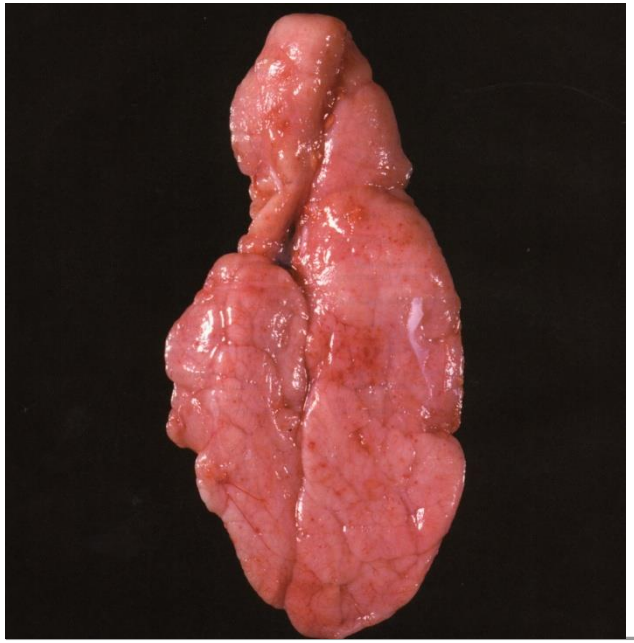


Chapter 7

The Development of T Lymphocytes

The thymus gland where T-cell development occurs.

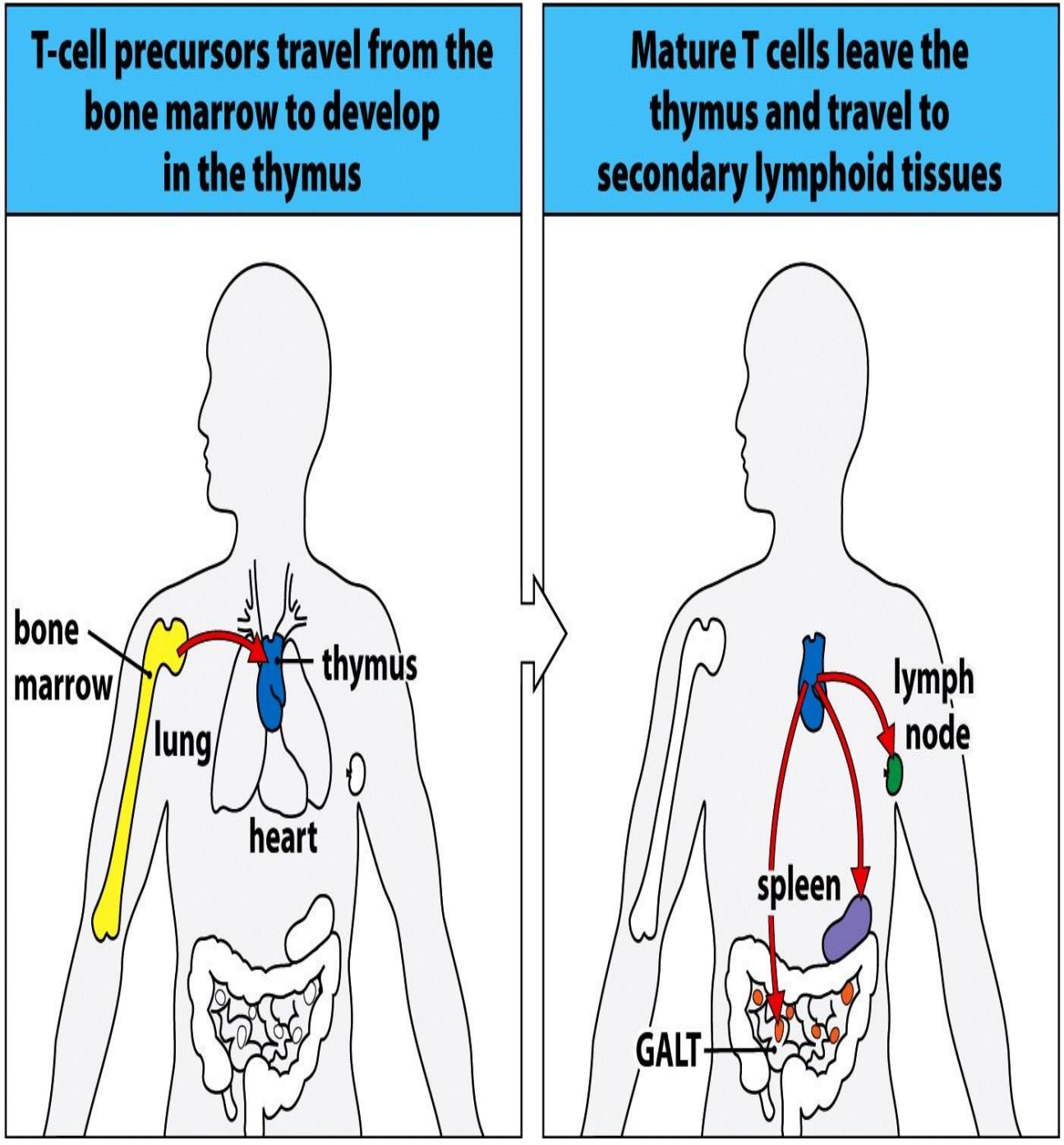


Figure 7.1 T-cell precursors migrate from the bone marrow to the thymus to mature. T cells derive from bone marrow stem cells whose progeny migrate in the blood from the bone marrow to the thymus (left panel), where the development of T cells occurs. Mature T cells leave the thymus in the blood, from where they enter secondary lymphoid tissues (right panel) and then return to the blood in the lymph. In the absence of activation by specific antigen, mature T cells continue to recirculate between the blood, secondary lymphoid tissues, and lymph. GALT, gut-associated lymphoid tissue.

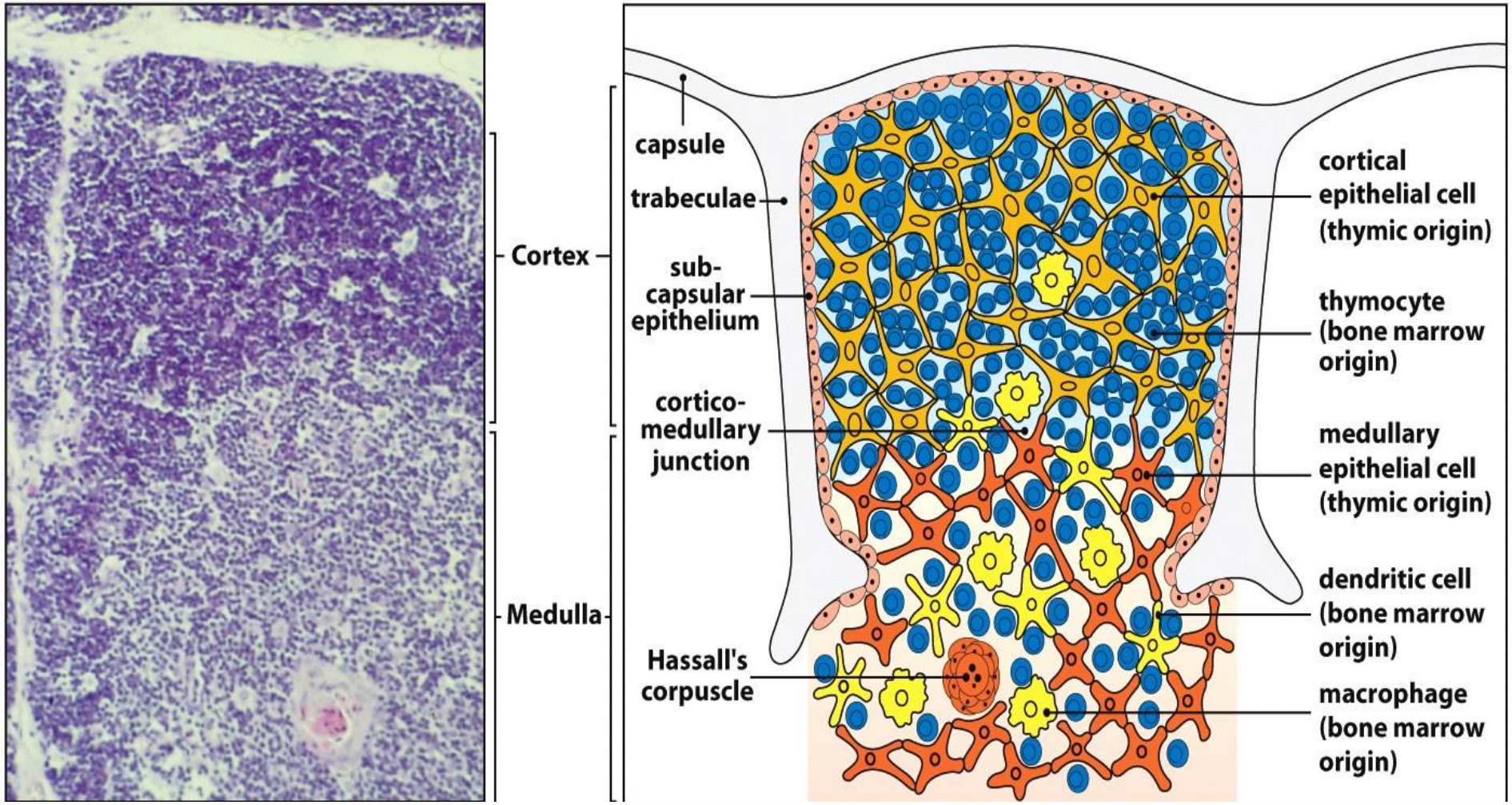
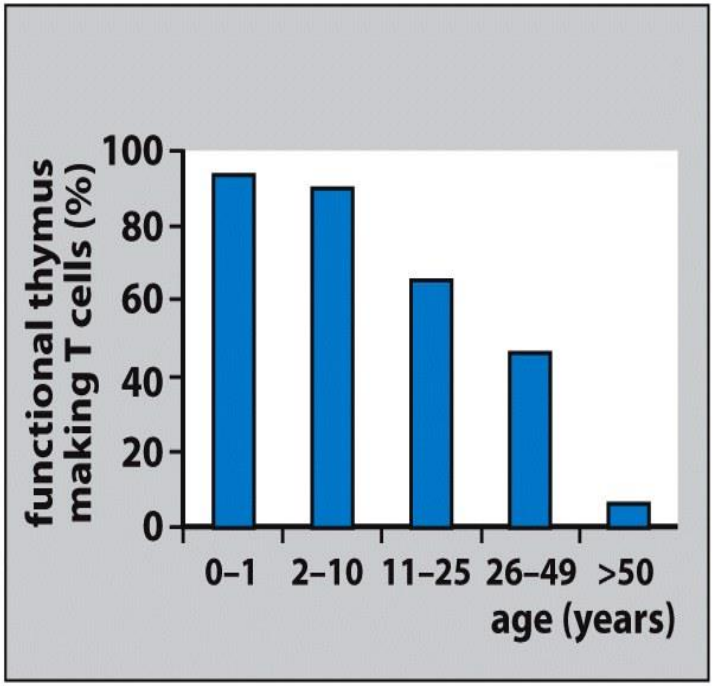
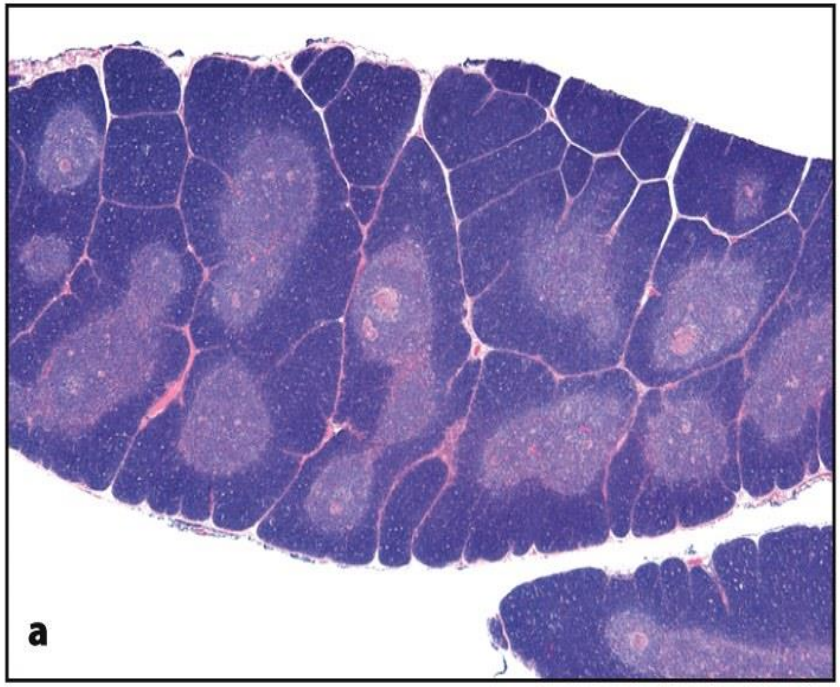


Figure 7.3 The cellular organization of the thymus. The thymus is made up of several lobules. A section through a lobule stained with hematoxylin and eosin and viewed with the light microscope is shown in the left panel. The cells in this view are shown in diagrammatic form in the right panel. In the left panel, the darker staining of cortex compared with the medulla can be discerned. As shown in the right panel, the cortex consists of immature thymocytes (blue), branched cortical epithelial cells (light orange), and a few macrophages (yellow). The medulla consists of mature thymocytes (blue), medullary epithelial cells (orange), dendritic cells (yellow), and macrophages (yellow). One of the functions of the macrophages in both cortex and medulla is to remove the many thymocytes that fail to mature properly. A characteristic feature of the medulla is Hassall's corpuscles, which are believed to be sites of cell destruction. Photograph courtesy of C.J. Howe.





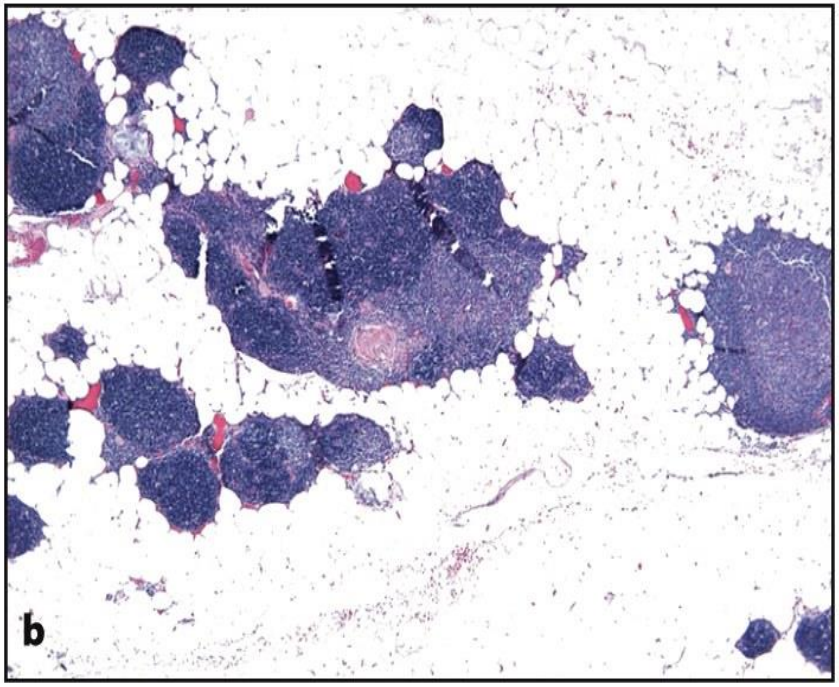


Figure 7.4 The proportion of the thymus that produces T cells decreases with age. Starting at birth, the T-cell-producing tissue of the thymus is gradually replaced by fatty tissue. This process is called the involution of the thymus. The graph shows the percentage of thymic tissue that is still producing T cells at different ages. The micrograph in panel a shows a section through the thymus of a 3-day-old infant; the micrograph in panel b shows a section through the thymus from a 70-year-old person for comparison. Tissue is stained with hematoxylin and eosin (red and blue). Magnification × 20. Micrographs courtesy of Yasodha Natkunam.

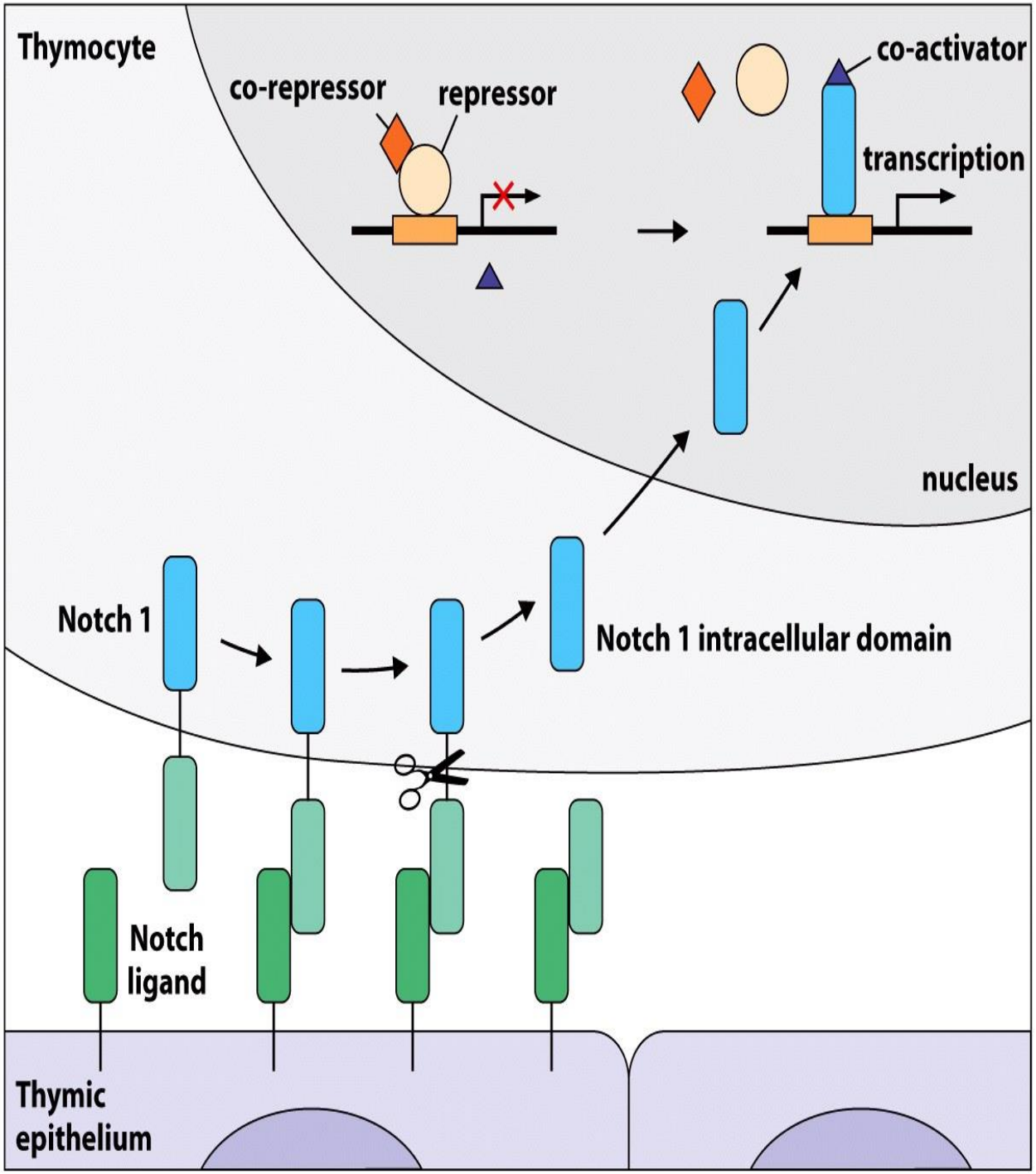


Figure 7.6 T-cell development is driven by the receptor Notch 1. The surface membrane-associated receptor called Notch 1 on the thymocyte binds to its ligand on thymic epithelium. This interaction induces a protease to cleave the intracellular domain from the plasma membrane. The soluble intracellular domain is translocated to the nucleus, where it turns on the expression of genes essential for T-cell development by removing repressive transcription factors and recruiting co-activating transcription factors.

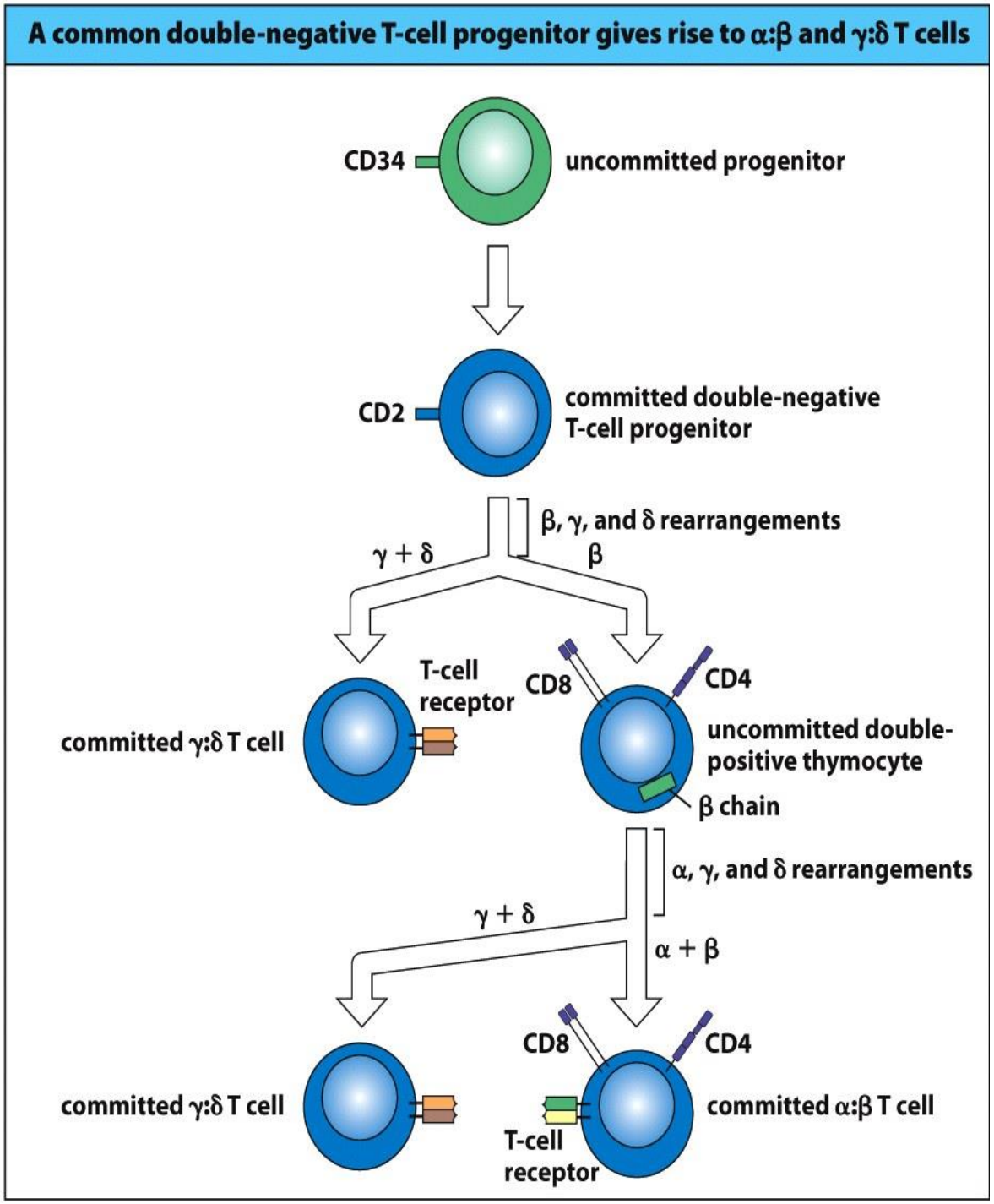


Figure 7.7 α:β and γ:δ T cells develop from a common double-negative T-cell progenitor. T-cell precursors that enter the thymus express the hematopoietic stem-cell marker CD34 but none of the characteristic markers of mature T cells. Proliferation of these common progenitors followed by rearrangement of the δ-, γ-, and β-chain genes leads to early commitment of some cells to the γ:δ T-cell lineage, whereas others rearrange the β-chain gene first and temporarily halt gene rearrangement at this point. As soon as they produce a complete receptor, γ:δ cells can leave the thymus and travel to other tissues via the blood. In the β-chain-positive cells in the thymus, rearrangement of the α-, γ-, and δ-chain genes resumes and productive α-chain gene rearrangements in these cells produce double-positive CD4 CD8 α:β cells. A minority of the double-positive thymocytes give rise to additional γ:δ T cells. This ends the early stage of α:β T-cell development.

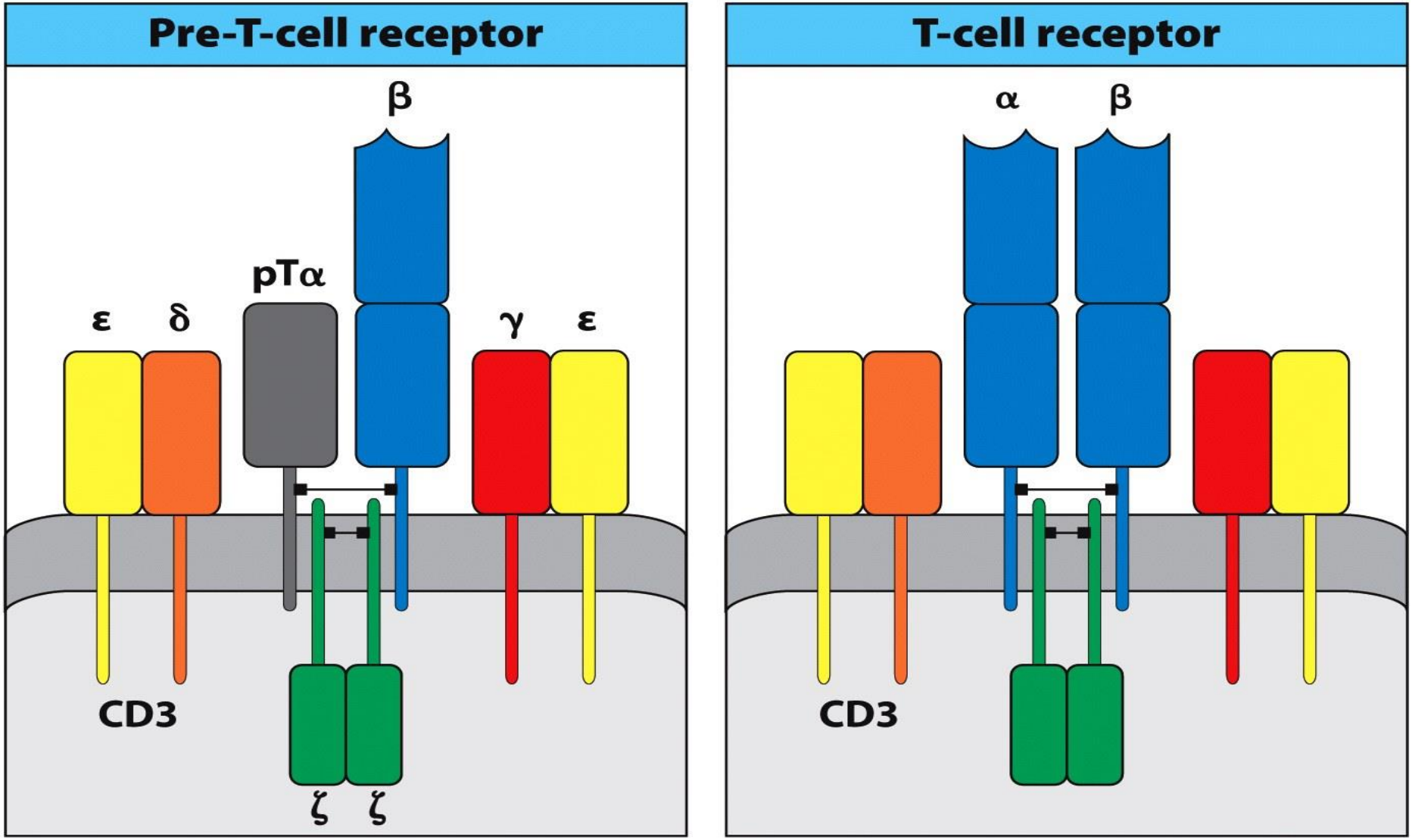


Figure 7.10 Comparison of the structures of the pre-T-cell receptor and the T-cell receptor. The only difference is that the α chain of the T-cell receptor is replaced by the pTα chain in the pre-T-cell receptor.

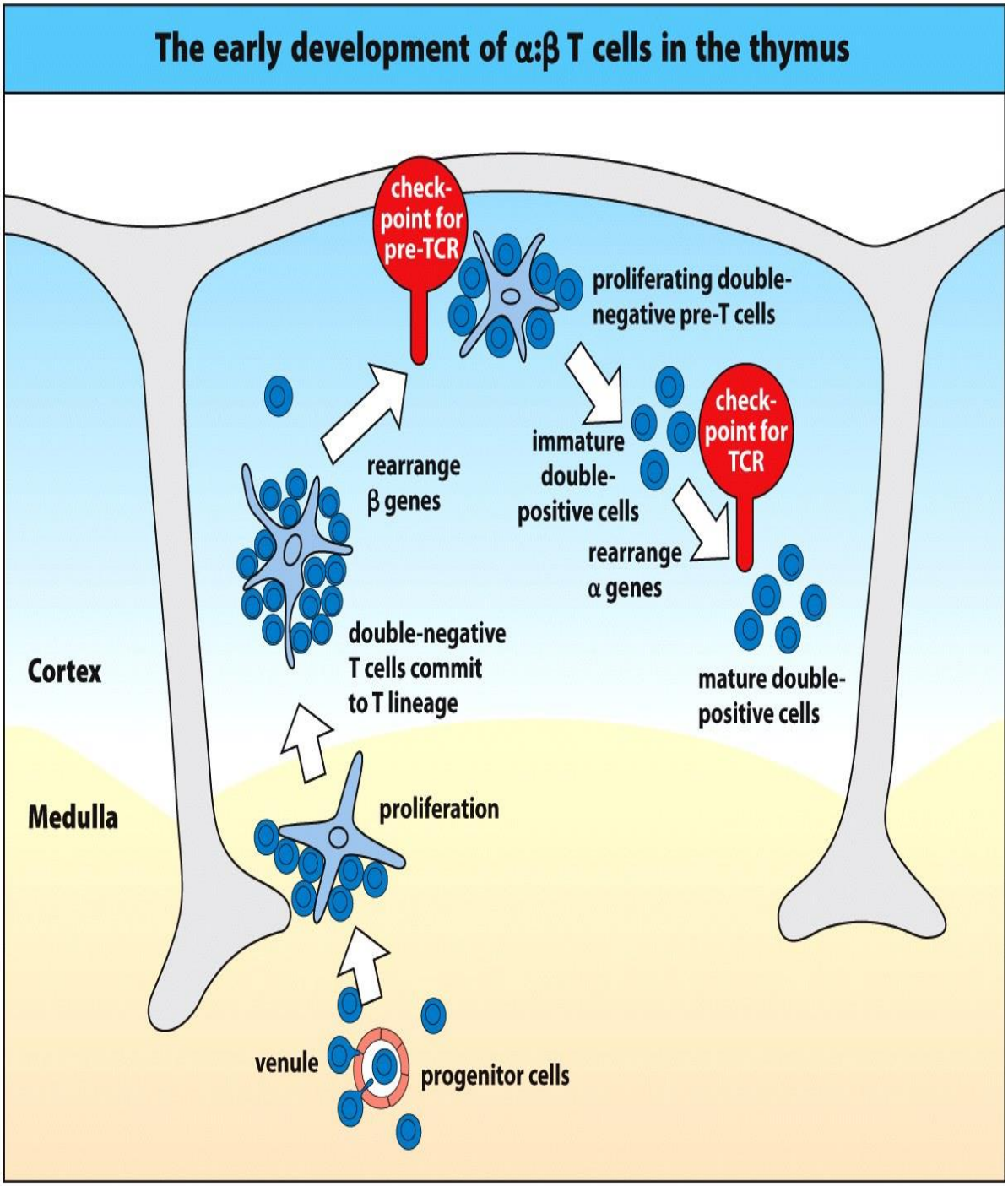


Figure 7.15 The development in the thymus of double-positive α:β T cells. This figure summarizes the early development of α:β T cells (round dark blue cells) in the thymus, from uncommitted progenitor cell to a double-positive cell bearing an α:β T-cell receptor. The two checkpoints of B-cell development are indicated. The paler blue cells are resident thymic cells.

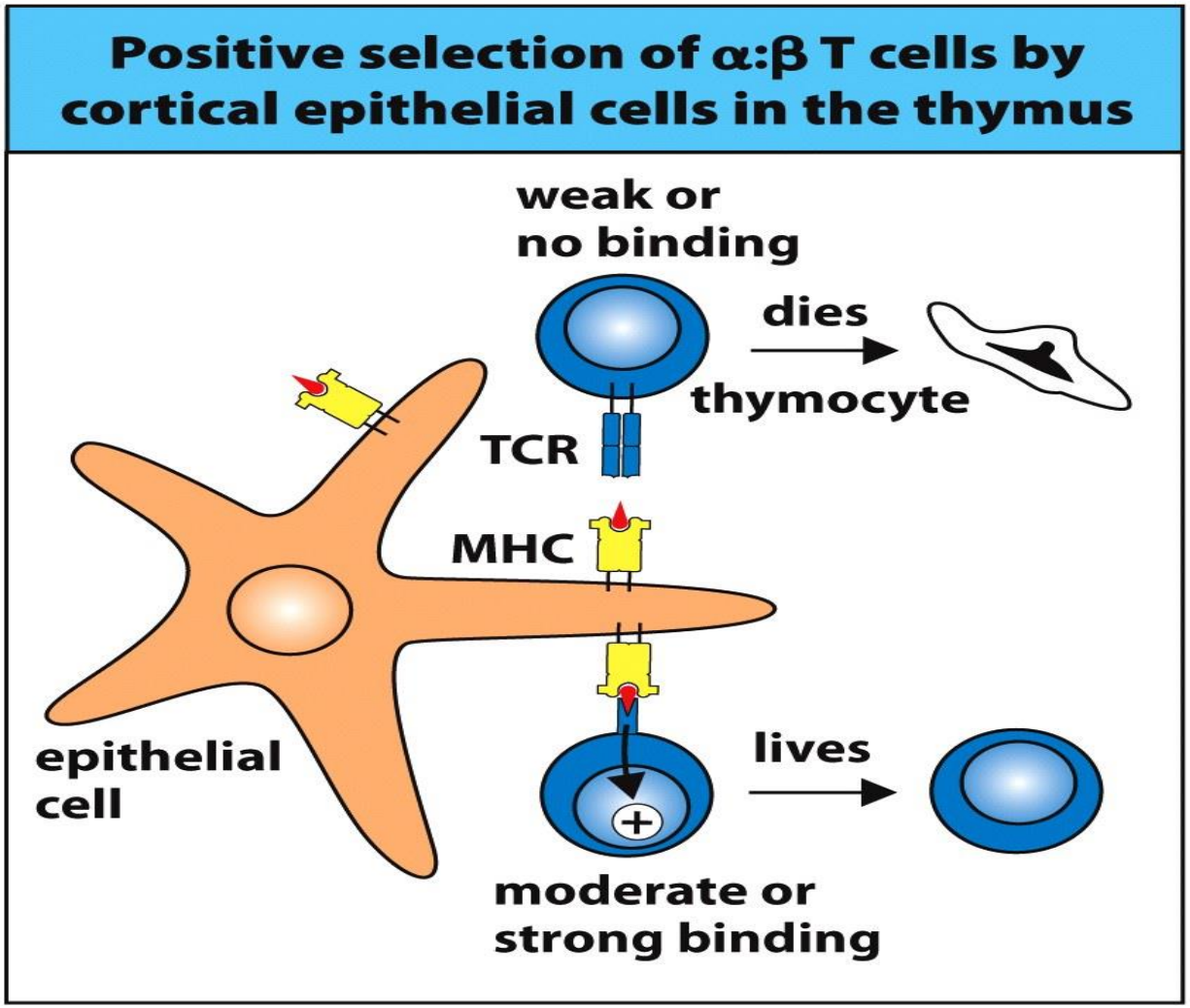


Figure 7.16 Positive selection of T cells in the thymus. T cells with a T-cell receptor (TCR) that binds to a self-MHC class I molecule on thymic cortical epithelial cells, macrophages, and other cells in the thymus are signaled to survive and proceed to negative selection. T cells with a T-cell receptor that binds to no self-MHC class I molecules are signaled to die.

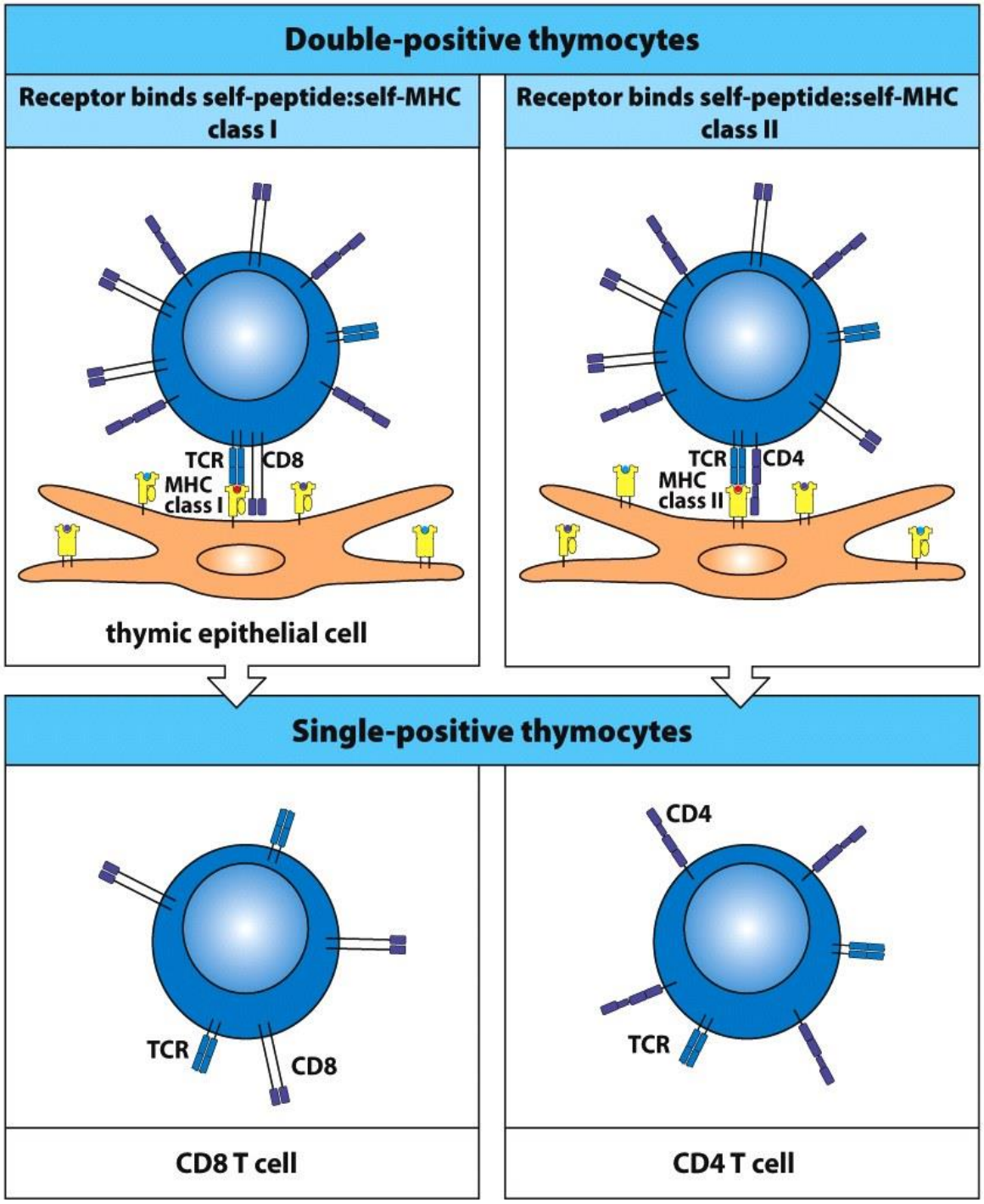


Figure 7.17 Interaction of a double-positive T cell with a self-peptide:self-MHC complex during positive selection determines whether the T cell will become a CD4 or a CD8 T cell. The left panels show the selection of a T cell whose T-cell receptor (TCR) interacts with peptide:MHC class I complexes on a thymic epithelial cell. The right panels show the outcome for a cell bearing a receptor that interacts with peptide:MHC class II complexes.

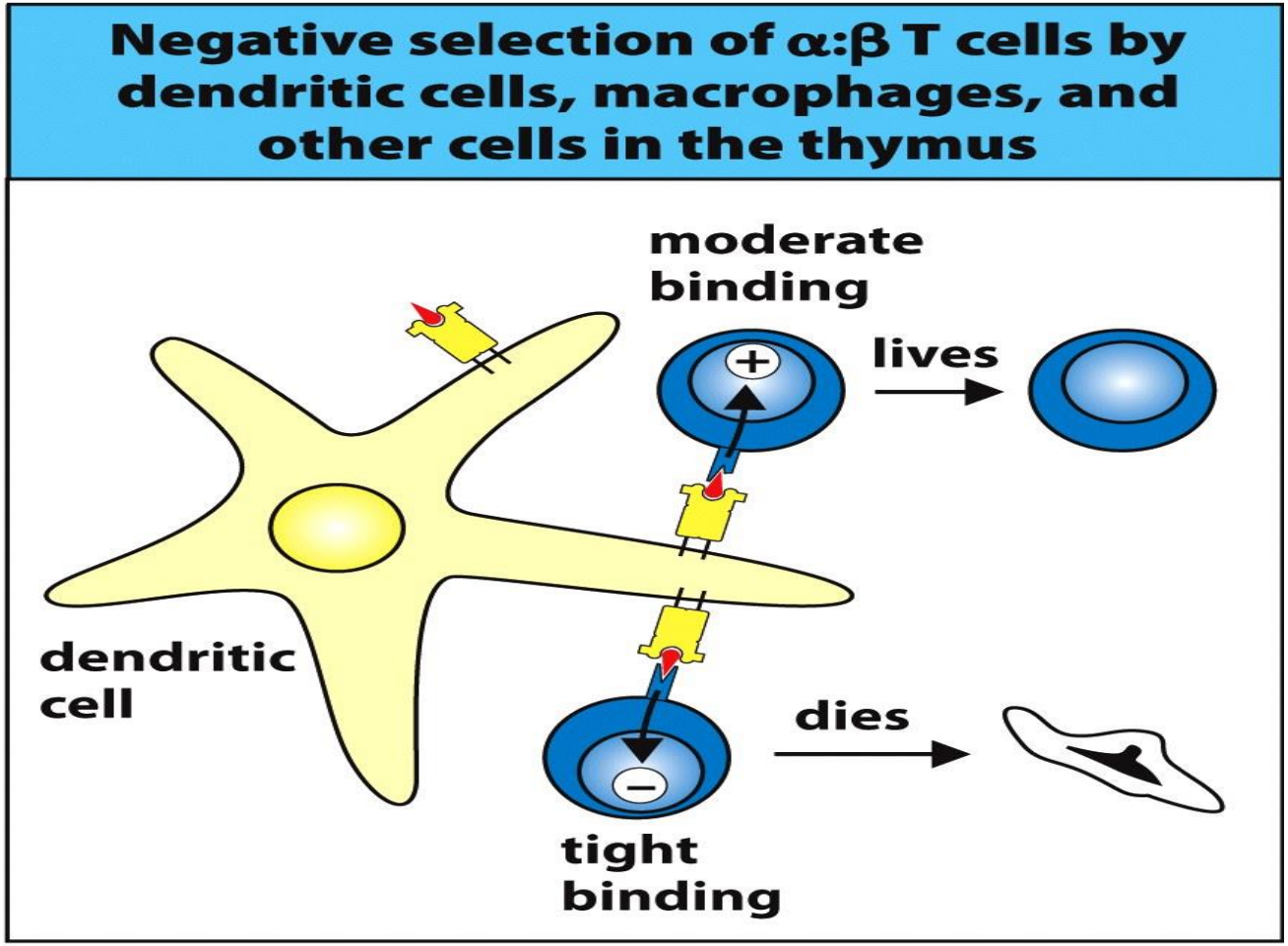


Figure 7.18 Negative selection of T cells in the thymus. T cells with a T-cell receptor (TCR) that binds too tightly to a self-MHC class I molecule on dendritic cells, macrophages, and other cells in the thymus are signaled to die. T cells with a receptor that binds moderately to a self-MHC class I molecule on dendritic cells, macrophages, and other cells in the thymus are signaled to survive, mature, and enter the peripheral circulation.

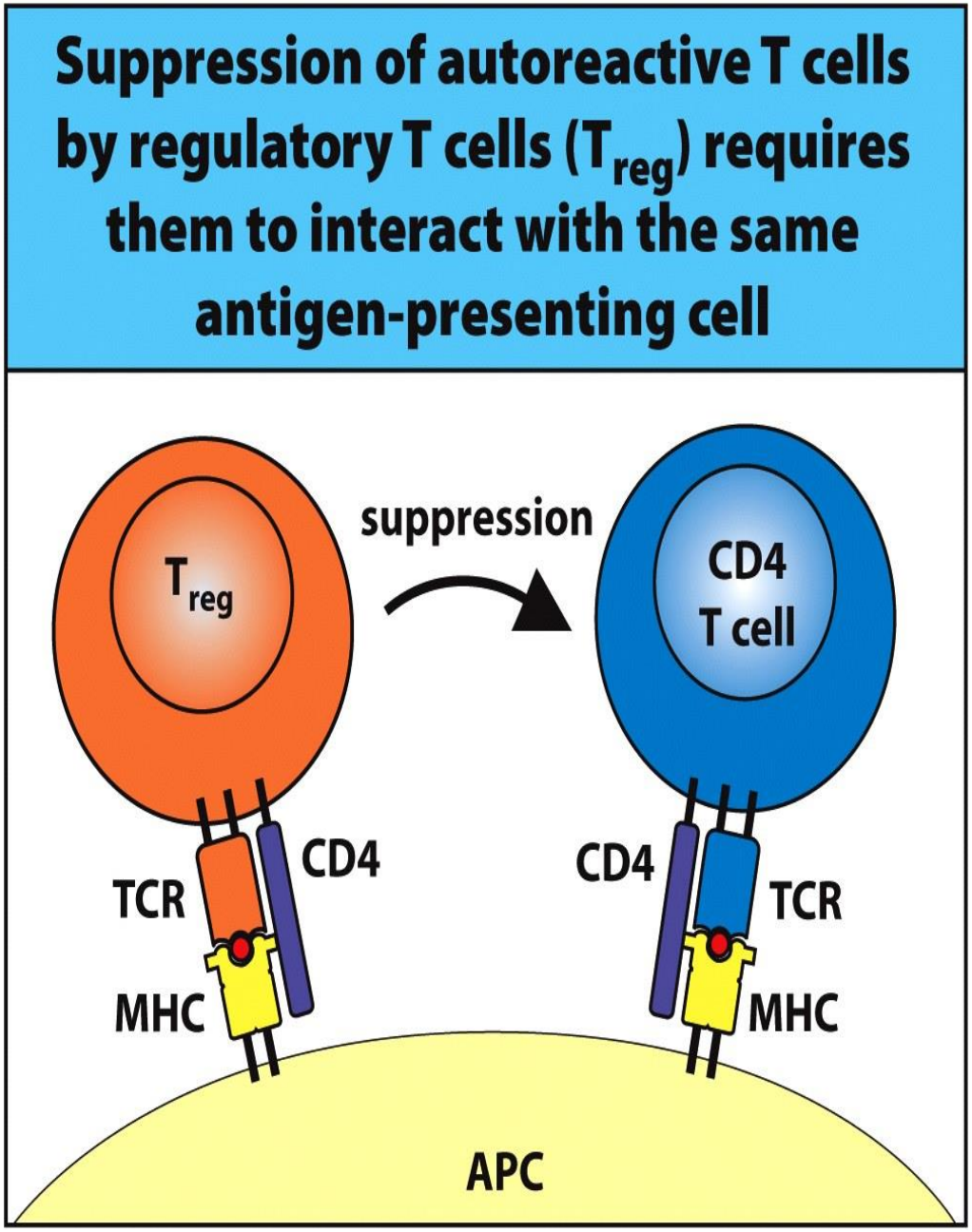
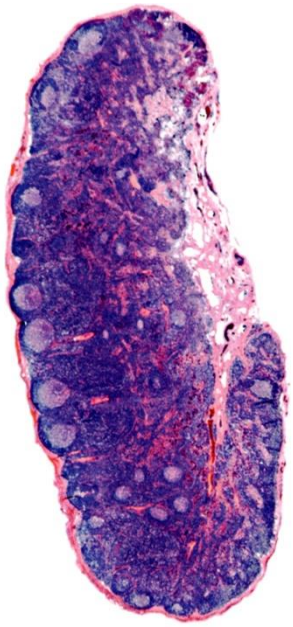


Figure 7.19 Autoreactive regulatory CD4 T cells prevent the proliferation of autoreactive helper CD4 T cells. Suppression of an autoreactive CD4 T cell by a regulatory T cell (T_{reg}) is dependent on the interaction of both T cells with the same antigen-presenting cell (APC).



Chapter 8

T Cell-Mediated Immunity

The lymph node, an example of a secondary lymphoid tissue where adaptive immune responses are produced.

Physiology
or Medicine

Front

Back

The Nobel Prize in 1996

Cell Mediated Immunity in Virus Infections

Peter C. Doherty

Rolf M. Zinkernagel

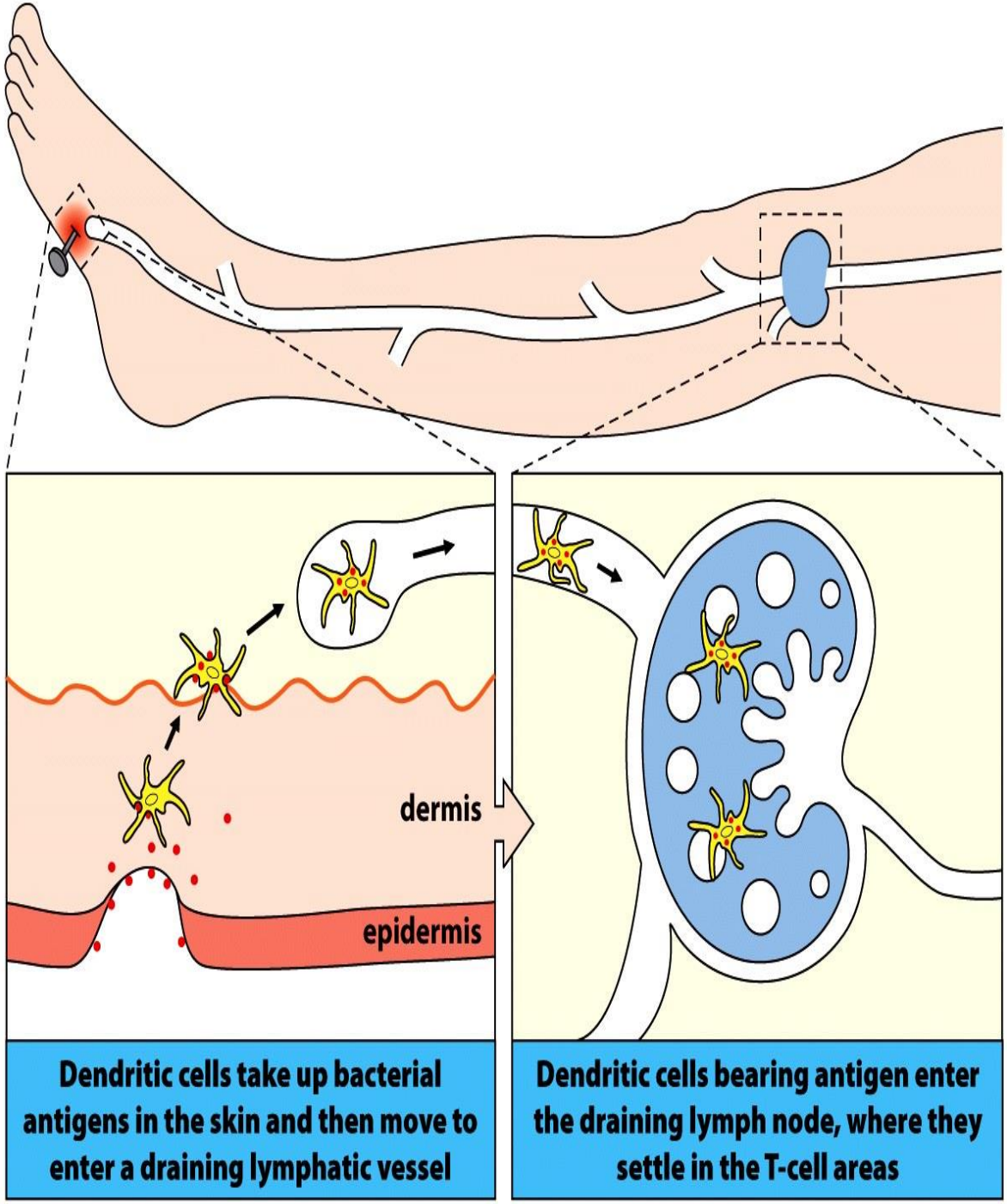
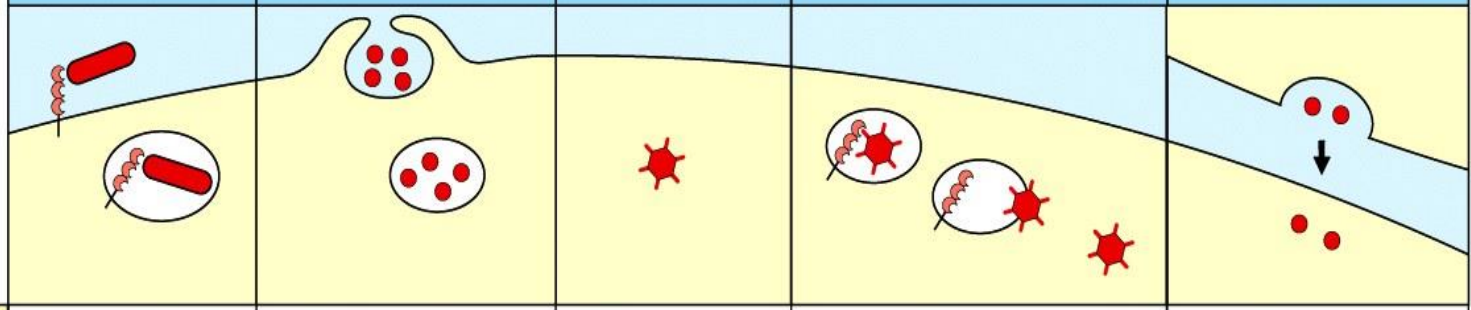


Figure 8.1 Dendritic cells take up antigen in the tissues, migrate to peripheral lymphoid organs, and present foreign antigens to naive T cells. In the example illustrated, of a wound in the skin, immature dendritic cells in the skin, known as Langerhans cells, take up antigen locally and migrate to a nearby lymph node. There they settle in the T-cell areas and differentiate into mature dendritic cells.

Routes of antigen processing and presentation by dendritic cells



	Receptor-mediated endocytosis	Macro-pinocytosis	Viral infection	Cross-presentation after phagocytic or macropinocytic uptake	Transfer from incoming dendritic cell to resident dendritic cell
Type of pathogen presented	Extracellular bacteria	Extracellular bacteria, soluble antigens, virus particles	Viruses	Viruses	Viruses
MHC molecules loaded	MHC class II	MHC class II	MHC class I	MHC class I	MHC class I
Type of naive T cell activated	CD4 T cells	CD4 T cells	CD8 T cells	CD8 T cells	CD8 T cells

Figure 8.3 Dendritic cells use several pathways to process and present protein antigens. Uptake of antigens by phagocytosis or macropinocytosis delivers antigens to endocytic vesicles for presentation by MHC class II molecules to CD4 T cells (first two panels). Viral infection of the dendritic cell delivers peptides processed in the cytosol to the endoplasmic reticulum for presentation by MHC class I molecules to CD8 T cells (third panel). Viral particles taken up by the 'class II' pathways of phagocytosis and macropinocytosis can be delivered to the cytosol for processing and presentation to CD8 T cells by MHC class I (fourth panel). The mechanism of this cross-presentation is poorly understood. Lastly, antigens taken up by one dendritic cell can be delivered to a second dendritic cell for presentation by MHC class I molecules to CD8 T cells (fifth panel).

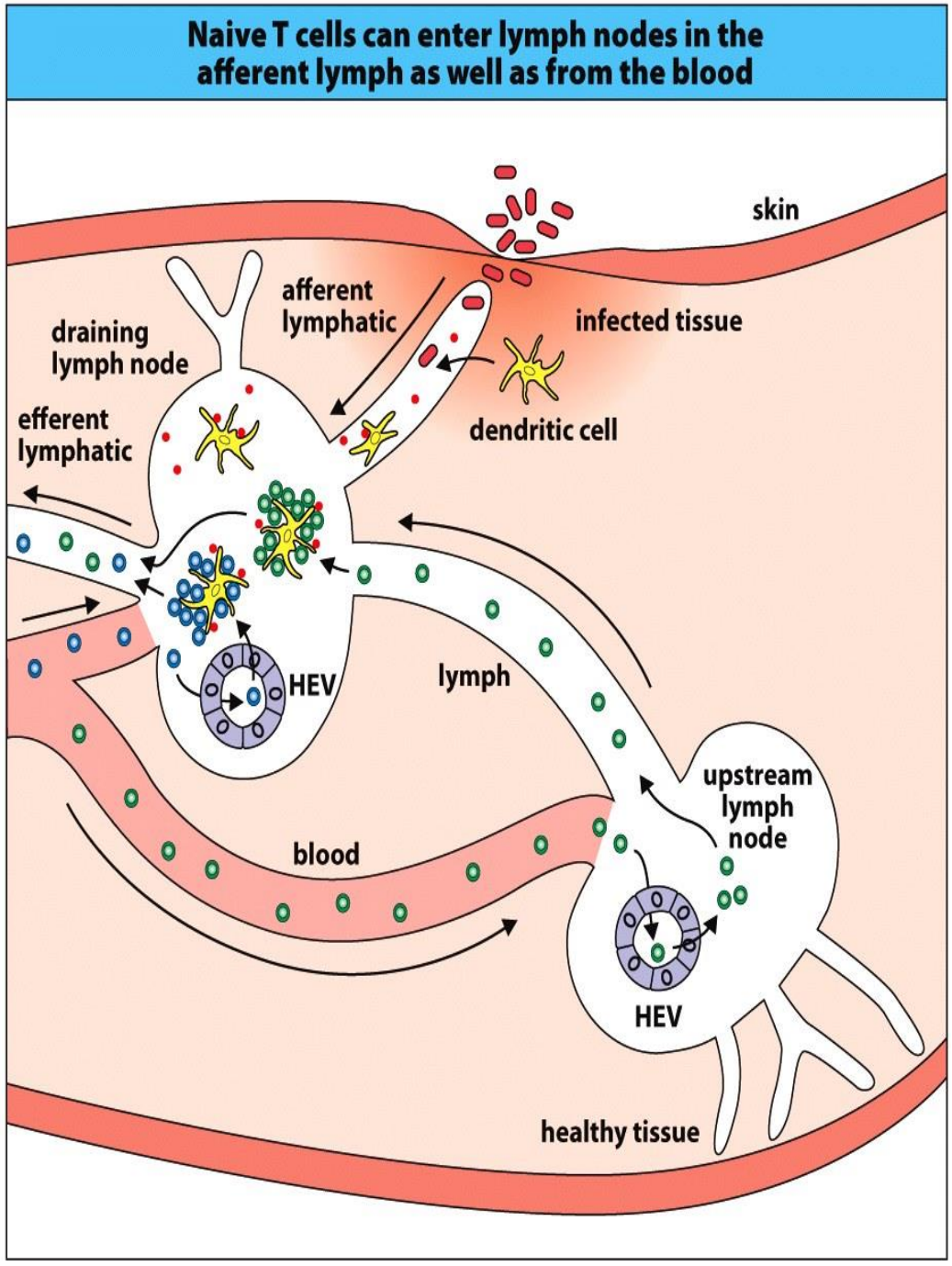


Figure 8.5 Naive T cells can enter lymph nodes from the blood or from the lymph. Recirculating naive T cells can enter a lymph node either directly from the blood or by moving from one lymph node to another via the lymphatics that connect them. In the case illustrated here, pathogen-specific T cells (blue) in the blood enter a lymph node that is draining an infected tissue. They encounter pathogen antigens, are activated, and leave as effector cells in the afferent lymphatic. At the same time, other pathogen-specific T cells (green) in the blood enter an 'upstream' lymph node that is draining healthy tissue. They do not encounter their antigen there, but they can be carried to the infected lymph node via a connecting lymphatic vessel. There they, too, will become activated by pathogen antigens.

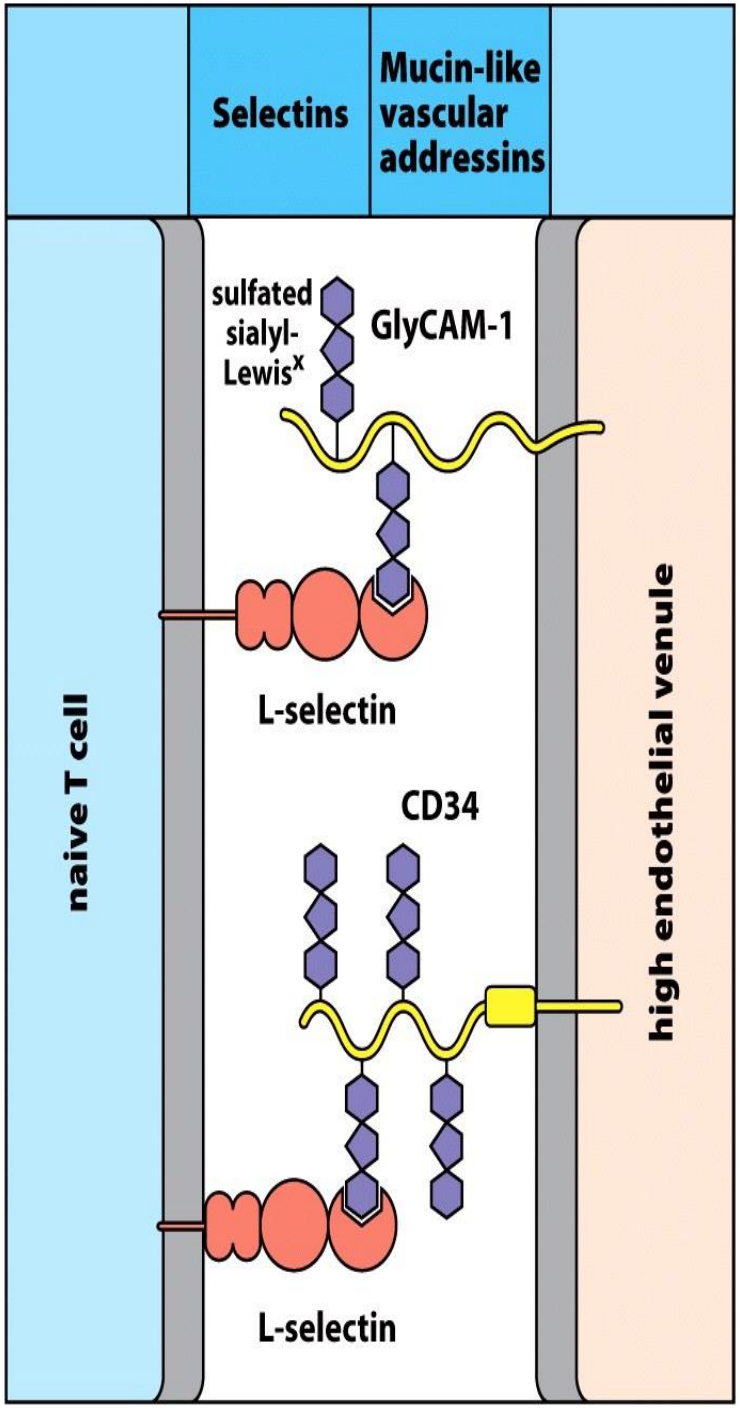


Figure 8.6 Binding of L-selectin to mucin-like vascular addressins directs naive lymphocyte homing to lymphoid tissues. L-selectin on naive T cells and naive B cells binds to sulfated carbohydrate sialyl-Lewis^x moieties of vascular addressins CD34 and GlyCAM-1 on the high endothelial cells of lymph venules.

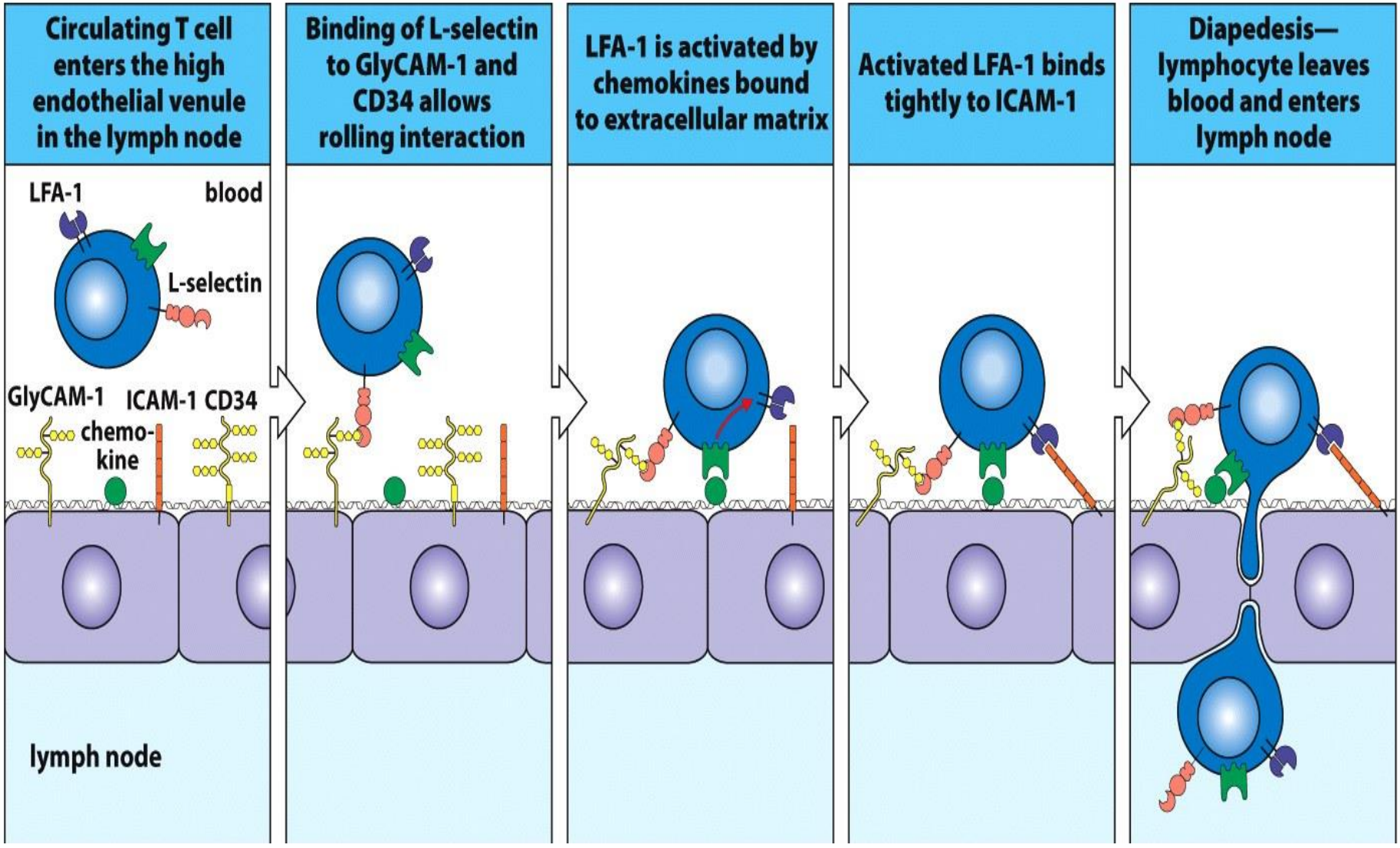


Figure 8.7 Naive T and B lymphocytes circulate in the blood and enter lymph nodes by crossing high endothelial venules. Lymphocytes bind to high endothelium in the lymph node through the interaction of L-selectin with vascular addressins. Chemokines, which are also bound to the endothelium, activate the integrin LFA-1 on the lymphocyte surface, enabling it to bind tightly to ICAM-1 on the endothelial cell. Establishment of tight binding allows the lymphocyte to squeeze between two endothelial cells, leaving the lumen of the blood vessel and entering the lymph node proper.

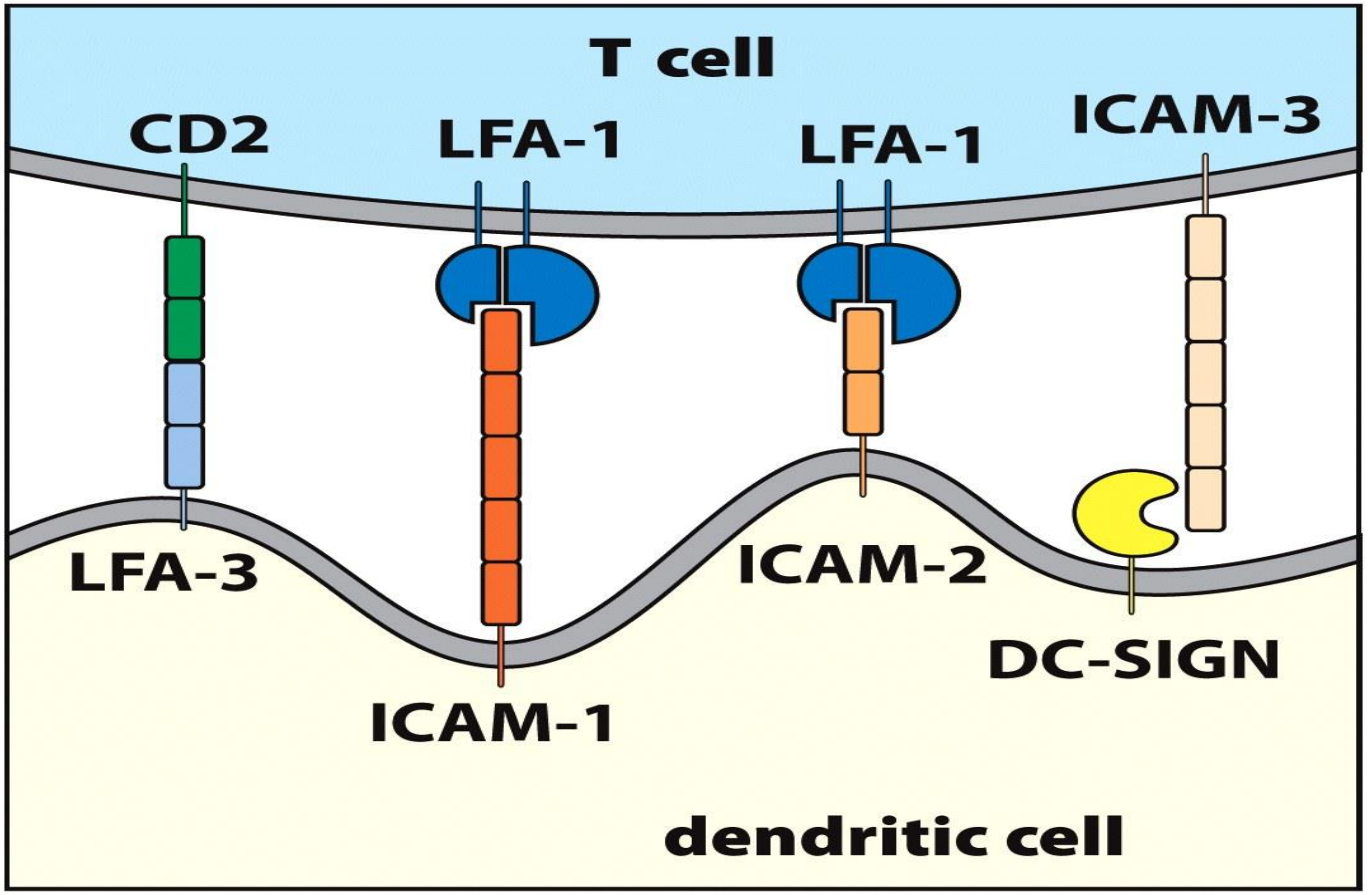


Figure 8.8 Cell-surface molecules of the immunoglobulin superfamily initiate lymphocyte adhesion to professional antigen-presenting cells. In the initial encounter of T cells with antigen-presenting dendritic cells, CD2, binding to LFA-3 on the antigen-presenting cell, synergizes with LFA-1 binding to ICAM-1 and ICAM-2. An interaction that seems to be exclusive to the interaction of naive T cells with dendritic cells is that between ICAM-3 on the naive T cell and DC-SIGN, a C-type lectin specific to dendritic cells, which binds ICAM-3 with high affinity.

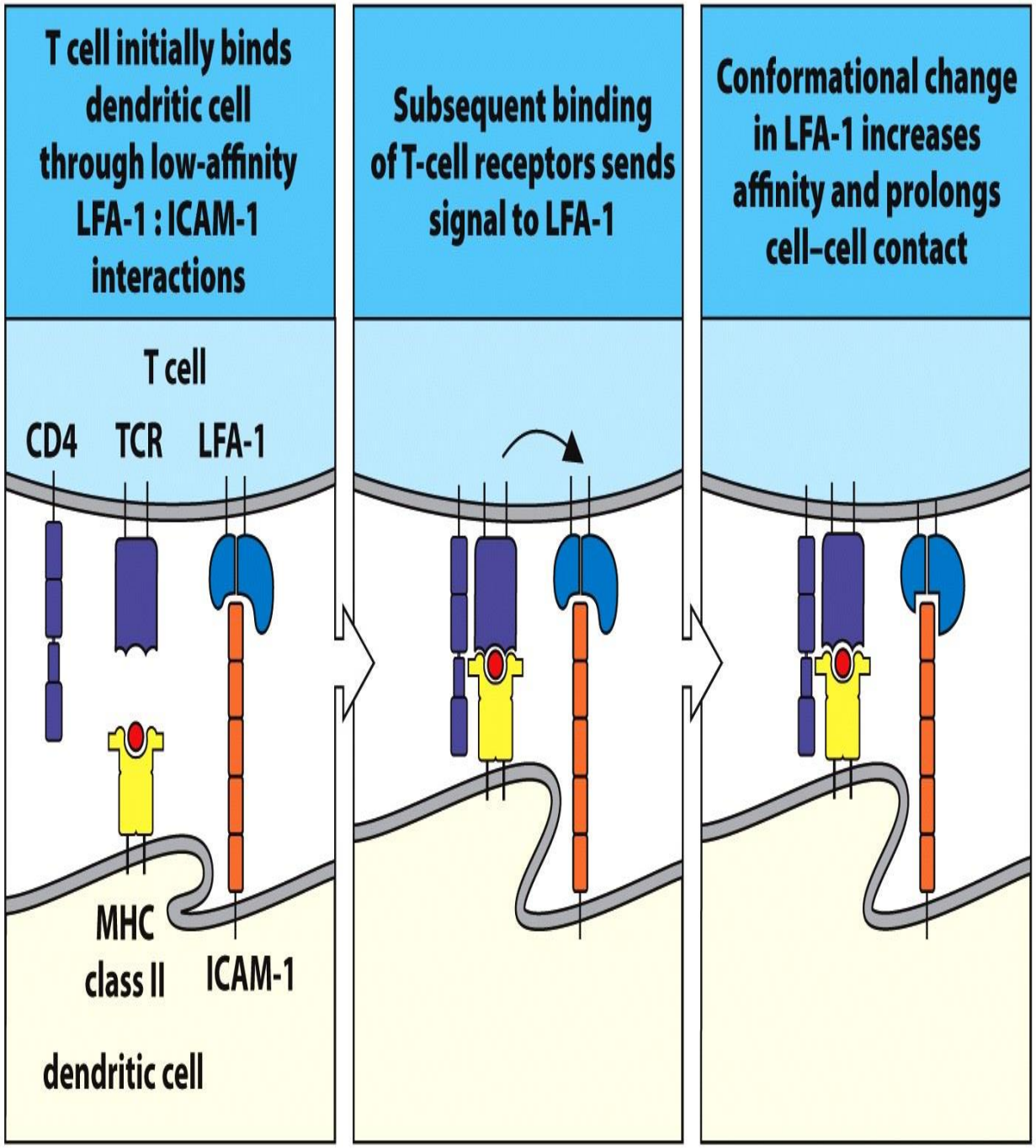


Figure 8.9 Transient adhesive interactions between T cells and dendritic cells are stabilized by specific antigen recognition. When a T cell binds to its specific ligand on an antigen-presenting dendritic cell, intracellular signaling through the T-cell receptor (TCR) induces a conformational change in LFA-1 that causes it to bind with higher affinity to ICAMs on the antigen-presenting cell. The T cell shown here is a CD4 T cell.

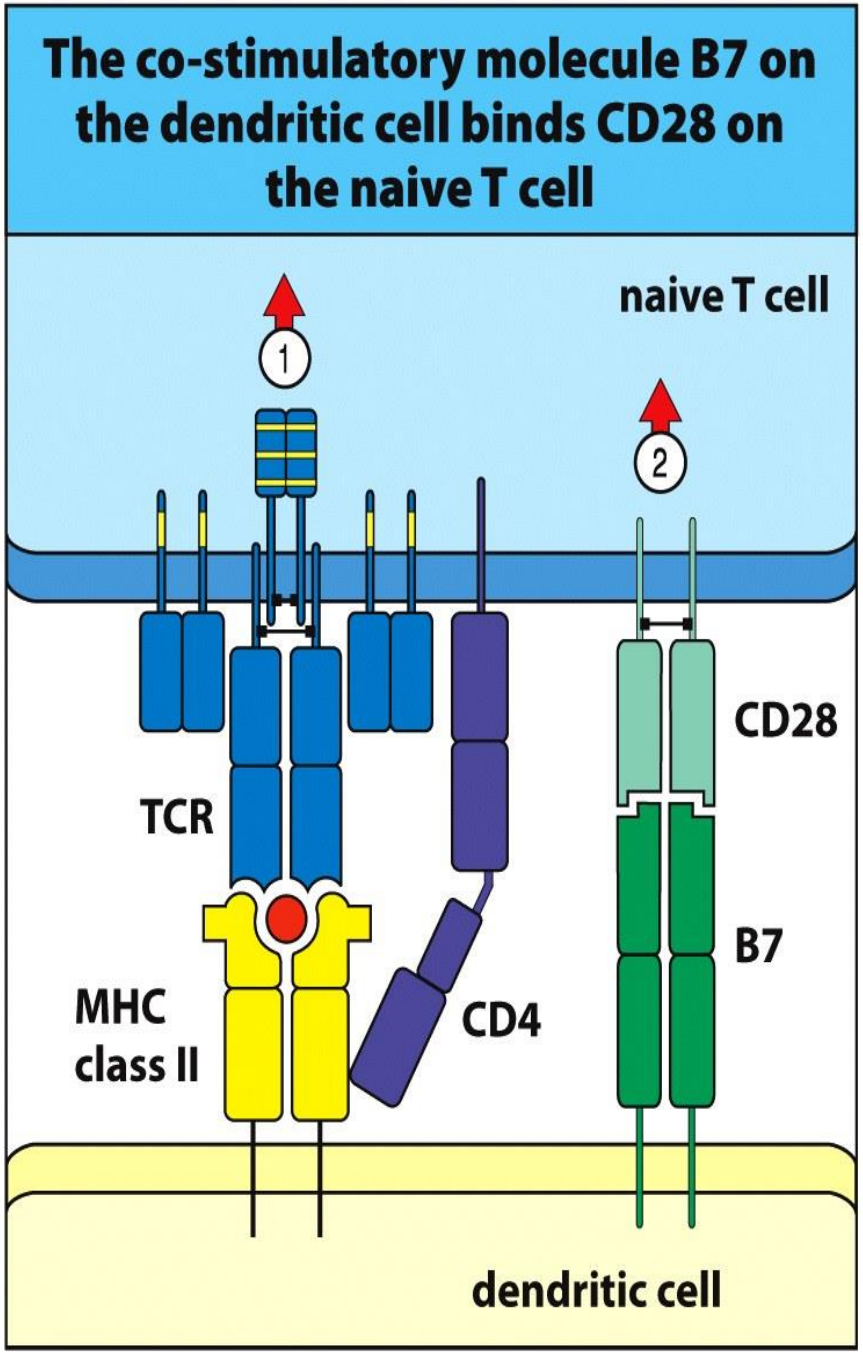


Figure 8.10 The principal co-stimulatory molecules on professional antigen-presenting cells are B7 molecules, which bind CD28 proteins on the T-cell surface. Binding of the T-cell receptor and its co-receptor CD4 to the peptide:MHC class II complex on the dendritic cell delivers a signal (arrow 1). This signal induces clonal expansion of T cells only when the co-stimulatory signal (arrow 2) is also given by the binding of CD28 to B7. Both CD28 and B7 are members of the immunoglobulin superfamily. There are two forms of B7, called B7.1 (CD80) and B7.2 (CD86), but their functional differences have yet to be understood.

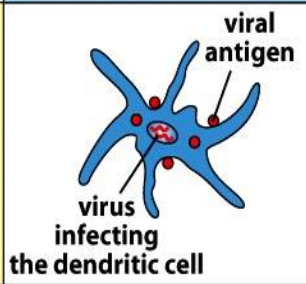
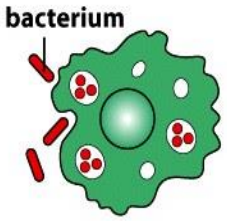
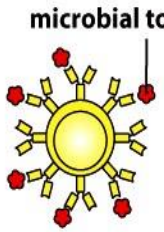
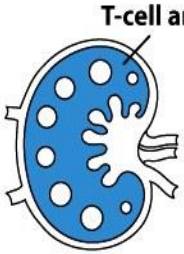
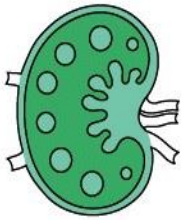
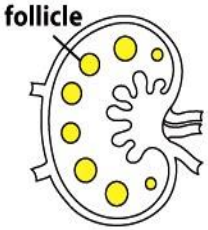
	Professional antigen-presenting cells		
	Dendritic cell	**Macrophage**	**B cell**
Cell type			
Location in lymph node			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Ubiquitous throughout the body	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood

Figure 8.11 Three types of professional antigen-presenting cell populate different parts of the lymph node. Dendritic cells are situated in the T-cell areas of the lymph-node cortex, whereas macrophages are distributed throughout the lymph node. B cells populate mainly the follicles. These distributions reflect differences in the functions of the three types of professional antigen-presenting cell.

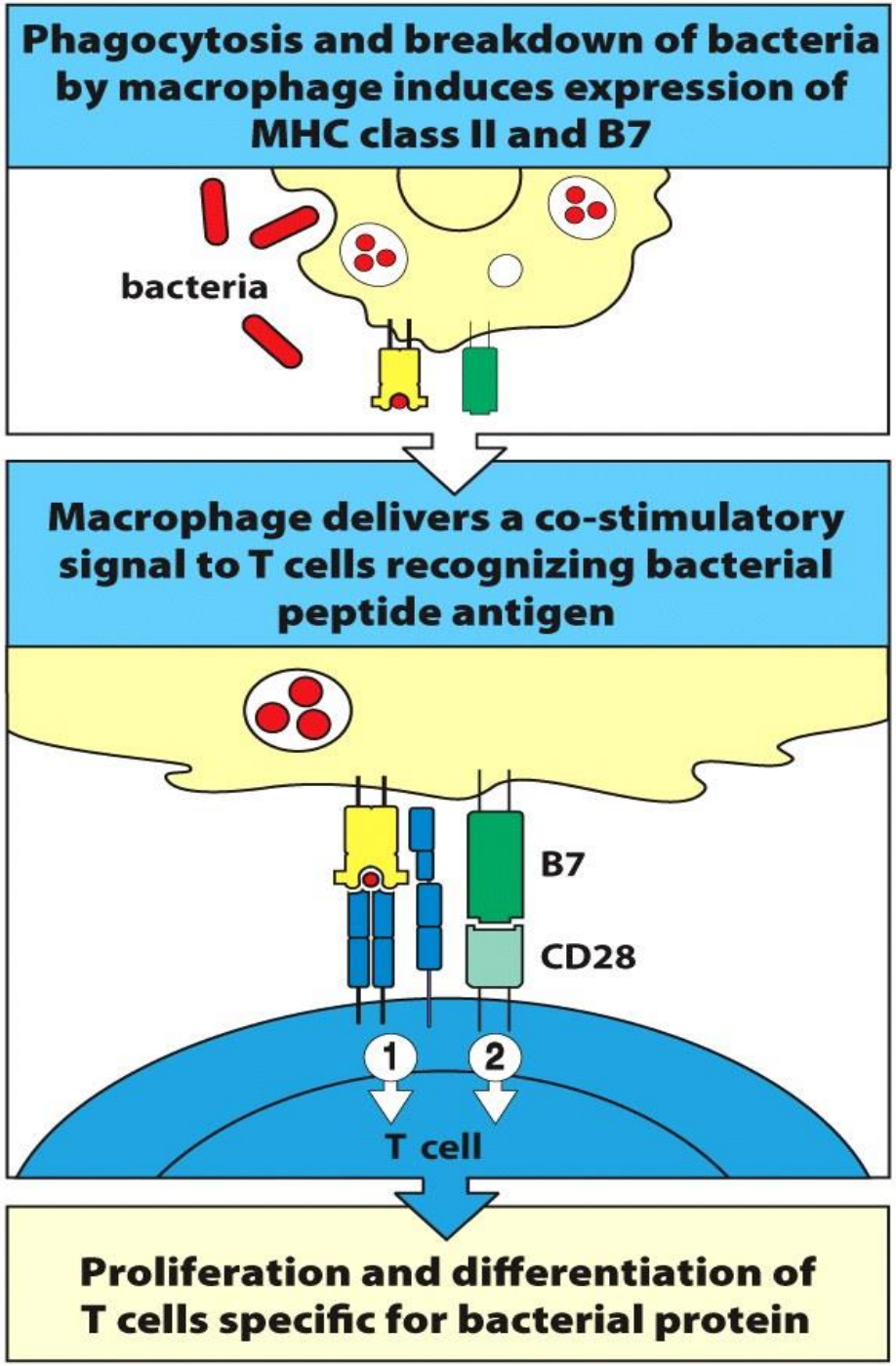


Figure 8.13 Microbial substances induce co-stimulatory activity in macrophages. Phagocytosis of bacteria by macrophages and their breakdown in the phagolysosomes lead to the release of substances such as bacterial lipopolysaccharide, which induce the expression of co-stimulatory B7 molecules on the surface of the macrophage. Peptides derived from the degradation of bacterial proteins in the macrophage vesicular system are bound by MHC class II molecules and presented on the macrophage surface. Activation of naive T cells is accomplished by the combination of B7 binding to CD28 and peptide:MHC complexes binding to the T-cell receptor.

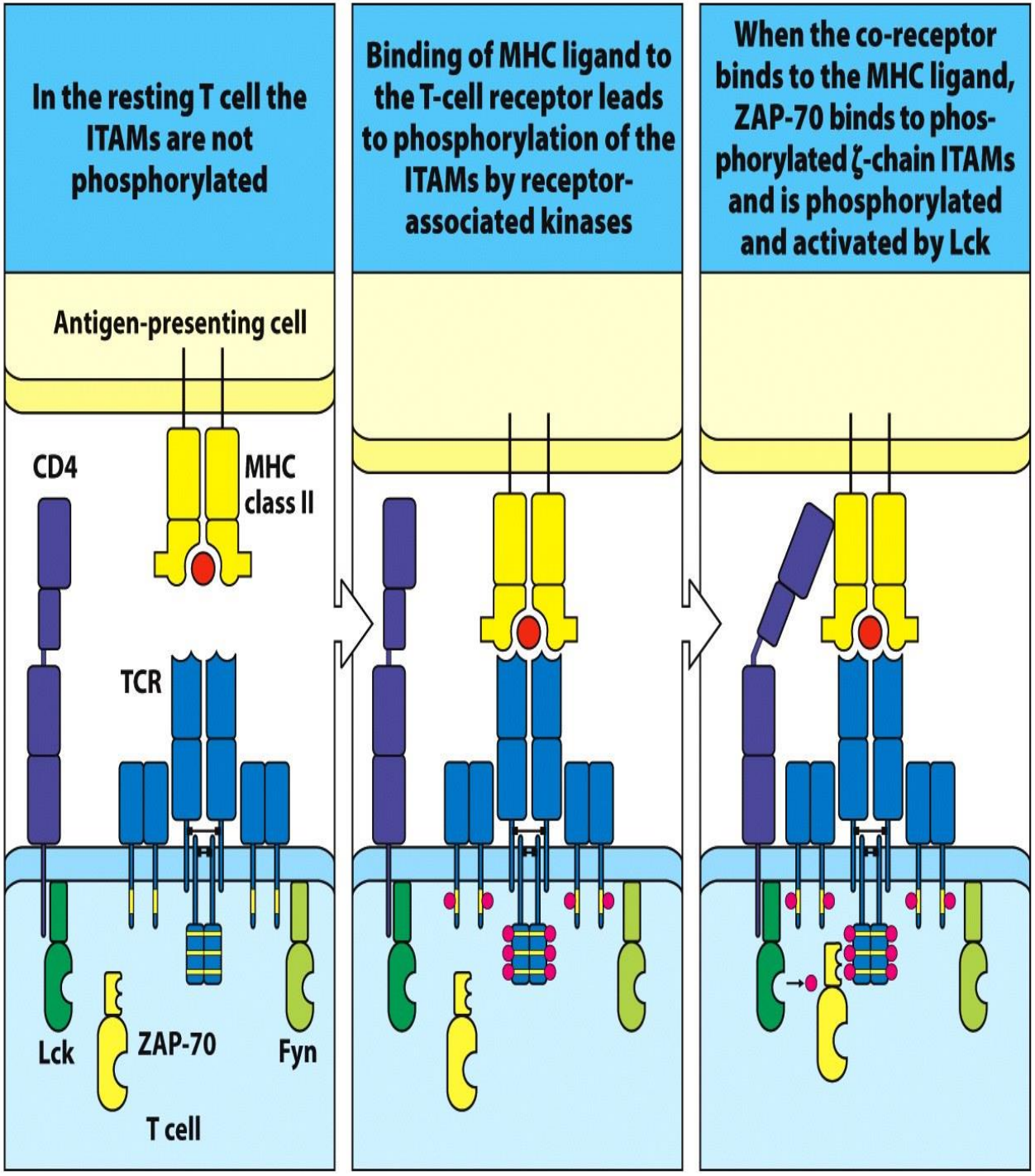


Figure 8.14 Clustering of the T-cell receptor and a co-receptor initiates signaling within the T cell. When T-cell receptors become clustered on binding peptide:MHC complexes on the surface of an antigen-presenting cell, activation of receptor-associated kinases, such as Fyn, leads to phosphorylation of the CD3γ, δ, and ε ITAMs (yellow, with phosphorylated tyrosines shown as small red circles) as well as those on the ζ chain. The tyrosine kinase ZAP-70 binds to the phosphorylated ITAMs of the ζ chain but is not activated until the co-receptor binds to the MHC molecule on the antigen-presenting cell (here shown as CD4 binding to an MHC class II molecule), which brings the kinase Lck into the complex. This phosphorylates and activates ZAP-70.

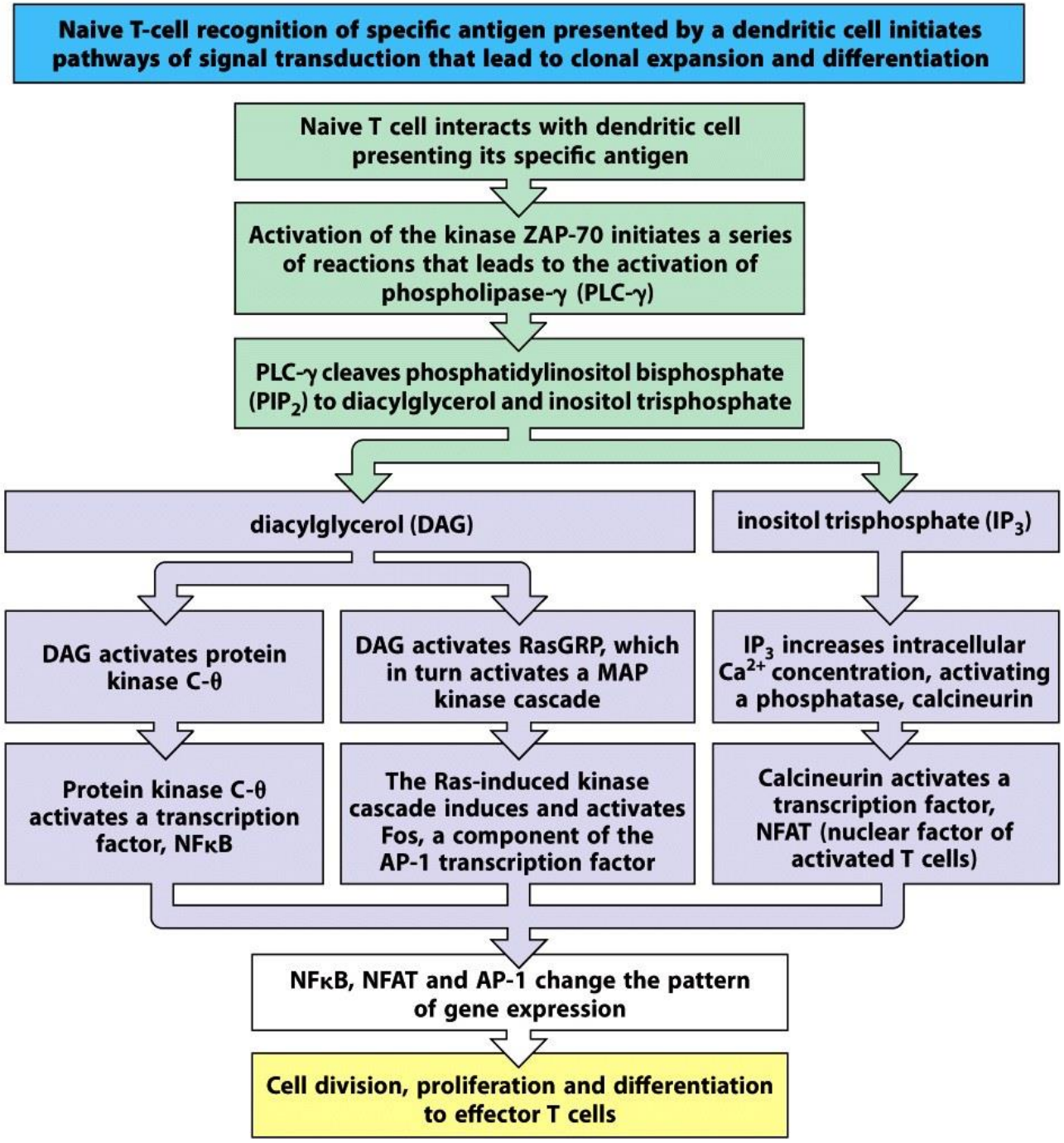


Figure 8.16 Simple outline of the intracellular signaling pathways initiated by the T-cell receptor complex, its CD4 co-receptor, and CD28. Similar pathways operate in CD8 T cells, as CD8, like CD4, interacts with Lck.

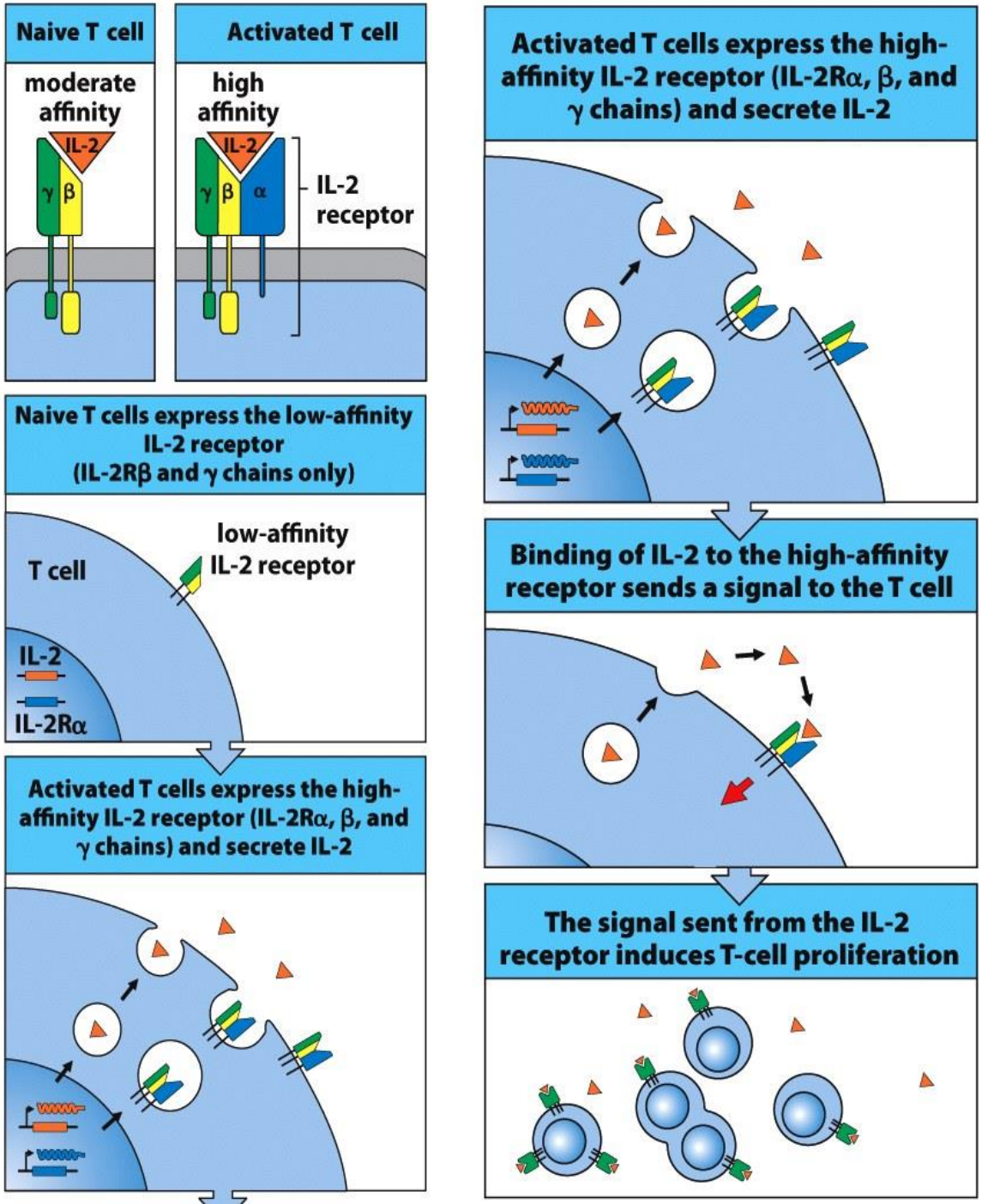


Figure 8.17 Activated T cells secrete and respond to interleukin-2 (IL-2).

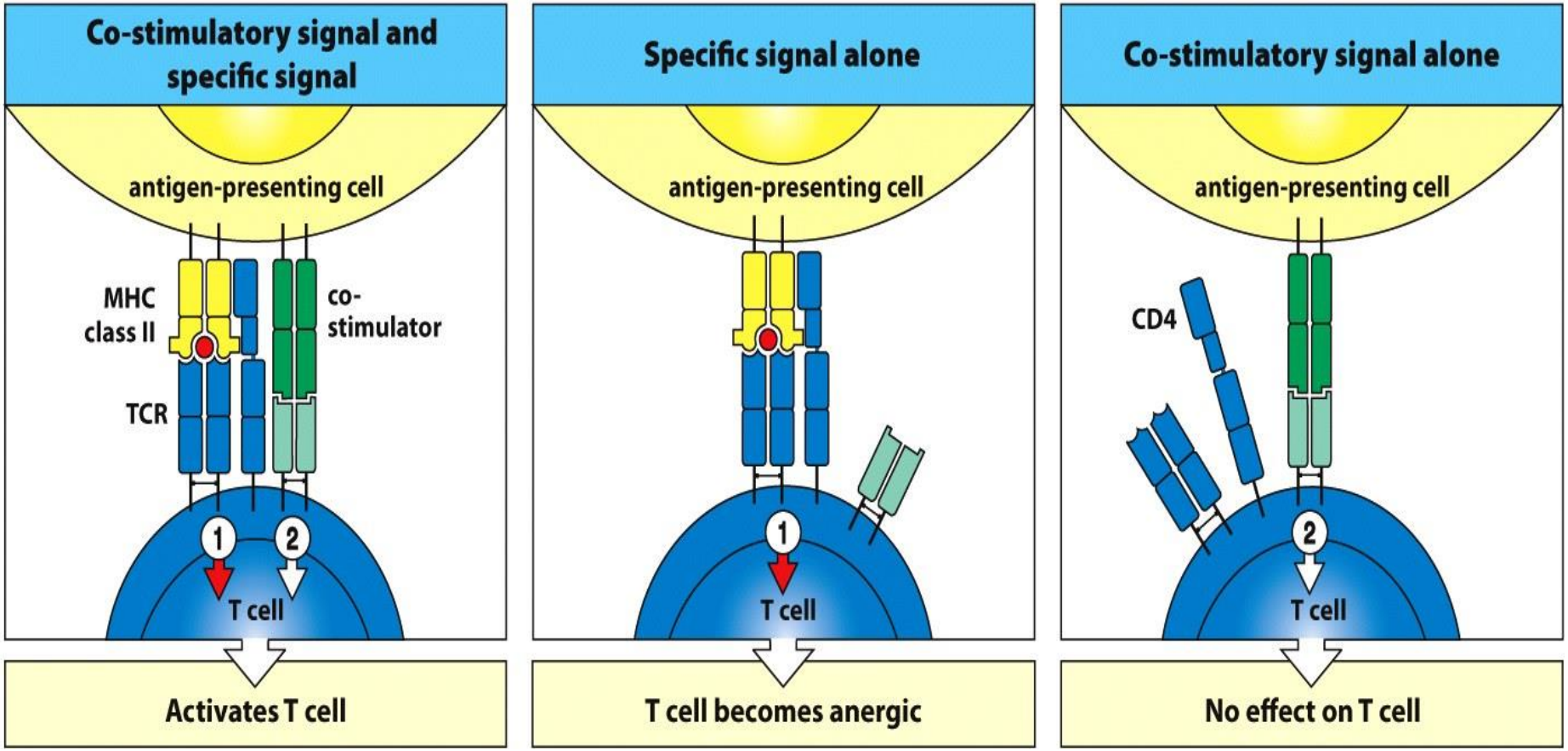


Figure 8.18 T-cell tolerance to antigens expressed on non-professional antigen-presenting cells results from antigen recognition in the absence of co-stimulation. A naive T cell can be activated only by an antigen-presenting cell carrying both a specific peptide:MHC complex and a co-stimulatory molecule on its surface. This combination results in the naive T cell's receipt of signal 1 from the T-cell receptor and signal 2 from the co-stimulator (left panel). When the antigen-presenting cell has the specific peptide:MHC complex to deliver signal 1, but no co-stimulator to deliver signal 2, the T cell enters a nonresponsive state called anergy (center panel). When the antigen-presenting cell has a co-stimulator to deliver signal 2, but no specific peptide:MHC complex to deliver signal 1, the naive T cell neither responds nor becomes anergic (right panel).

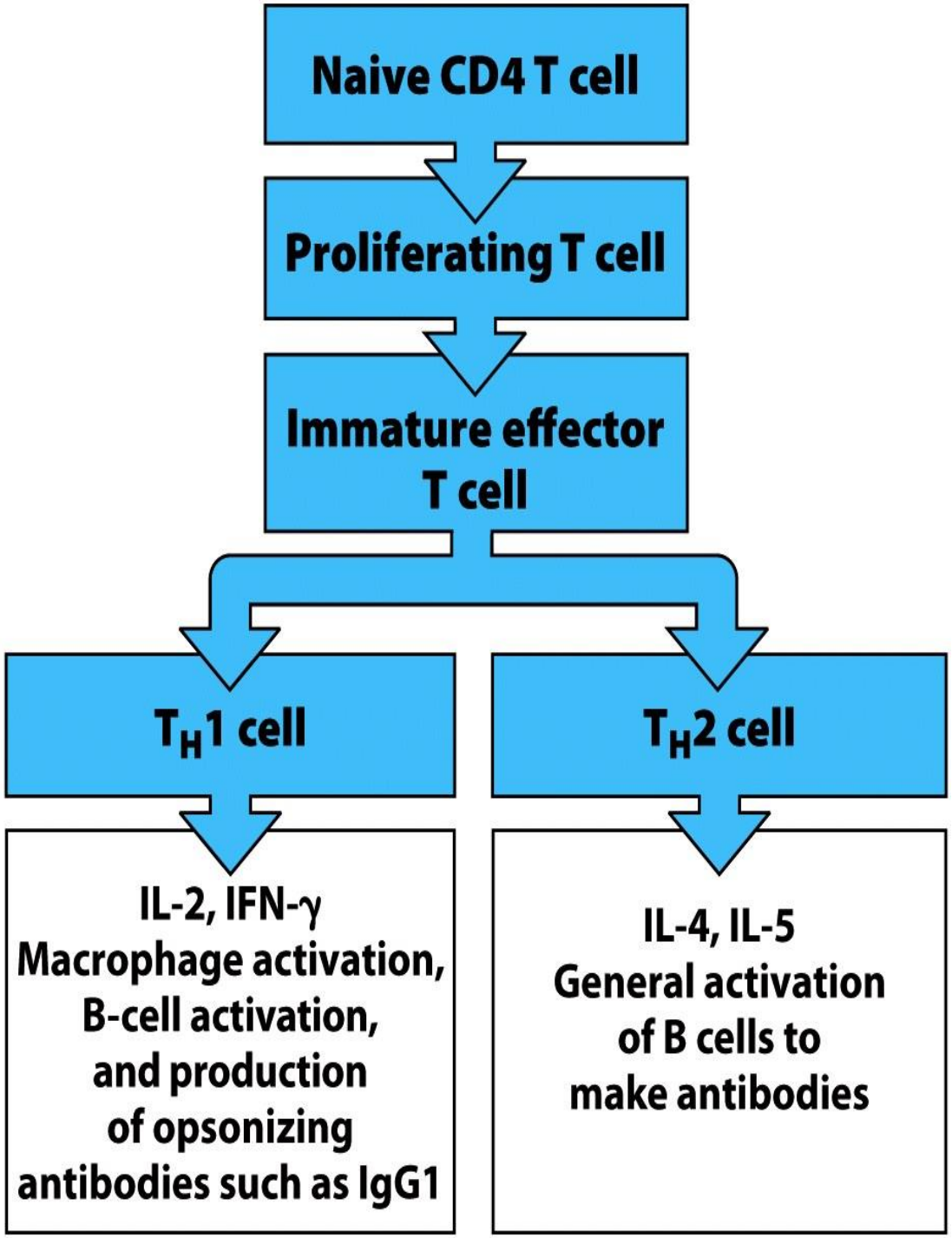


Figure 8.19 The stages of activation of CD4 T cells. Naive CD4 T cells first respond to peptide:MHC class II complexes by synthesis of IL-2 and proliferation. The progeny cells have the potential to become either T_H1 or T_H2 cells.

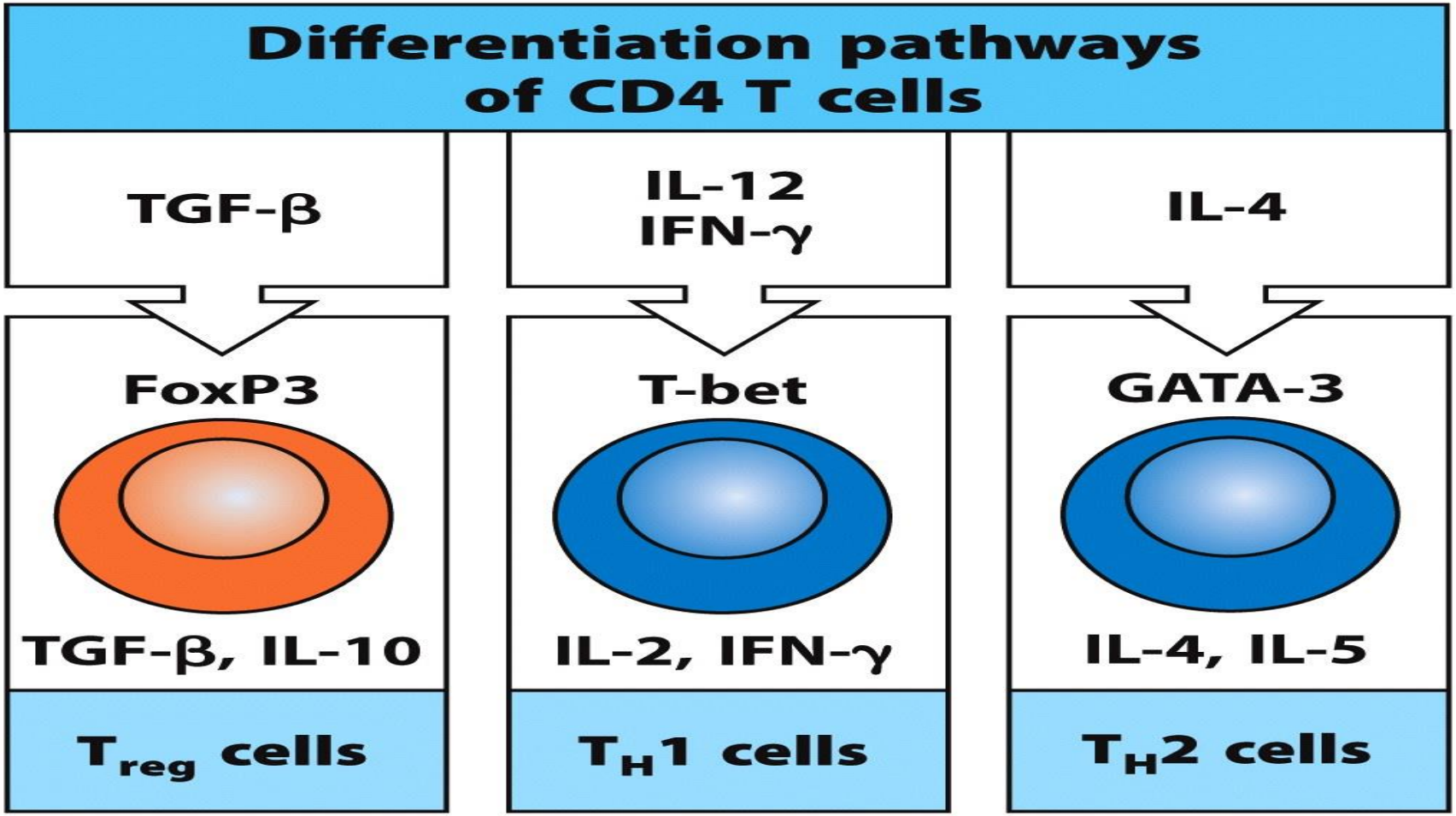


Figure 8.20 Different cytokine environments drive the differentiation of CD4 T cells that make different cytokines and have different functions. The principal cytokines that induce each type of effector T cell are shown in the top panels, the transcription factors that characterize these cell types are shown immediately above the cell, and the cytokines that the differentiated T cells produce are shown underneath. Differentiation of T_H1 and T_H2 is described in the text. The T_{reg} cells shown here are the regulatory CD4 T cells described in Section 7-13 (p. 203), whose function is to keep the activity of other effector T cells in check and prevent autoimmunity.

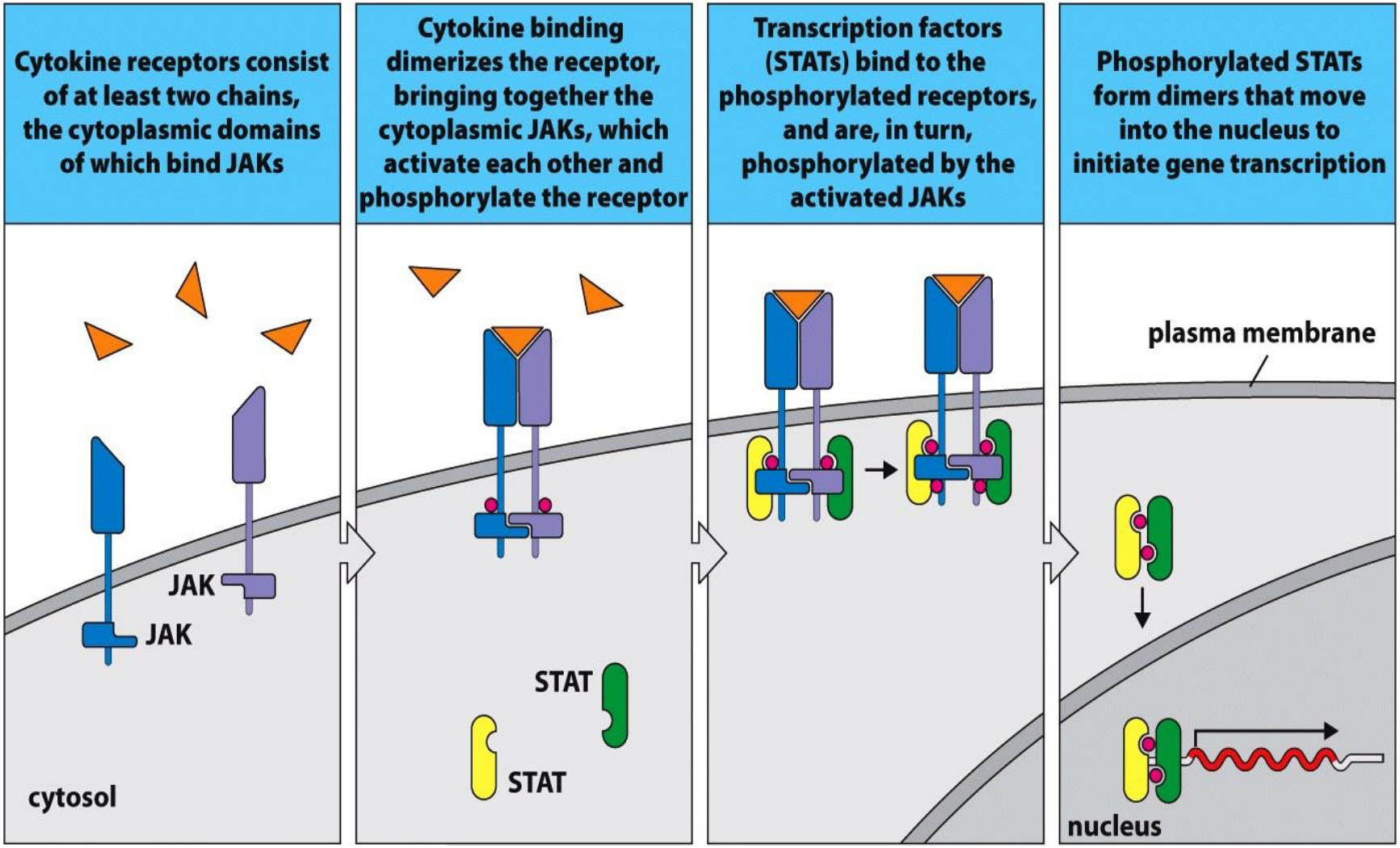


Figure 8.26 Many cytokine receptors signal through a pathway in which receptor-associated kinases activate transcription factors directly. These receptors consist of at least two chains, each associated with a specific Janus kinase (JAK) (first panel). Ligand binding and dimerization of the receptor chains brings together the JAKs, which transactivate each other, subsequently phosphorylating tyrosines in the receptor tails (second panel). Members of the STAT (signal transducer and activator of transcription) family of proteins bind to the phosphorylated receptors and are themselves phosphorylated by the JAKs (third panel). On phosphorylation, STAT proteins dimerize and go to the nucleus, where they activate transcription from a variety of genes important for adaptive immunity (fourth panel).

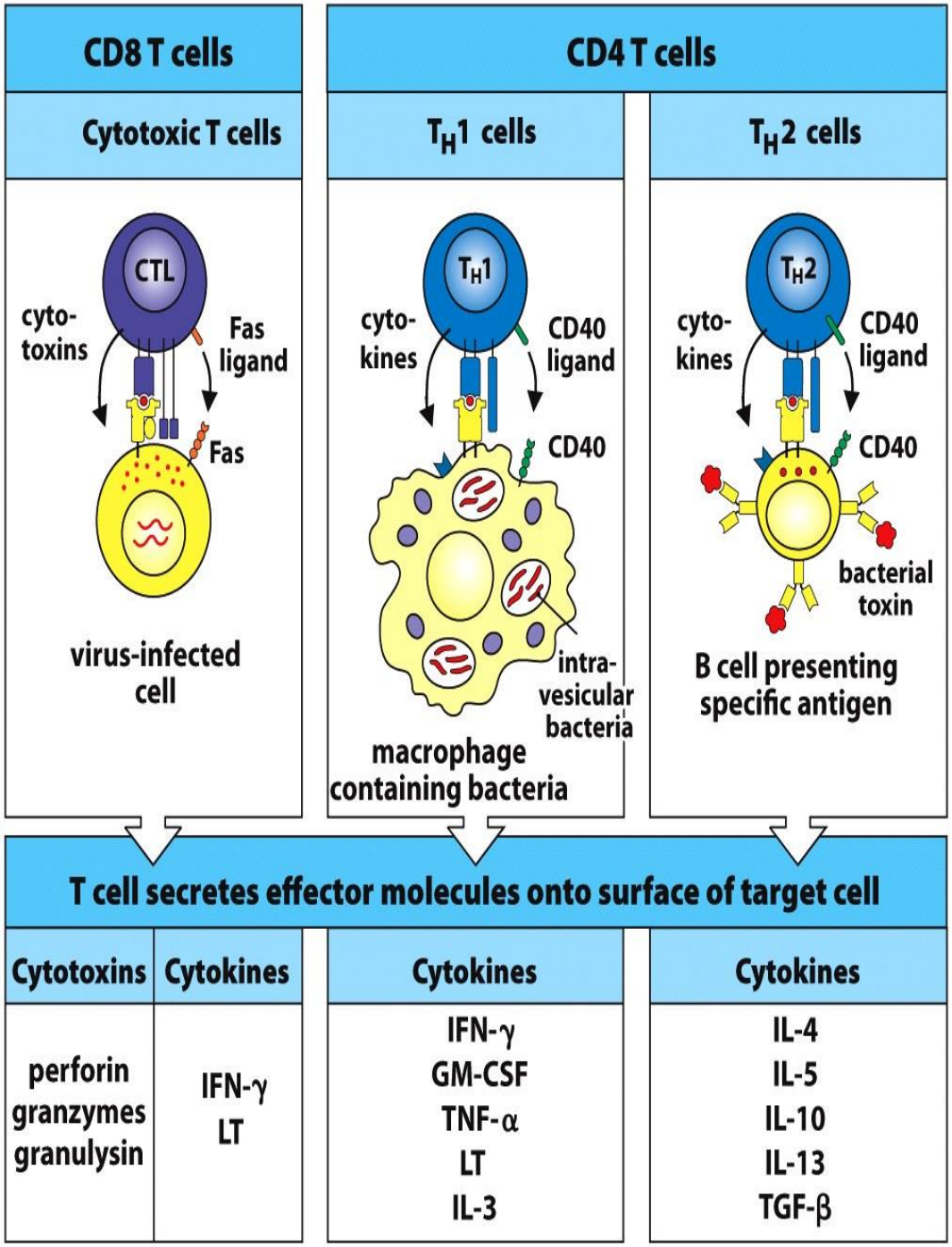


Figure 8.27 The three types of effector T cell produce distinct sets of effector molecules. The three main types of effector T cell are shown, as are the types of target cell with which they interact, and the effector molecules that they make.