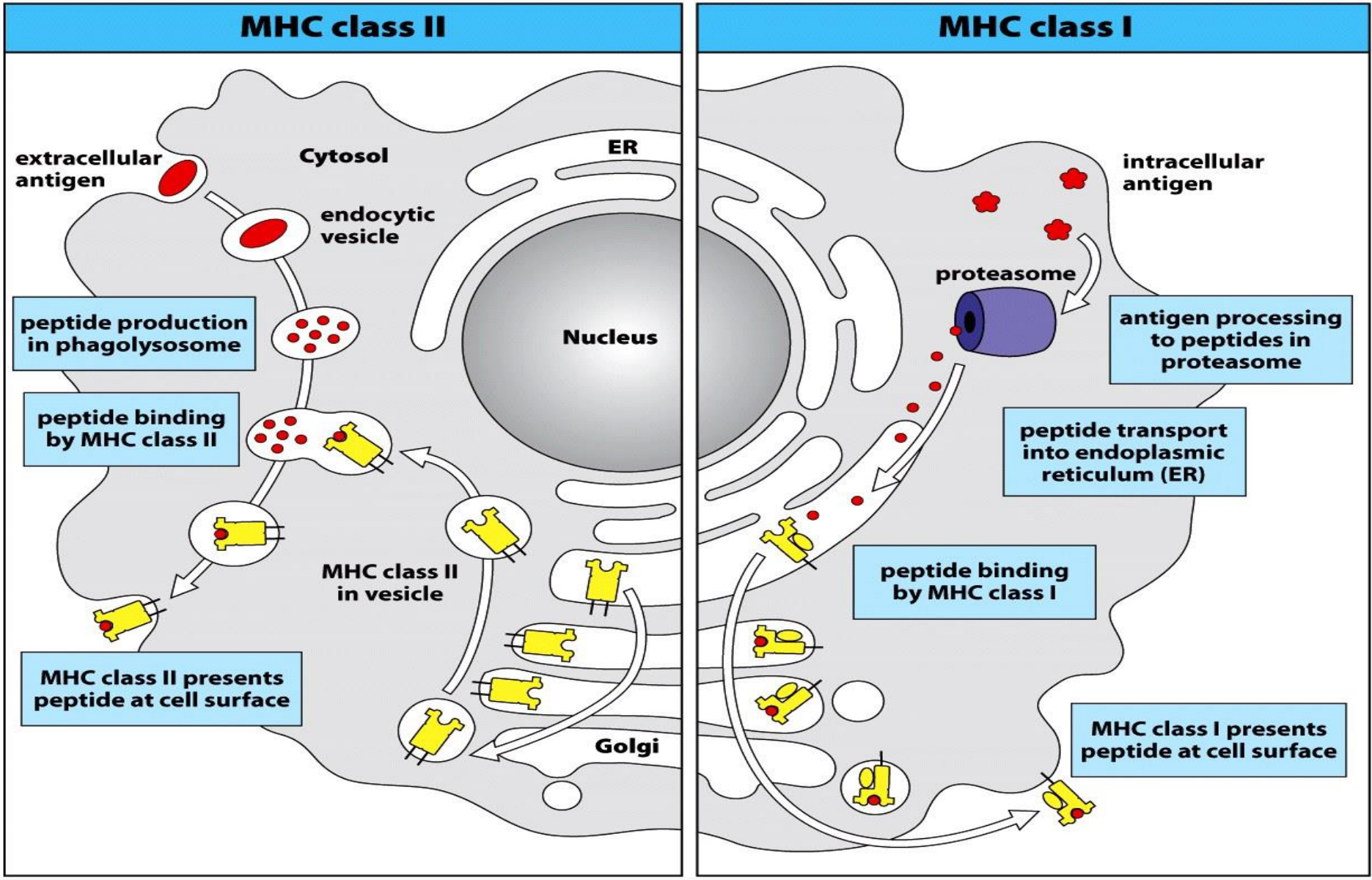


Figure 5.20 Processing of antigens for presentation by MHC class II or MHC class I molecules occurs in different cellular compartments.

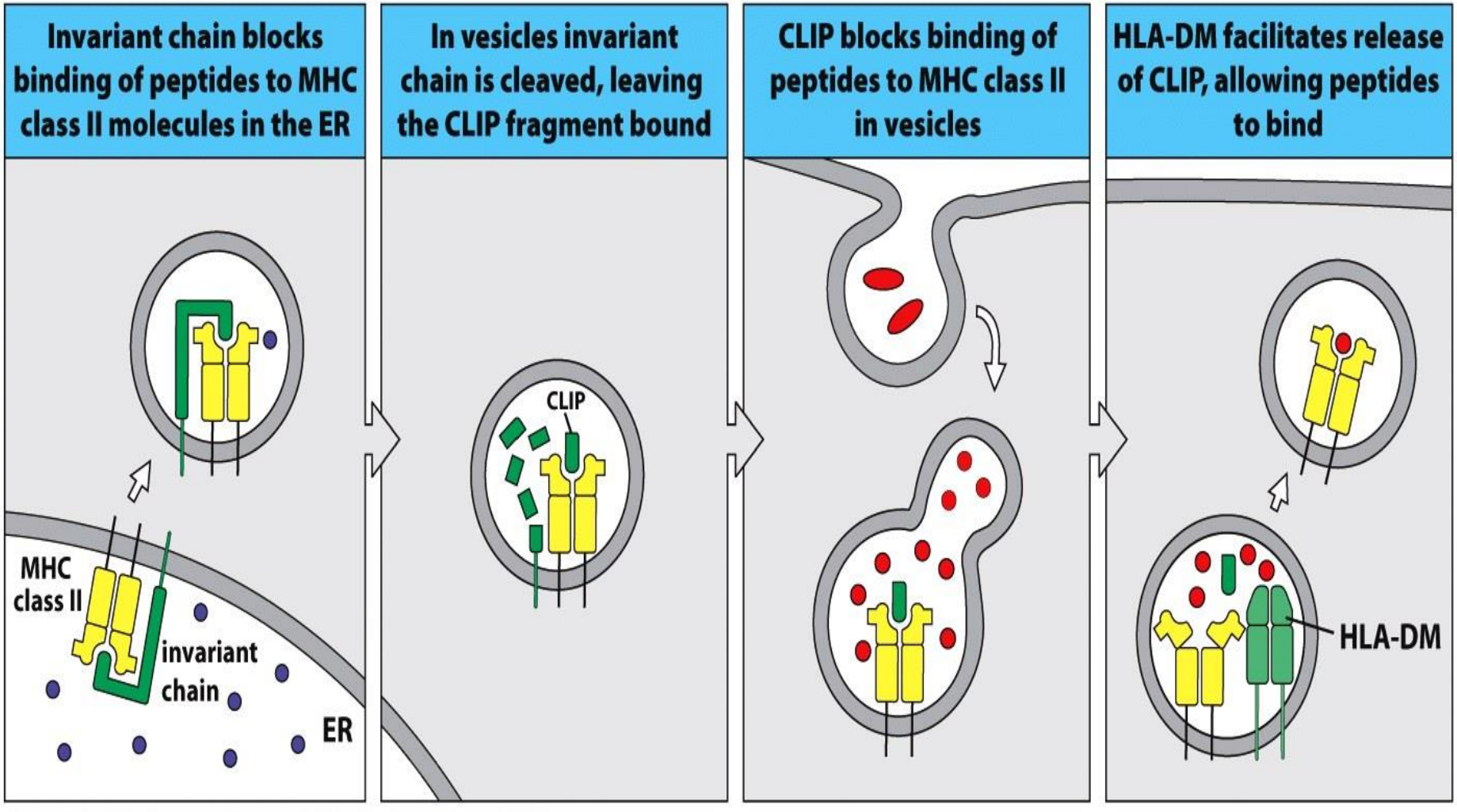


Figure 5.21 The invariant chain prevents peptides from binding to an MHC class II molecule until it reaches the site of extracellular protein breakdown. In the endoplasmic reticulum (ER), MHC class II α and β chains are assembled with an invariant chain that fills the peptide-binding groove; this complex is transported to the acidified vesicles of the endocytic system. The invariant chain is broken down, leaving a small fragment called class II-associated invariant-chain peptide (CLIP) attached in the peptide-binding site. The vesicle membrane protein HLA-DM catalyzes the release of the CLIP fragment and its replacement by a peptide derived from endocytosed antigen that has been degraded within the acidic interior of the vesicles.

Tissue/cell	MHC	
	class I	class II
Hematopoietic		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Neutrophils	+++	–
Erythrocytes	–	–
Non-hematopoietic		
Thymic epithelium	+	+++
Liver hepatocytes	+	–
Kidney epithelium	+	–
Brain	+	–†

Figure 5.23 Most human cells express MHC class I, whereas only selected cell types express MHC class II. MHC class I molecules are expressed on almost all nucleated cells, although they are most abundant on hematopoietic cells. MHC class II molecules are normally expressed by only a subset of hematopoietic cells and by stromal epithelial cells in the thymus, although they can be produced by other cell types on exposure to the cytokine interferon-γ. *Activated T cells express MHC class II molecules, whereas resting T cells do not. †Most cell types in the brain are MHC class II-negative, but microglial cells, which are related to macrophages, are MHC class II-positive.

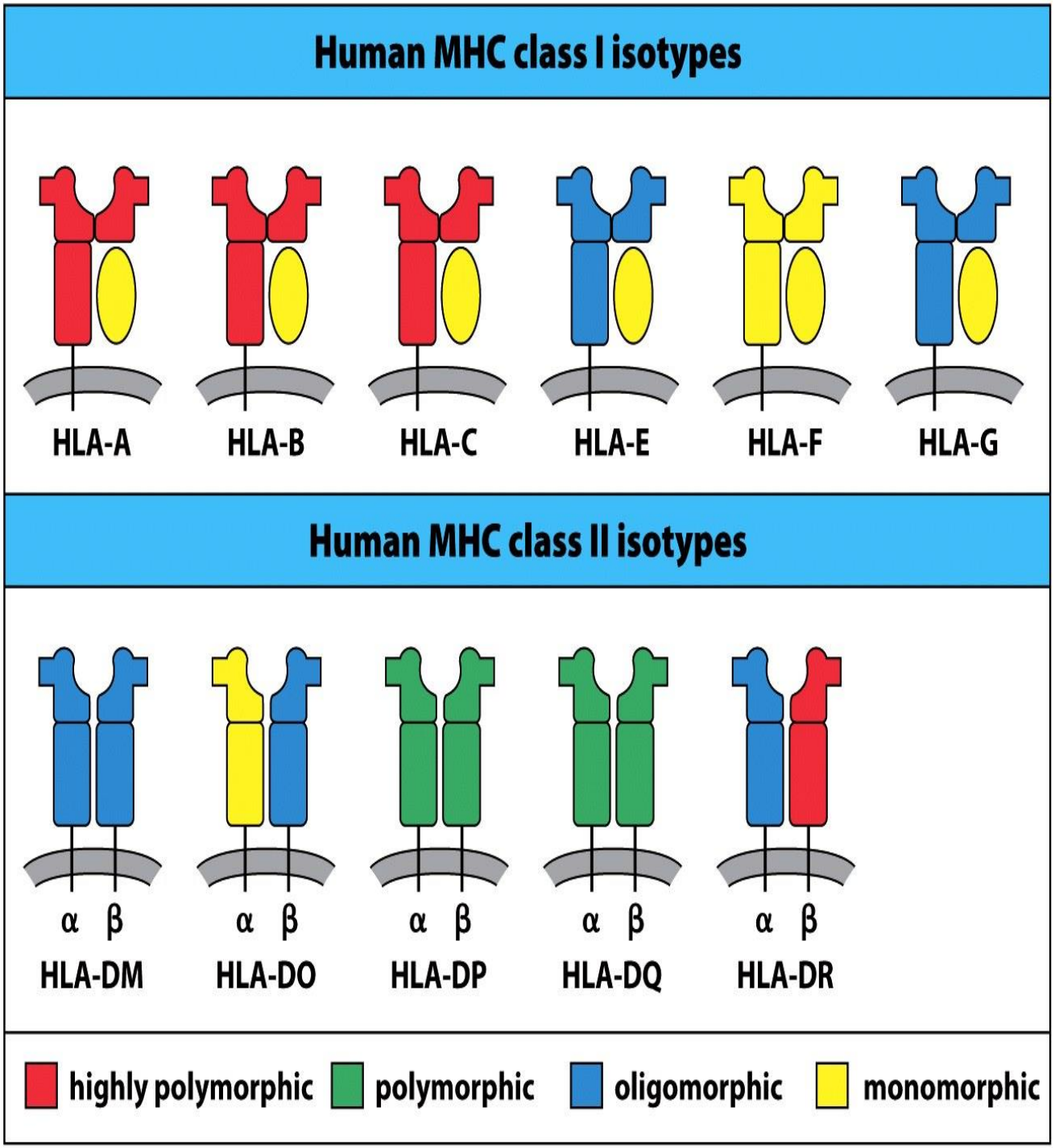


Figure 5.24 Human MHC class I and II isotypes differ in function and in the extent of their polymorphism. Of the human MHC class I isotypes, HLA-A, HLA-B, and HLA-C are highly polymorphic. They present peptide antigens to CD8 T cells and also interact with NK-cell receptors. HLA-E and HLA-G are oligomorphic and interact with NK-cell receptors. HLA-F is intracellular and of unknown function, and occurs as a single isotype. Of the human MHC class II isotypes, HLA-DP, HLA-DQ, and HLA-DR are polymorphic and present peptide antigens to CD4 T cells, whereas HLA-DM and HLA-DO occur in only a few isotypes, are intracellular, and regulate the loading of peptides onto HLA-DP, HLA-DQ, and HLA-DR.

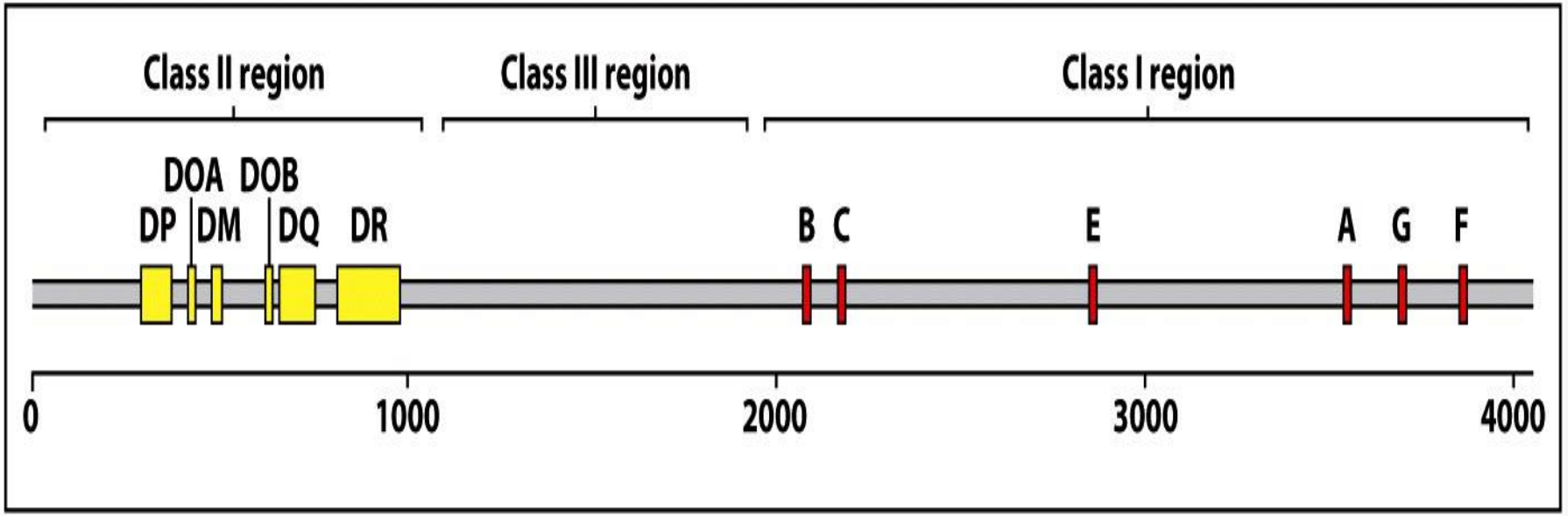


Figure 5.26 The MHC is divided into three regions containing different types of gene. The positions within the HLA complex (the human MHC) of the HLA class I and II genes are shown here. The class I genes (red) are all contained in the class I region, and the class II genes (yellow) are all contained in the class II region. Separating the class I and class II regions is the class III region, which contains a variety of genes (not shown), none of which contributes to antigen processing and presentation. For HLA-DM, HLA-DP, HLA-DQ, and HLA-DR, the α-chain and β-chain genes are close together and are shown as a single yellow block; for HLA-DO the α and β genes (DOA and DOB, respectively) are separated by the DM genes and are therefore shown separately. Approximate distances are given in thousands of base pairs (kb).

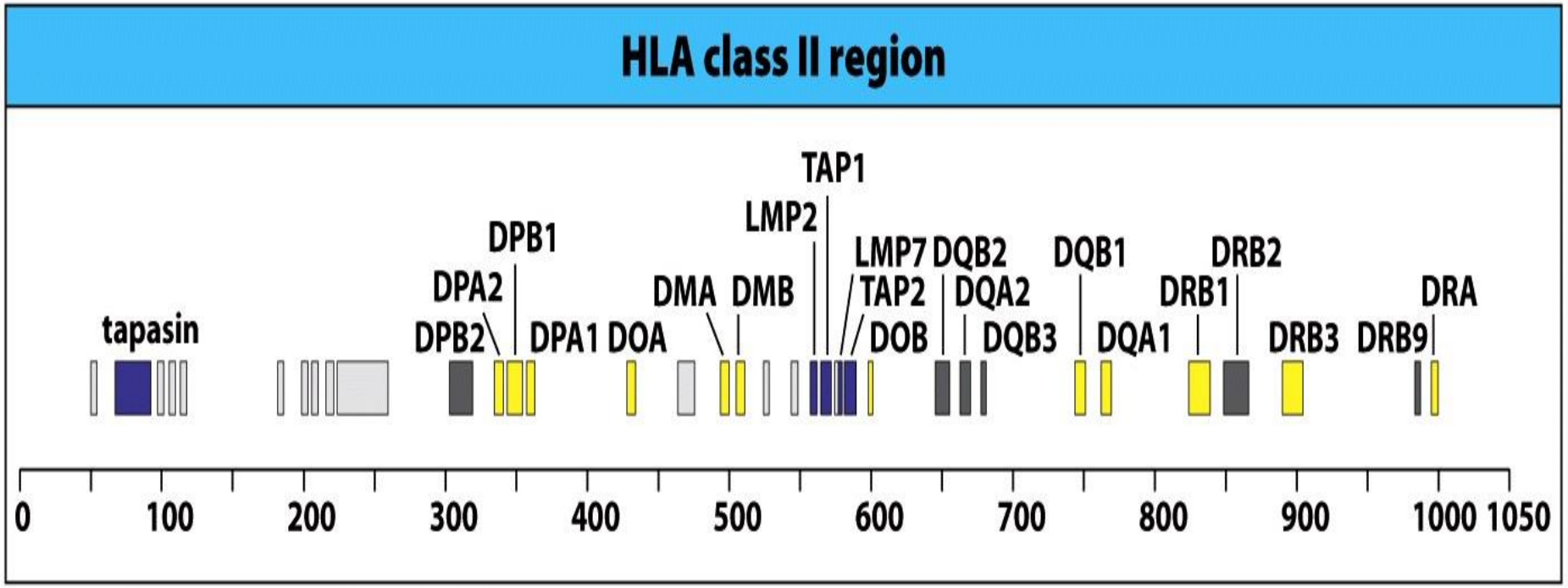


Figure 5.28 Almost all of the genes in the HLA class II region are involved in the processing and presentation of antigens to T cells. A detailed map of the HLA class II region is shown. Genes shown in dark gray are pseudogenes that are related to functional genes but are not expressed. Unnamed genes in light gray are not involved in immune system function. In addition to genes encoding the MHC class II isoforms, the class II region includes genes for the peptide transporter (TAP), proteasome components (LMP) and tapasin. Approximate distances are given in thousands of base pairs (kb).

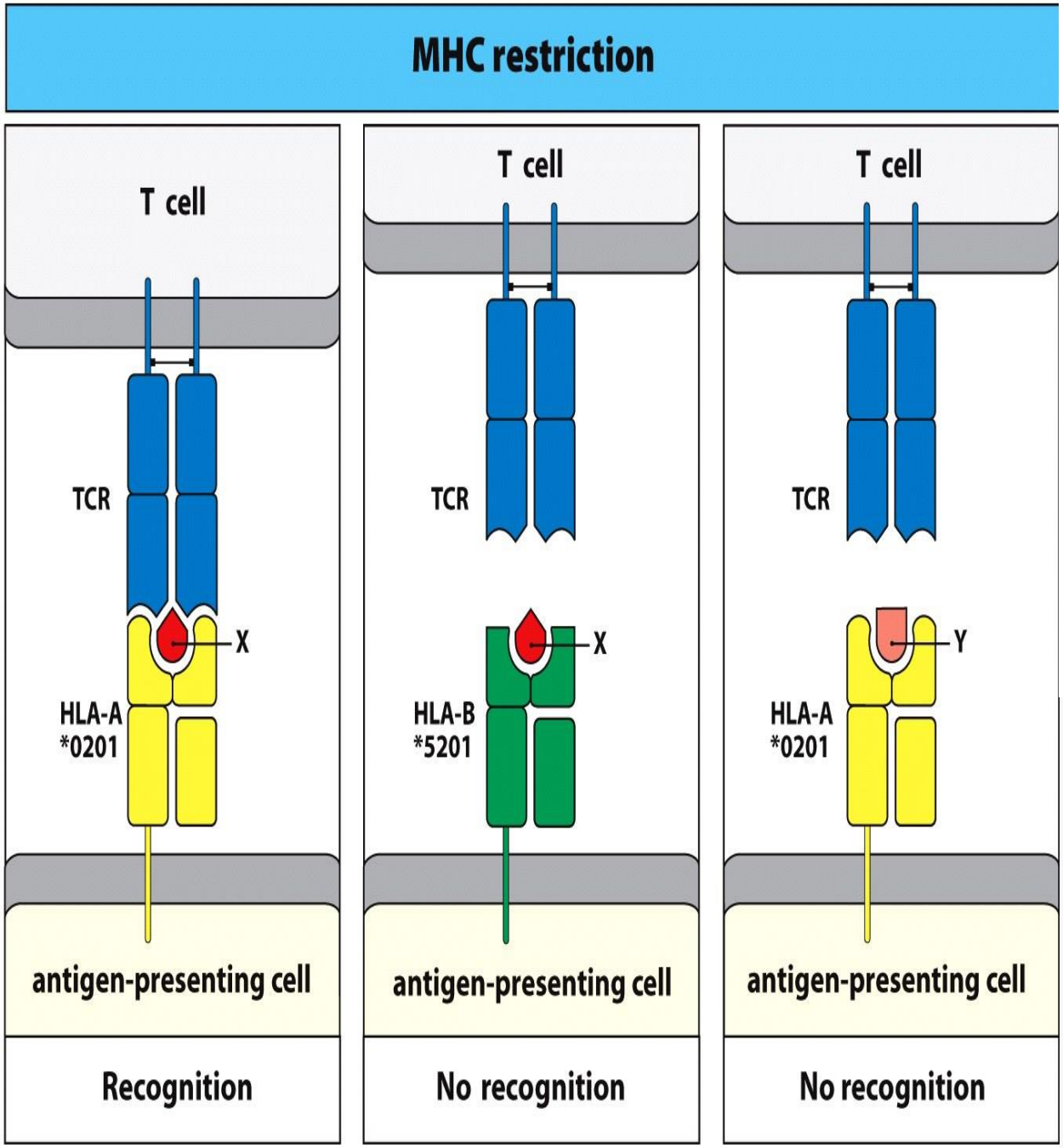
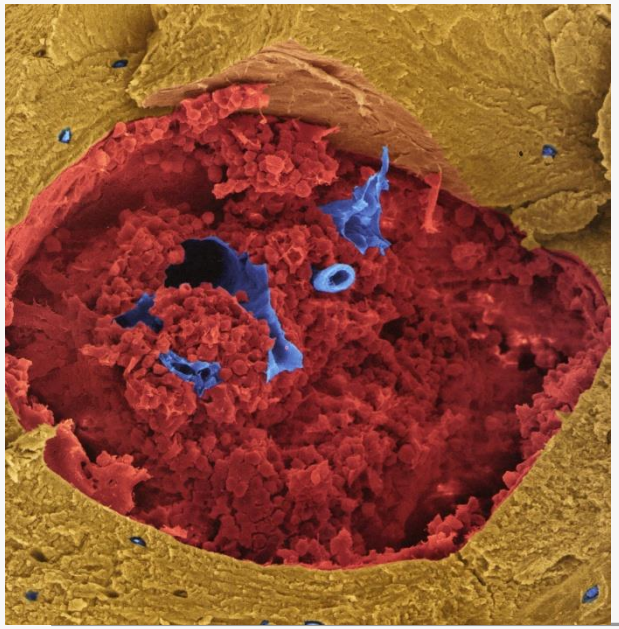


Figure 5.31 T-cell recognition of antigens is MHC restricted. The receptor of the CD8 T cell shown in the left panel is specific for the complex of peptide X with the class I molecule HLA-A*0201. Because of this co-recognition, which is called MHC restriction, the T-cell receptor (TCR) does not recognize the same peptide when it is bound to a different class I molecule, HLA-B*5201 (middle panel). Nor does the T-cell receptor recognize the complex of HLA-A*0201 with a different peptide, Y (right panel). X is HIV-1 Nef residues 190–198, AFHHVAR. Y is influenza A matrix protein residues 58–68, GILGFVFTL.



Chapter 6

The Development of B Lymphocytes

The marrow cavities of the bones in which B-cell development occurs.

	Stem cell	Early pro-B cell	Late pro-B cell	Large pre-B cell	Small pre-B cell	Immature B cell
H-chain genes	Germline	D–J rearrangement	V–DJ rearrangement	VDJ rearranged	VDJ rearranged	VDJ rearranged
L-chain genes	Germline	Germline	Germline	Germline	V–J rearranging	VJ rearranged
Ig status	None	None	None	μ heavy chain is made	μ chain in endoplasmic reticulum	μ heavy chain. λ or κ light chain. IgM on surface.

Figure 6.4 The development of B cells in the bone marrow proceeds through stages defined by the rearrangement and expression of the immunoglobulin genes. In the stem cell, the immunoglobulin (Ig) genes are in the germline configuration. The first rearrangements are of the heavy-chain (H chain) genes. Joining D_H to J_H defines the early pro-B cell, which becomes a late pro-B cell on joining V_H to DJ_H. Expression of a functional μ chain defines the large pre-B cell. Large pre-B cells proliferate, producing small pre-B cells in which rearrangement of the light-chain (L chain) gene occurs. Successful light-chain gene rearrangement and expression of IgM on the cell surface define the immature B cell.

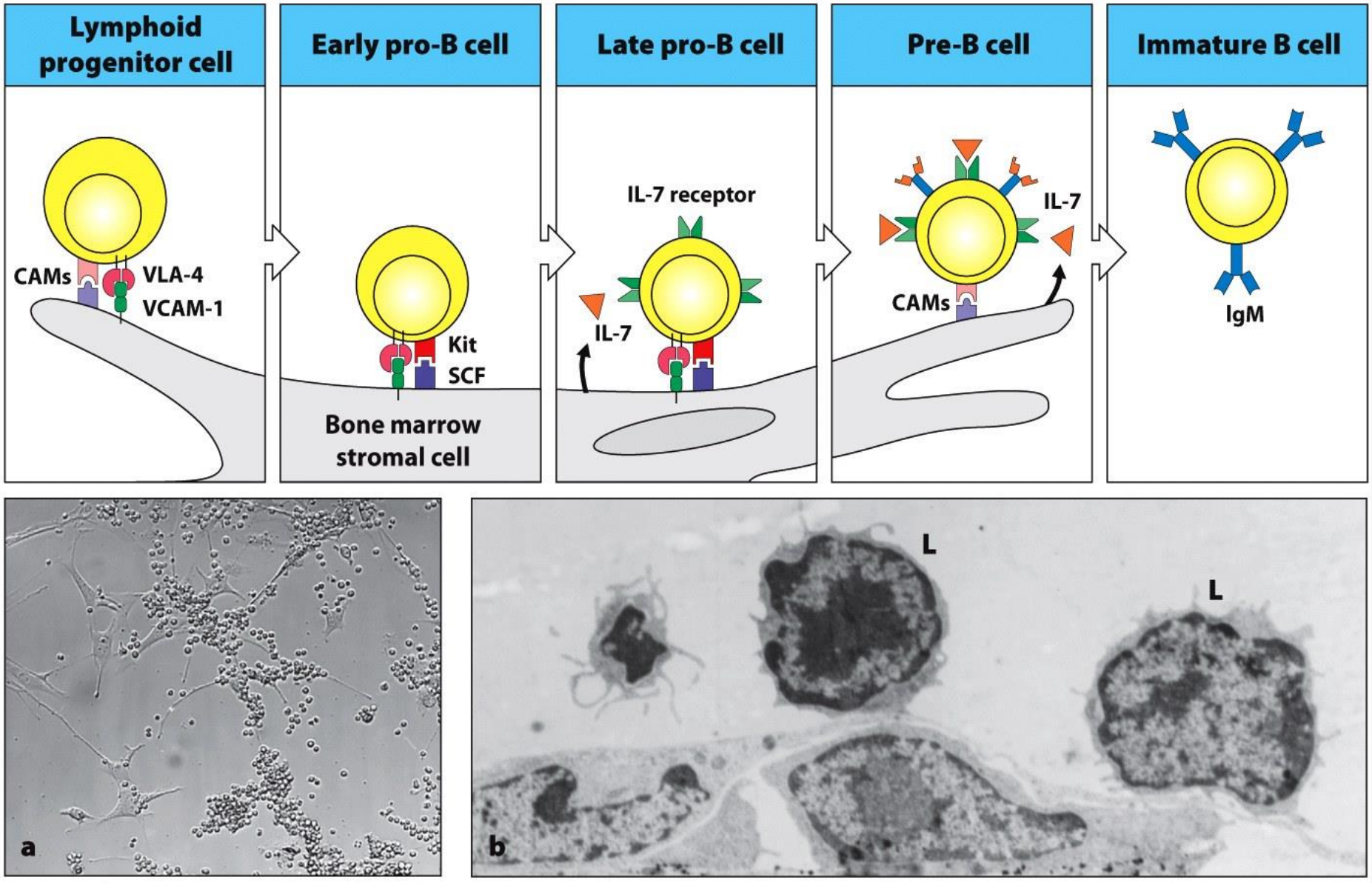


Figure 6.5 The early stages of B-cell development are dependent on bone marrow stromal cells.

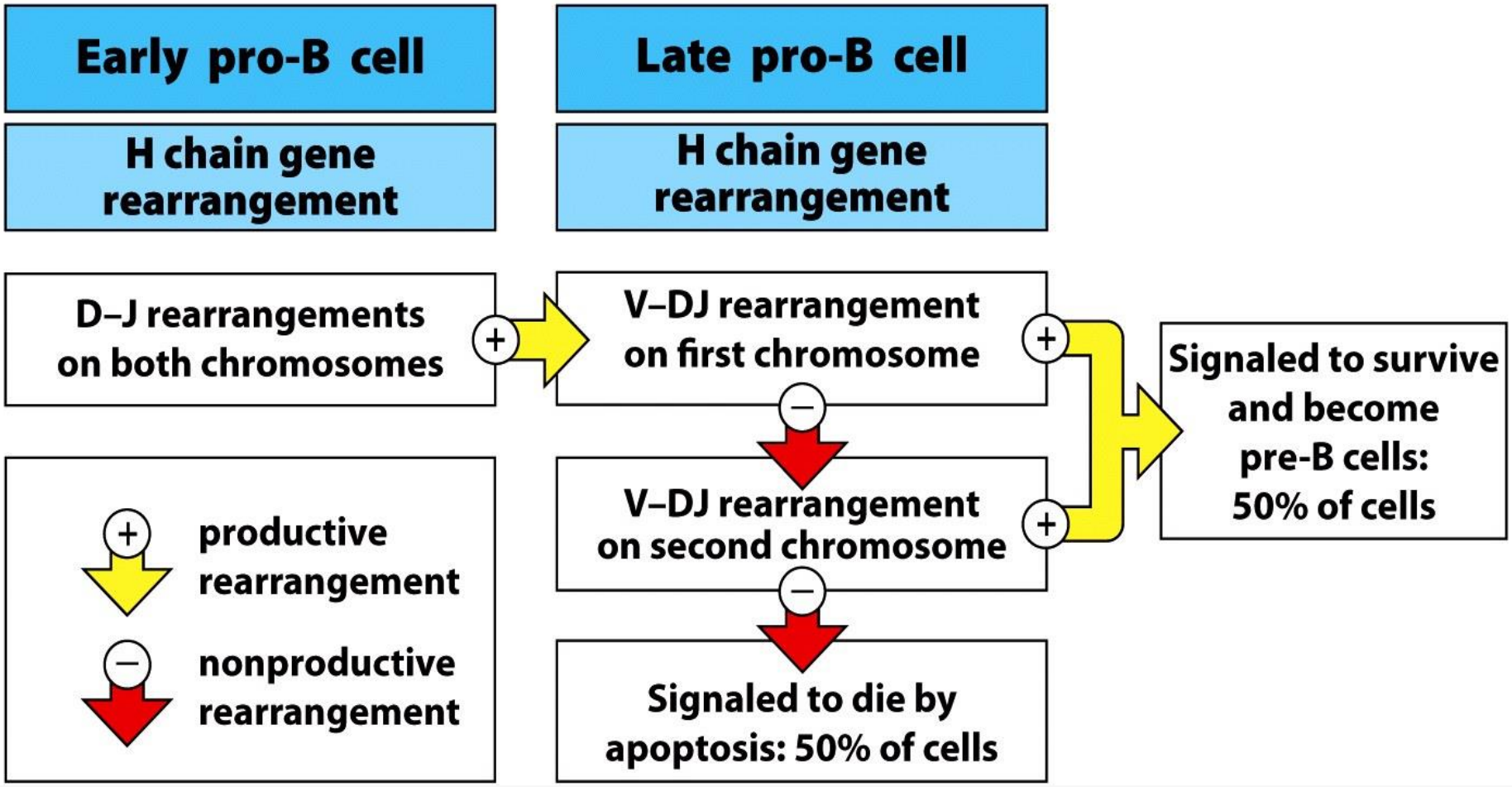
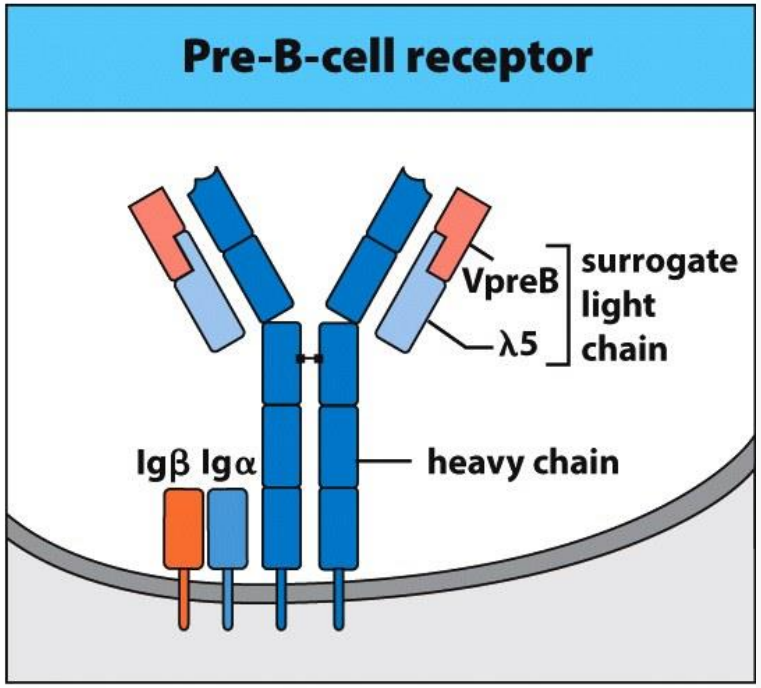


Figure 6.6 Immunoglobulin heavy-chain gene rearrangement in pro-B cells gives rise to both productive and nonproductive rearrangements. A productive rearrangement enables the B cell to proceed to the next stage of development. Rearrangements occur at the H-chain genes on both chromosomes, and if neither is successful the cell dies.



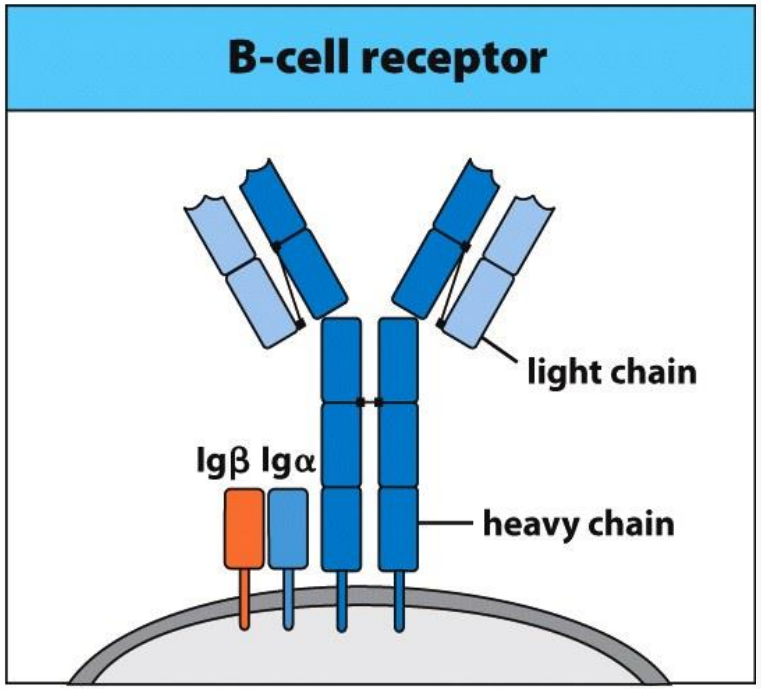


Figure 6.7 The pre-B-cell receptor resembles the B-cell receptor. The pre-B-cell receptor is distinguished from the B-cell receptor in that it lacks an immunoglobulin light chain, which is replaced by the surrogate light chain made up from the VpreB and λ5 polypeptides. It is thought that the pre-B-cell receptor does not appear on the cell surface but remains inside the cell in the cytoplasm, as part of membrane-enclosed vesicles.

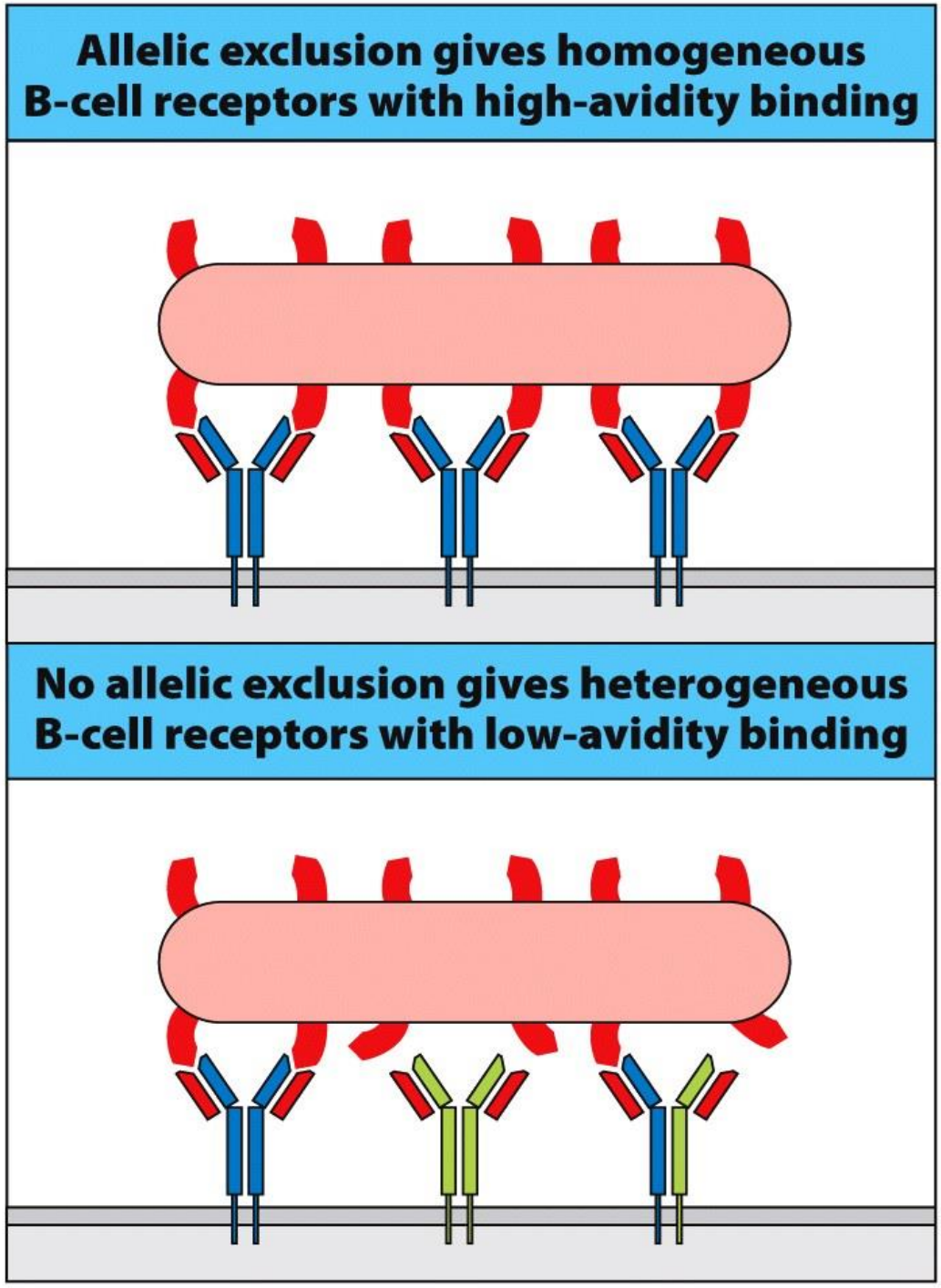


Figure 6.8 Allelic exclusion at the immunoglobulin loci results in B cells with antigen receptors of a single specificity. The top panel shows the binding to antigen of B-cell receptors produced in a B cell expressing immunoglobulin from one immunoglobulin heavy-chain locus and one immunoglobulin light-chain locus only. All the receptors have identical antigen-binding sites and bind their antigen with high avidity. The bottom panel shows the B-cell receptors formed in a hypothetical B cell expressing immunoglobulin from both the immunoglobulin heavy-chain loci and one light-chain locus. Hybrid immunoglobulins are formed with disparate antigen-binding sites and bind the antigen poorly and with low avidity. The disparities would be even greater in a B cell expressing two heavy-chain and two light-chain genes.

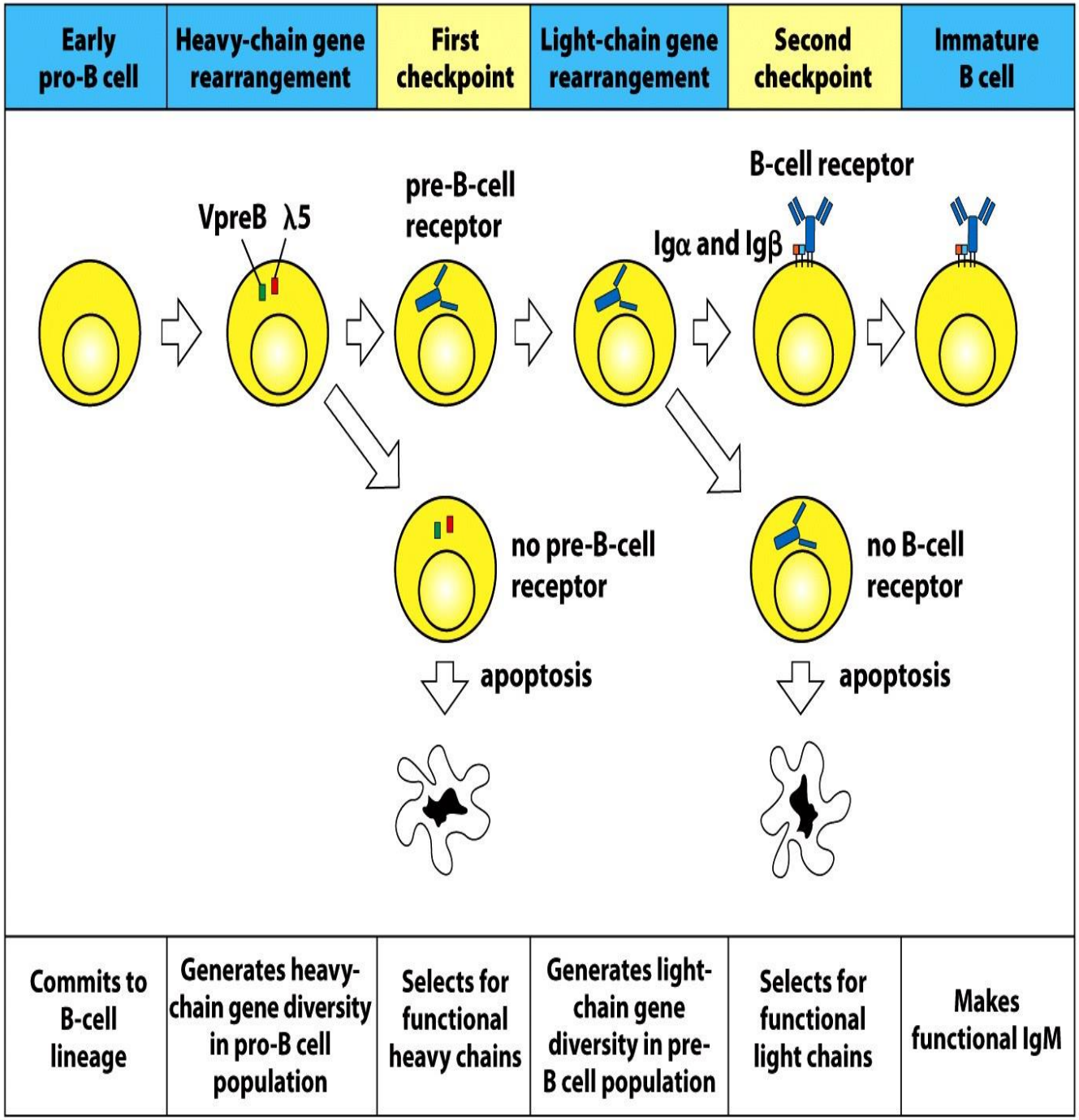


Figure 6.11 There are two fate-determining checkpoints during B-cell development in the bone marrow. Both checkpoints are marked by whether a functional receptor is made, which is a test of whether a functional heavy chain (at the first checkpoint) or a functional light chain (at the second checkpoint) has been produced. Cells that fail either of these checkpoints die by apoptosis.

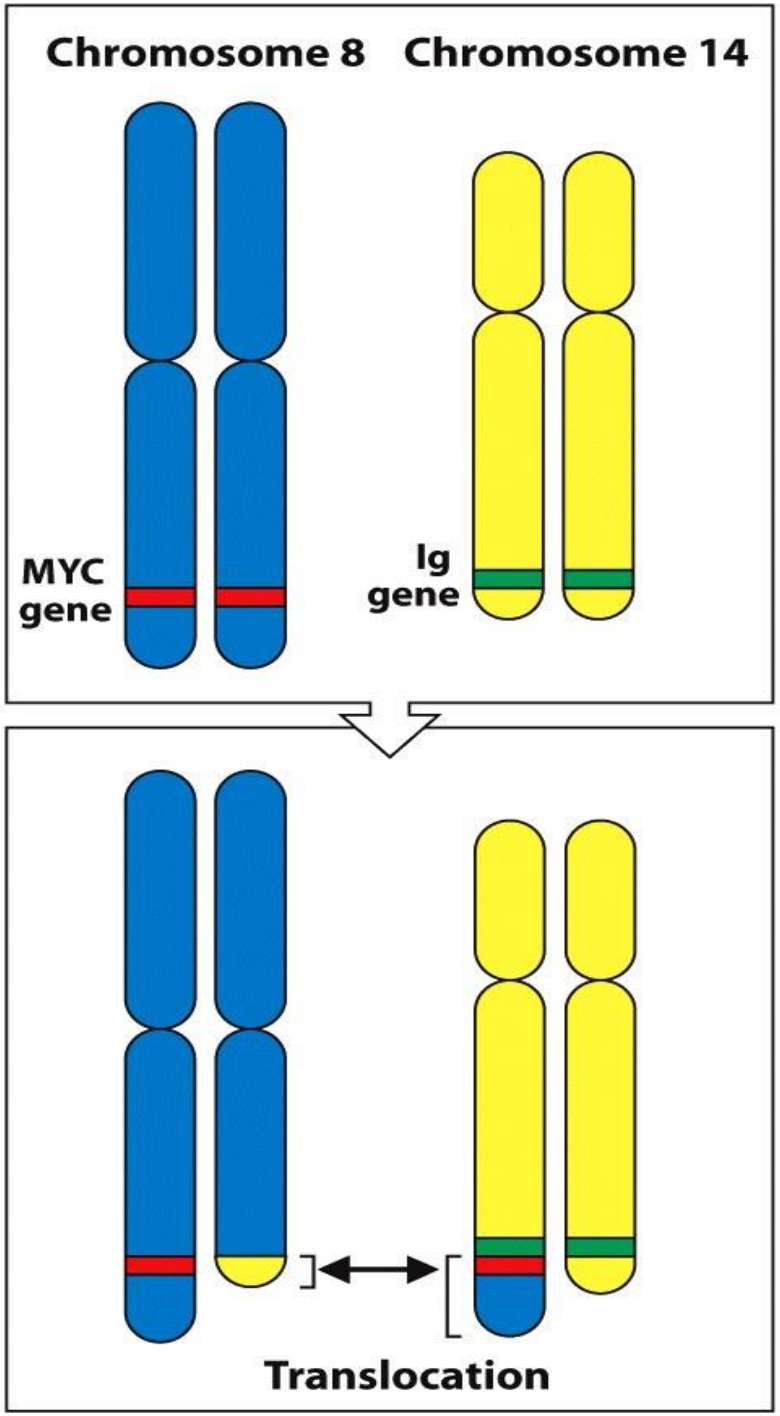


Figure 6.14 Chromosomal rearrangements in Burkitt's lymphoma. In this example from a Burkitt's lymphoma, parts of chromosome 8 and chromosome 14 have been exchanged. The sites of breakage and rejoining are in the proto-oncogene *MYC* on chromosome 8 and the immunoglobulin heavy-chain gene on chromosome 14. In these tumors it is usual for the second immunoglobulin gene to be productively rearranged and for the tumor to express cell-surface immunoglobulin. The translocation probably occurred during the first attempt to rearrange a heavy-chain gene. This counted as a nonproductive rearrangement and so the other gene was rearranged. In cases where the second rearrangement is also nonproductive, the cell dies and thus cannot give rise to a tumor.

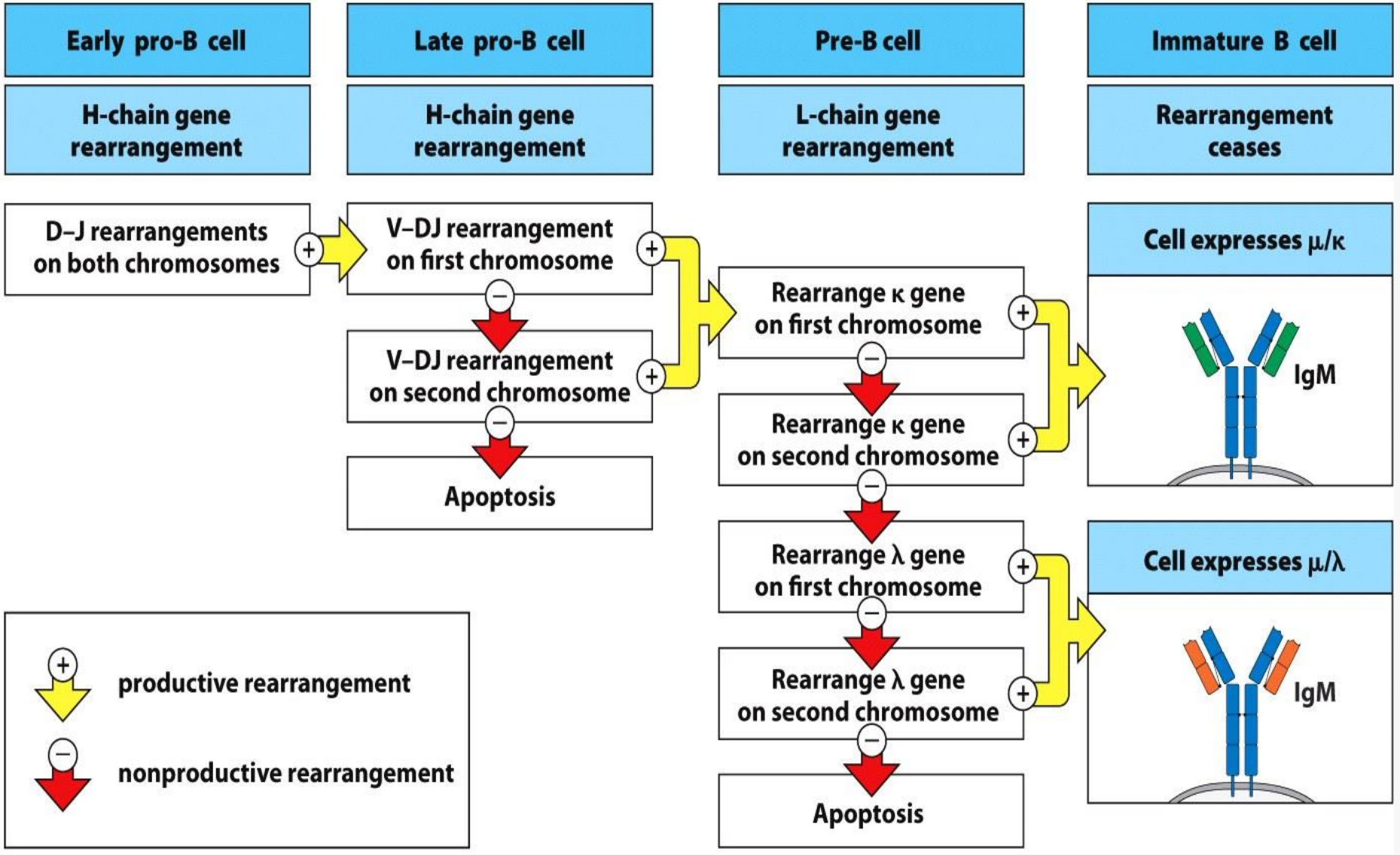


Figure 6.16 Summary of the order of gene rearrangements leading to the expression of cell-surface immunoglobulin. The heavy-chain genes are rearranged before the light-chain genes. Developing B cells are allowed to proceed to the next stage only when a productive rearrangement has been made. If a nonproductive rearrangement is made on one chromosome of a homologous pair, then rearrangement is attempted on the second chromosome.

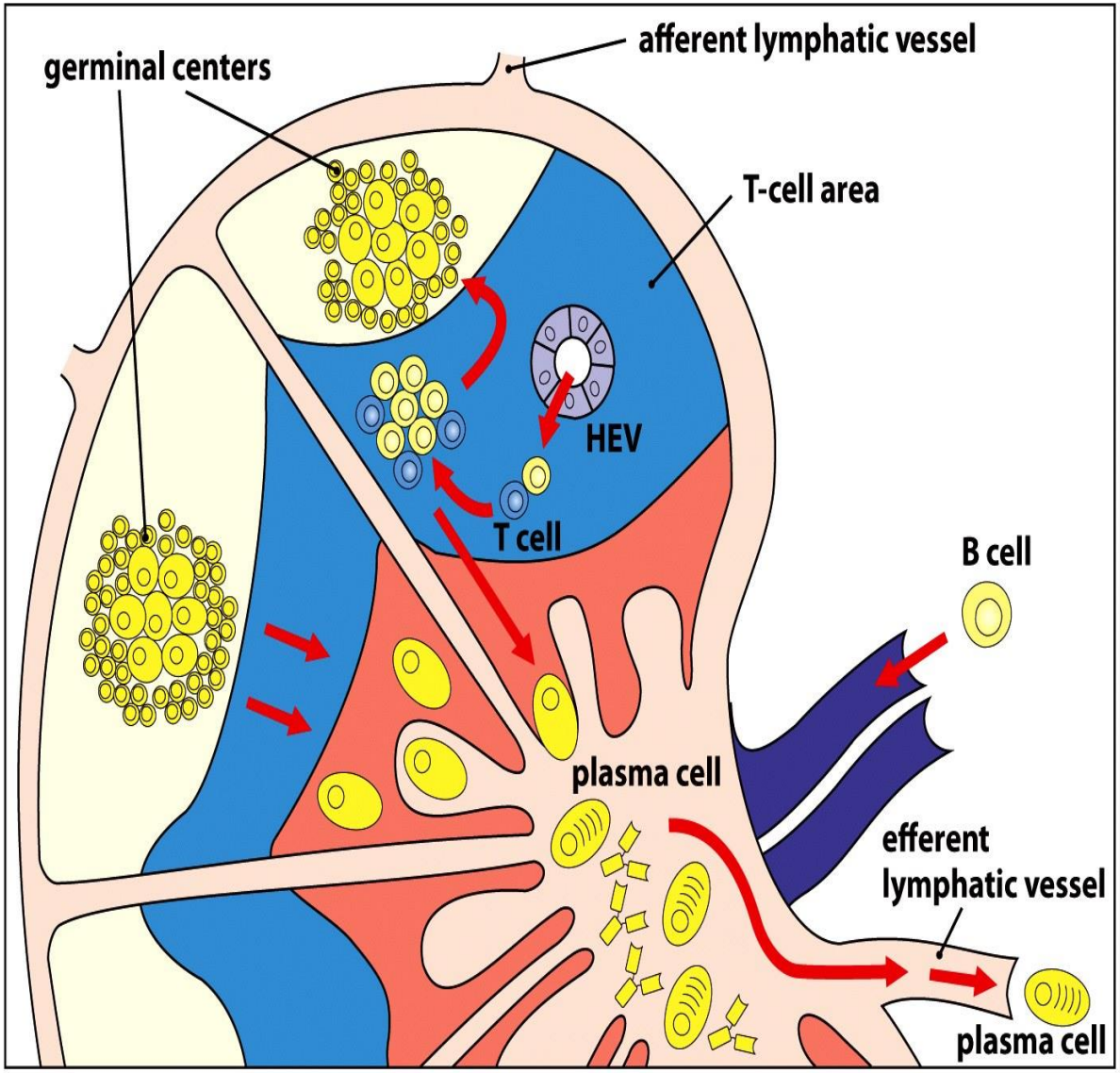


Figure 6.22 Mature B cells encountering antigen in secondary lymphoid tissues form germinal centers and undergo differentiation to plasma cells. A lymph node is illustrated here. A mature naive B cell entering the lymph node through an HEV and circulating through the lymph node encounters antigen within the cortex. Antigen is delivered in the afferent lymph that drains from infected tissue. The B cell is activated by CD4 helper T cells (blue) at the border between the follicle and the T-cell areas to form a primary focus of dividing cells. From this, some B cells migrate directly to the medullary cords and differentiate into antibody-secreting plasma cells. Other B cells migrate into a primary follicle to form a germinal center. B cells continue to divide and differentiate within the germinal center. Activated B cells migrate from the germinal center to the medulla of the lymph node or to the bone marrow to complete their differentiation into plasma cells.

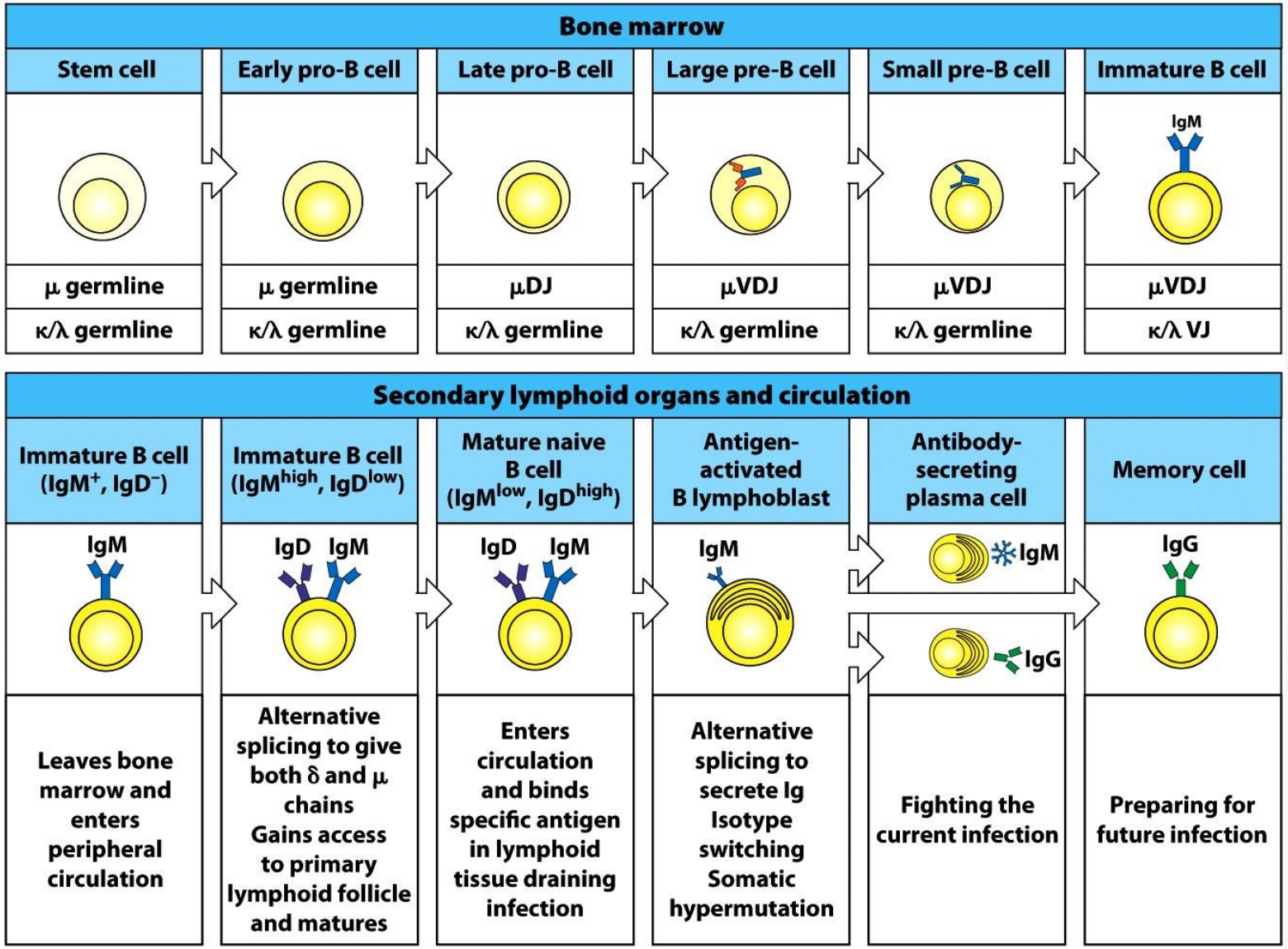


Figure 6.25 Summary of the main stages in B-cell development. The top panels summarize the early stages of development in the bone marrow. The status of the immunoglobulin heavy-chain (μ) and light-chain (κ/λ) genes is shown below each panel. The bottom panels summarize the development of B cells after they leave the bone marrow, enter secondary lymphoid tissues and are activated by pathogen-derived specific antigen. The diagram refers only to the development of B-2 cells.

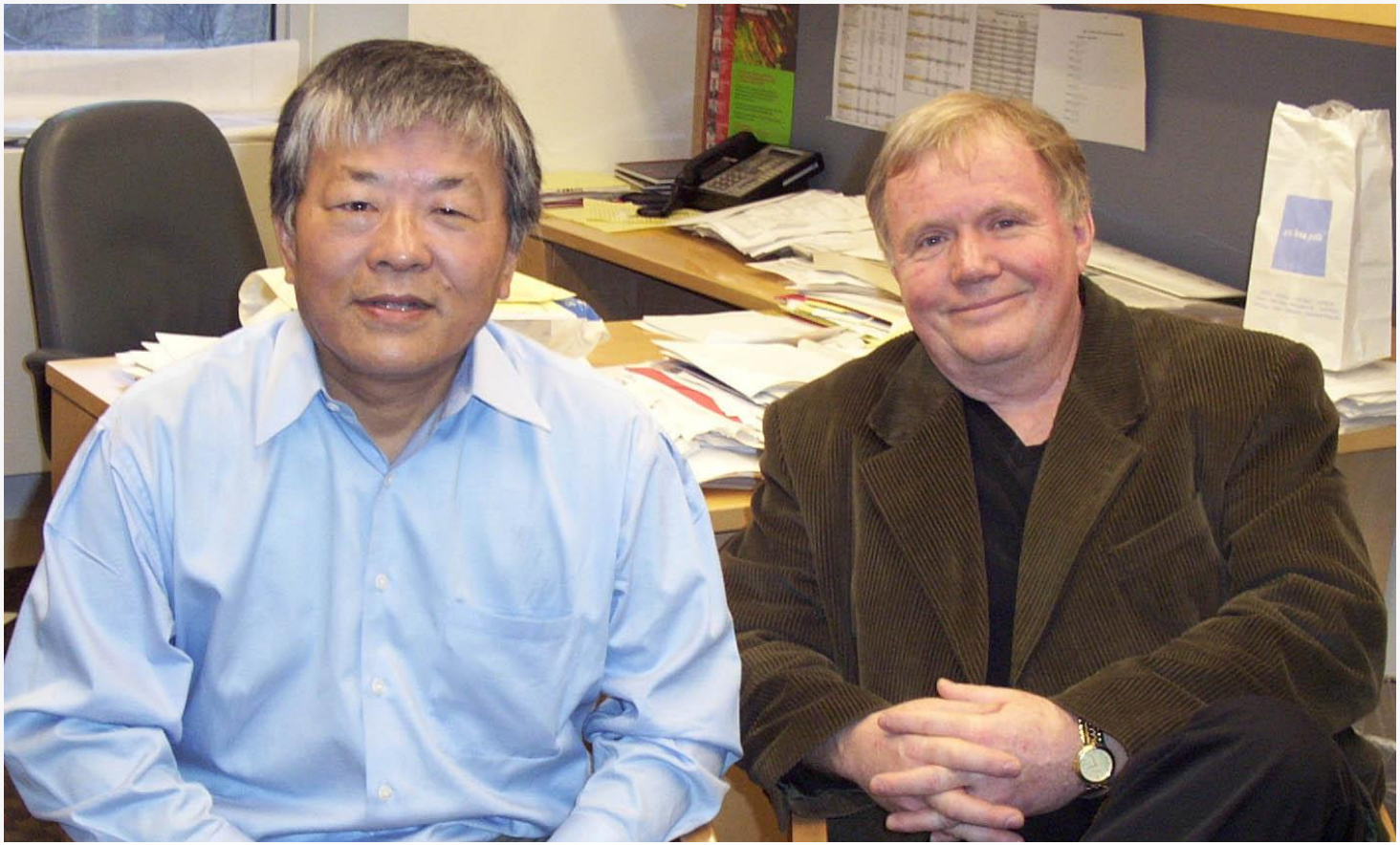
The Nobel Prize in 1984

"for theories concerning the specificity in **development and control** of the immune system and the discovery of the principle for production of **monoclonal antibodies**“ **idiotype anti-idiotype network theory**

Niels K. Jerne, Georges J.F. Köhler, César Milstein

The Nobel Prize 1987

"for his discovery of the genetic principle for generation of antibody diversity"



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