Lecture VIII

Cell-mediated immunity

Regulation of the immune response

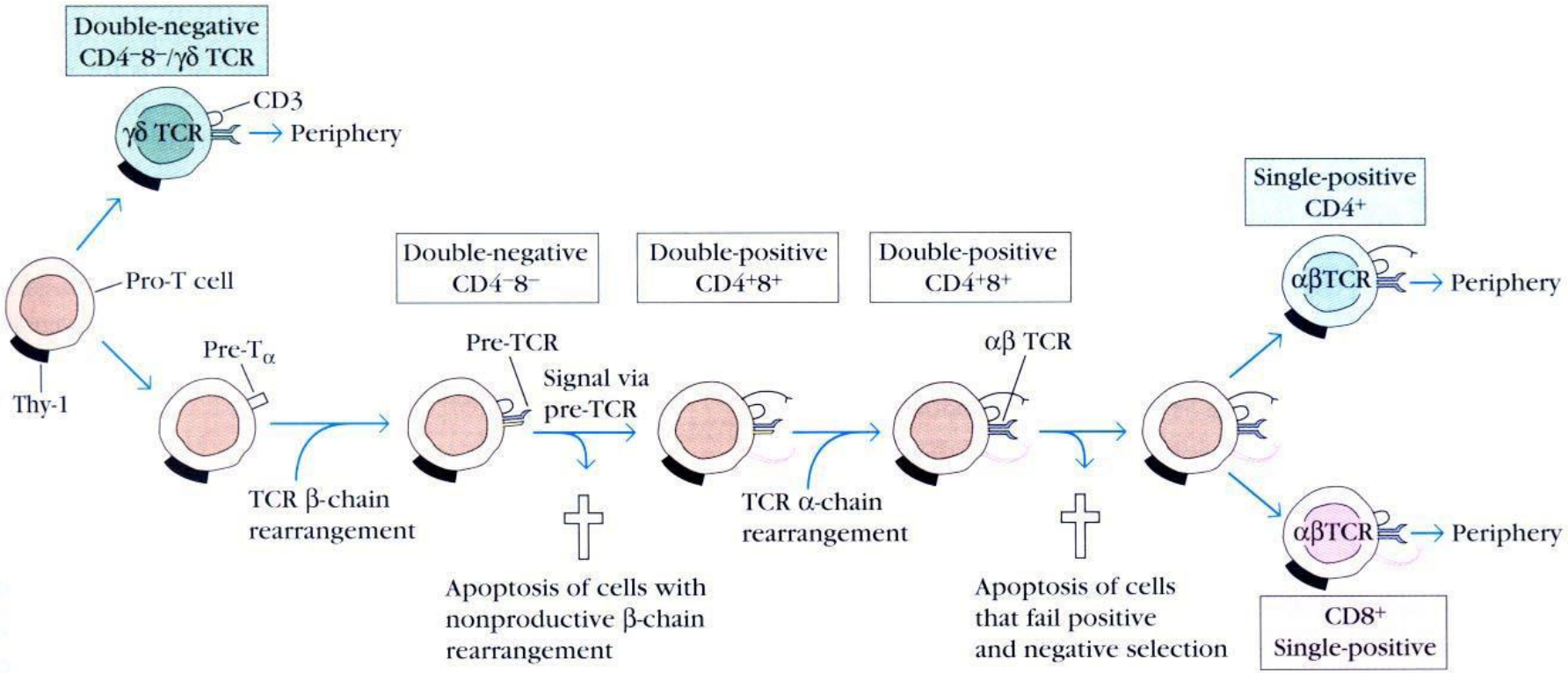


FIGURE 12-2

Proposed pathways for T-cell development in the thymus. Most of the immature thymocytes in the thymus die either because they make an unproductive TCR-gene rearrangement or because they fail positive or negative selection. Three mature T-cell populations (green, pink, blue) are produced and move to the peripheral lymphoid organs. The vast majority of peripheral T cells express the $\alpha\beta$ TCR and either CD4 (blue) or CD8 (pink). A few T cells express the $\gamma\delta$ TCR (green); most of these lack both CD4 and CD8. [Adapted from B. J. Fowlkes and D. M. Pardoll, 1989, *Adv. Immunol.* **44**:207.]

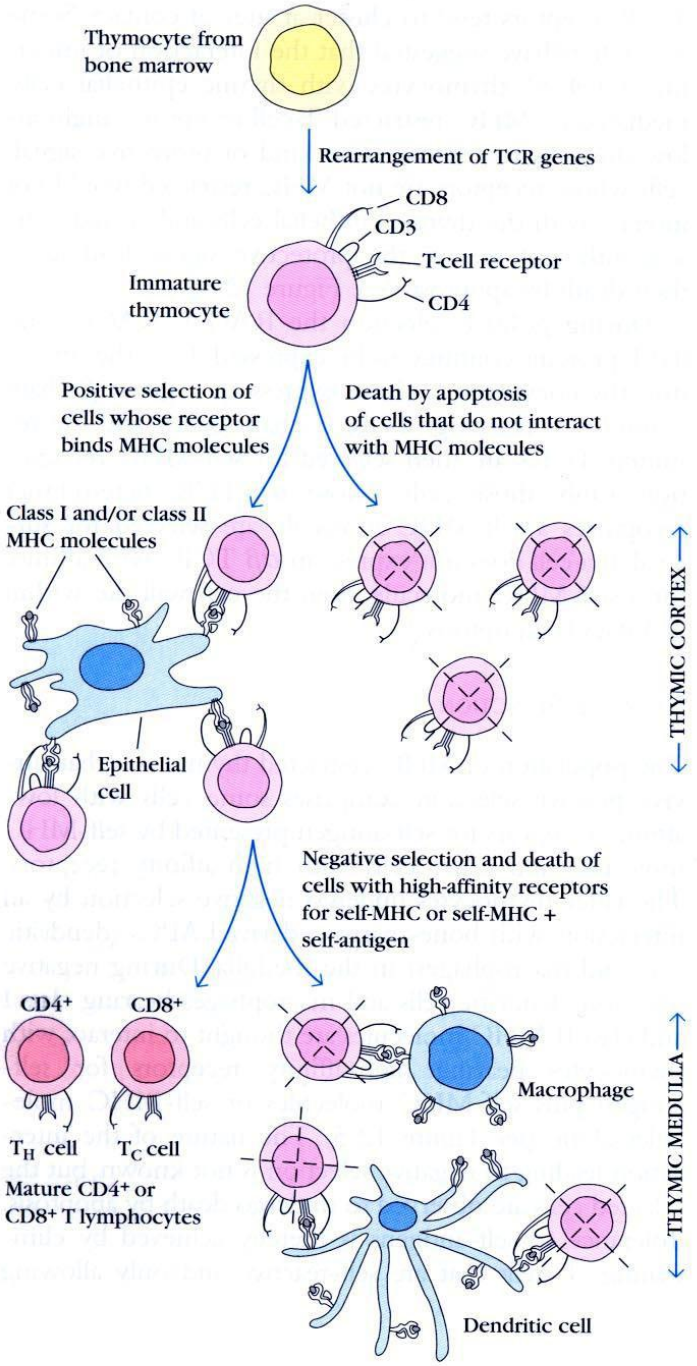


FIGURE 12-5

Positive and negative selection of thymocytes in the thymus. Because of thymic selection, which involves thymic stromal cells (epithelial cells, dendritic cells, and macrophages), mature T cells are both self-MHC restricted and self-tolerant.

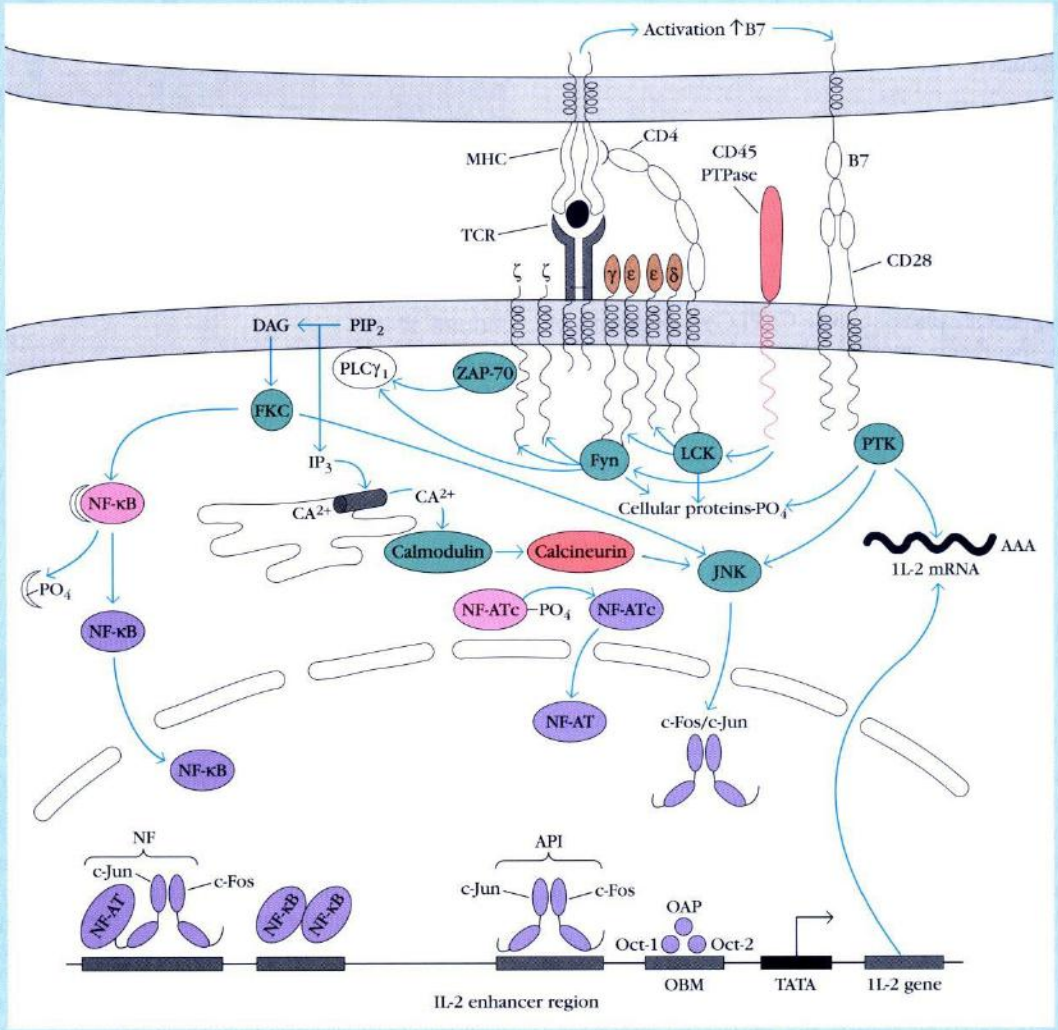


FIGURE 12-12

Overview of biochemical pathways thought to transduce the signals required for T_H-cell activation and the DNA-binding proteins that bind to the IL-2 enhancer region. The TCR-mediated signal results in production of two nuclear factors, NF-AT and NF-κB, via two separate pathways involving DAG and IP_3. In the presence of the co-stimulatory signal, generated by the CD28-B7 interaction, a third nuclear factor, c-Jun, is also produced. Binding of these and other nuclear factors to response elements in the IL-2 enhancer region (*bottom*) stimulates transcription of the IL-2 gene, leading to increased secretion of IL-2 about 45 min after antigen recognition. The co-stimulatory signal also appears to stabilize IL-2 mRNA. PTPase = protein tyrosine phosphatase; $PLC\gamma_1$ = phospholipase C; PKC = protein kinase C; PTK = protein tyrosine kinase; PIP_2 = phosphatidylinositol 4,5-bisphosphate; IP_3 = inositol 1,4,5-trisphosphate; DAG = diacylglycerol.

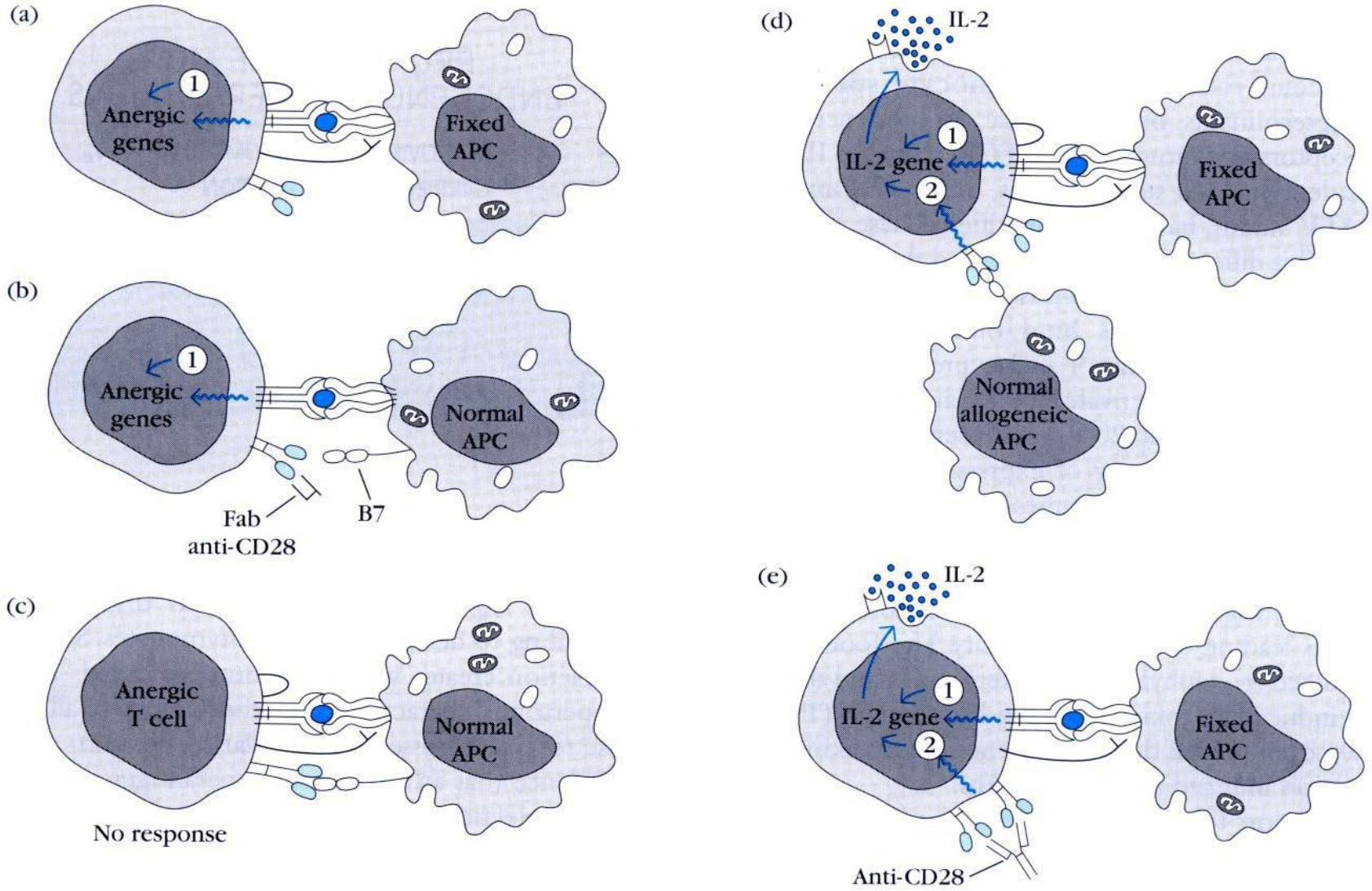


FIGURE 12-15

Experimental demonstration of clonal anergy versus clonal expansion. (a,b) Only signal 1 is generated when resting T_H cells are incubated with glutaraldehyde-fixed antigen-presenting cells (APCs) or with normal APCs in the presence of the Fab portion of anti-CD28. (c) The resulting anergic T cells cannot respond to normal APCs. (d,e) In the presence of normal allogeneic APCs or anti-CD28, both of which produce the co-stimulatory signal 2, T cells are activated by fixed APCs.

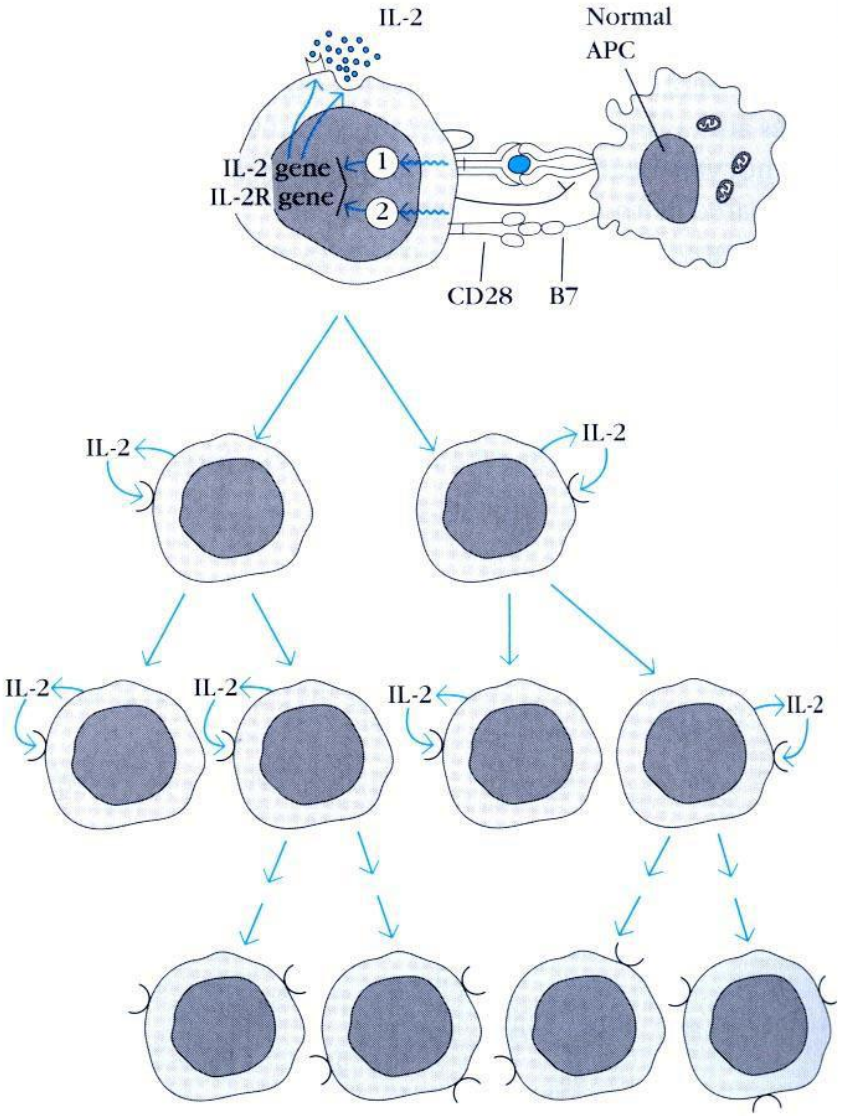


FIGURE 12-17

Activation of a T_H cell by both signal 1 and co-stimulatory signal 2 up-regulates expression of IL-2 and the high-affinity IL-2 receptor, leading to proliferation and differentiation.

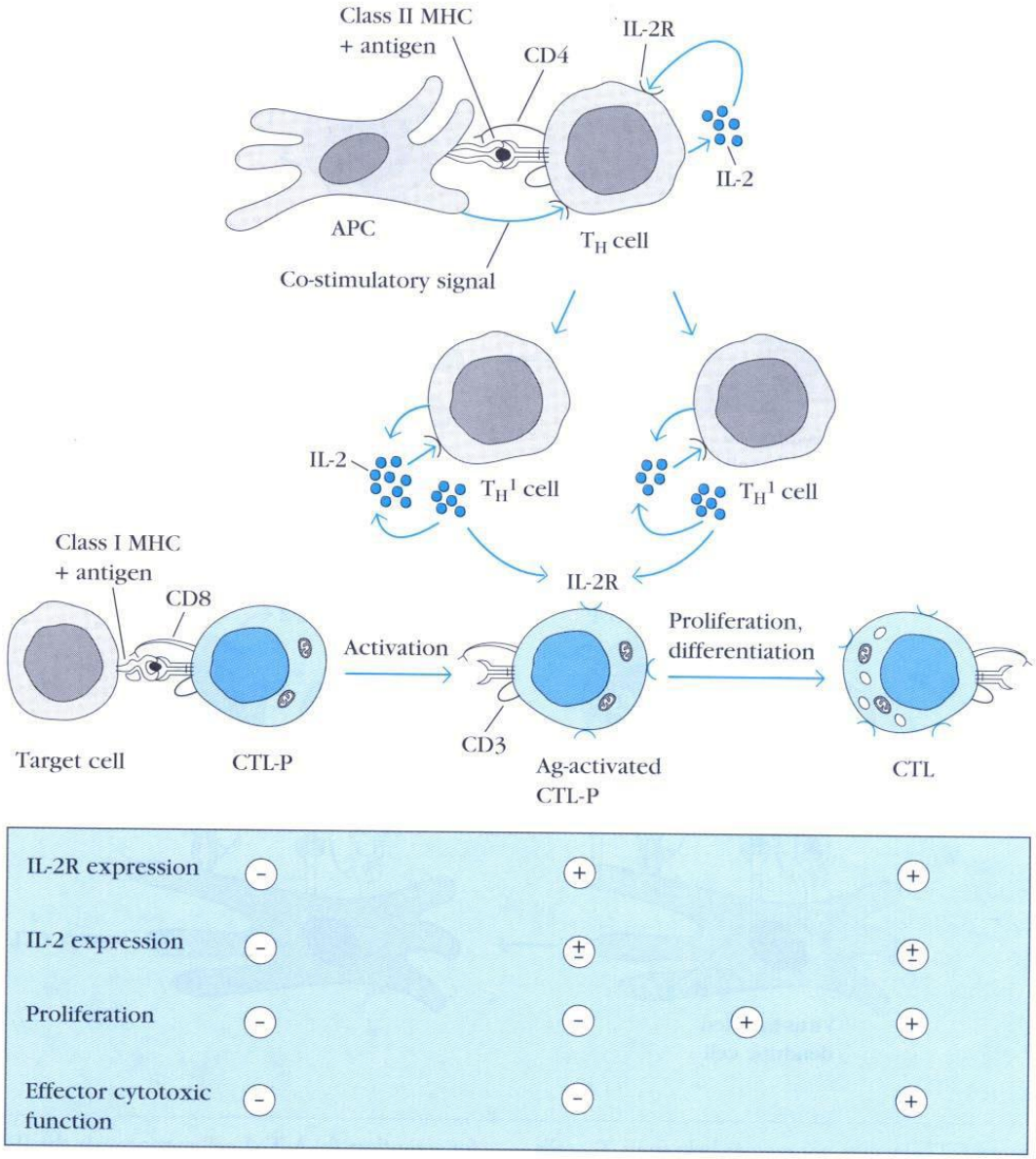


FIGURE 16-1

Generation of effector CTLs. Upon interaction with antigen–class I MHC complexes on appropriate target cells, CTL-Ps begin to express IL-2 receptors (IL-2R) and lesser amounts of IL-2. Proliferation and differentiation of antigen-activated CTL-Ps generally require additional IL-2 secreted by T_H1 cells resulting from antigen activation and proliferation of $CD4^+$ T_H cells. In the subsequent effector phase, CTLs destroy specific target cells.

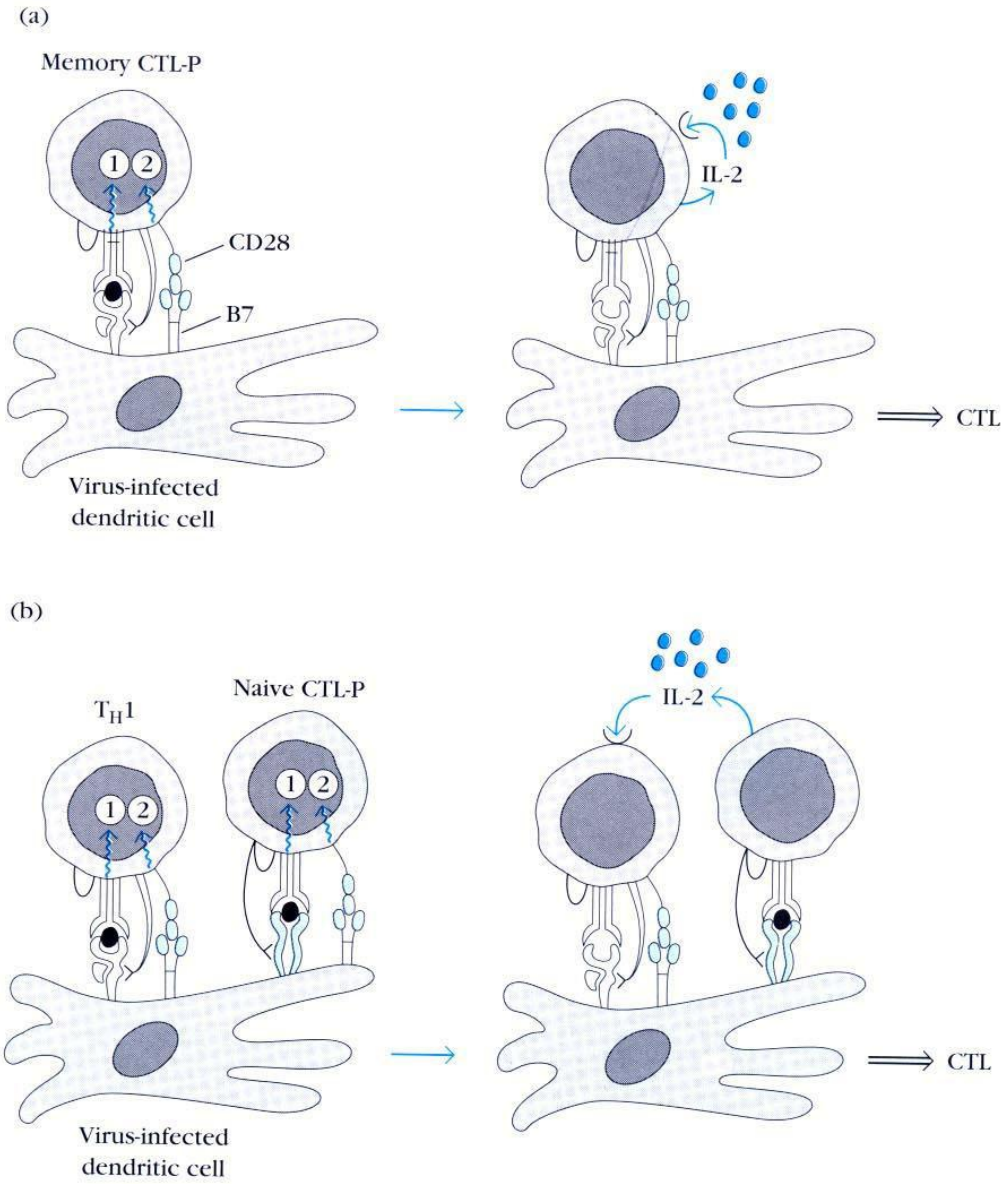


FIGURE 16-2

Proliferation of memory CTL-Ps may not require help from T_H cells. (a) Antigen-activated memory CTL-Ps appear to secrete sufficient IL-2 to autostimulate their own proliferation and differentiation into effector CTLs. They also may not require the CD28-B7 co-stimulatory signal for activation. (b) A T_H1 cell may provide the IL-2 necessary for proliferation of an antigen-activated naive CTL-P when it binds to the same APC as the CTL-P.

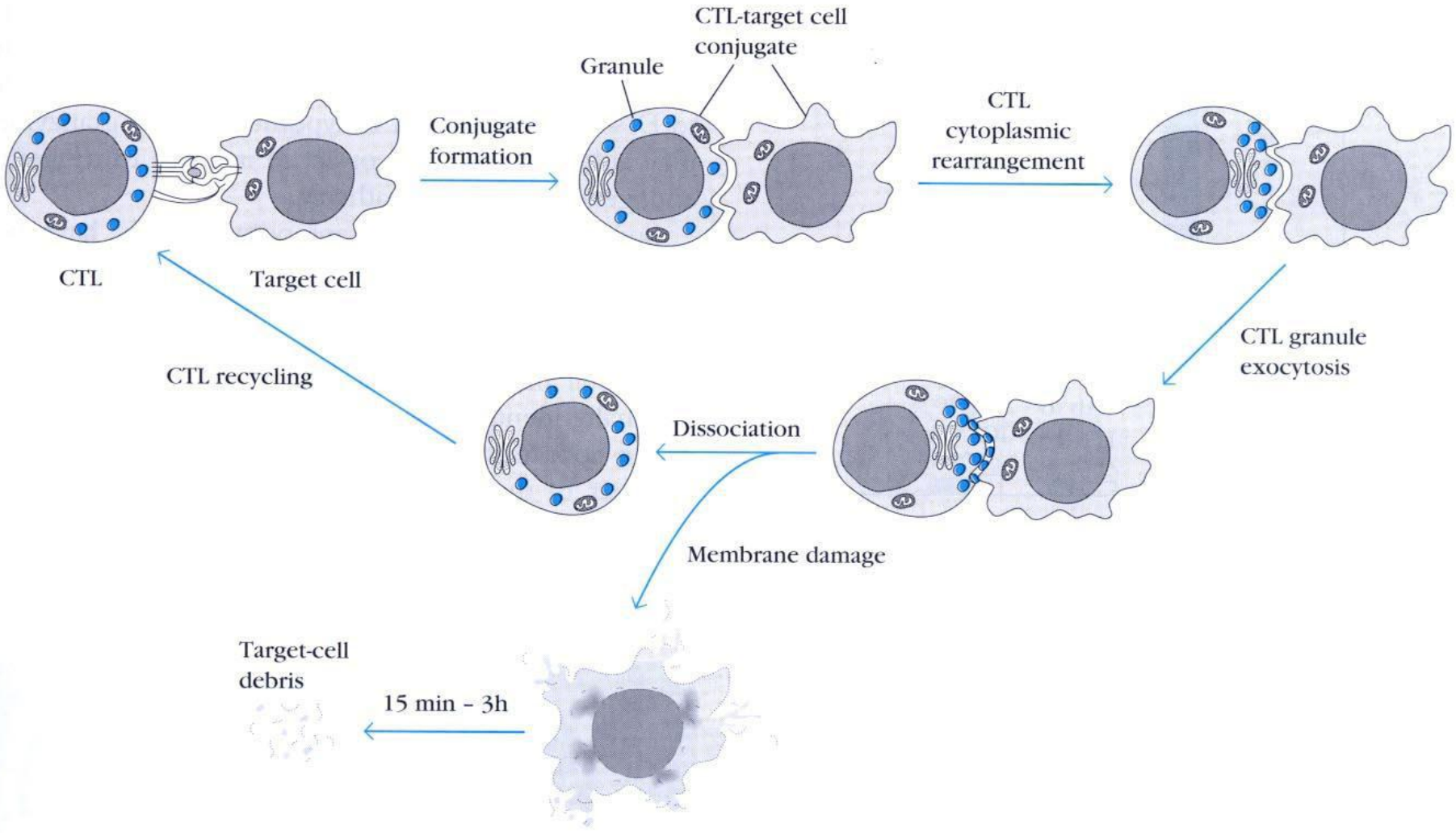


FIGURE 16-4

Stages in CTL-mediated killing of target cells. T-cell receptors on a CTL interact with processed antigen–class I MHC complexes on an appropriate target cell, leading to formation of a CTL/target-cell conjugate. The Golgi stacks and granules in the CTL reorient towards the point of contact with the target cell, and the granules' contents are released by exocytosis. Following dissociation of the conjugate, the CTL is recycled and the target cell is destroyed in time as the result of damage to its membrane and/or the action of cytotoxic mediators. [Adapted from P. A. Henkart, 1985, *Annu. Rev. Immunol.* **3**:31.]

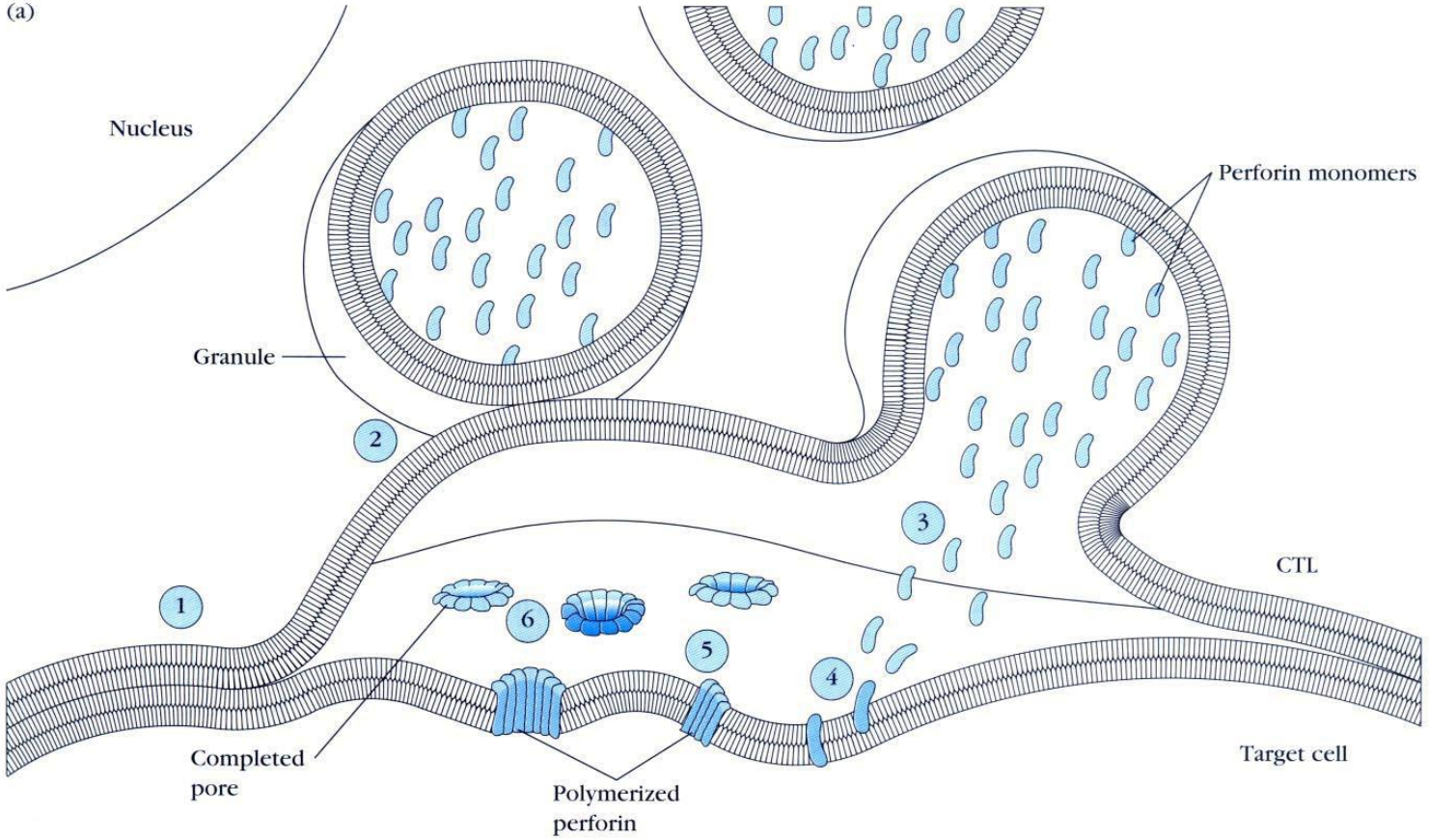
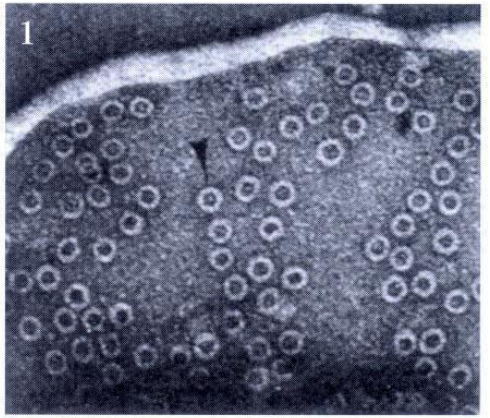


FIGURE 16-7

CTL-mediated pore formation in target-cell membrane. (a) In this model, a rise in intracellular $Ca2^+$ triggered by CTL–target cell interaction (1) induces exocytosis, in which the granules fuse with the CTL cell membrane (2) and release monomeric perforin into the small intracellular space between the two cells (3). The released perforin monomers undergo a $Ca2^+$-induced conformational change that allows it to insert into the target-cell membrane (4). In the presence of $Ca2^+$, the monomers polymerize within the membrane (5), forming cylindrical pores (6). (b) Electron micrograph of perforin pores on the surface of a rabbit erythrocyte target cell. [Part (a) adapted from J. D. E. Young and Z. A. Cohn, 1988, *Sci. Am.* **258**(1):38; part (b) from E. R. Podack and G. Dennert, 1983, *Nature* **301**:442.]

(b)



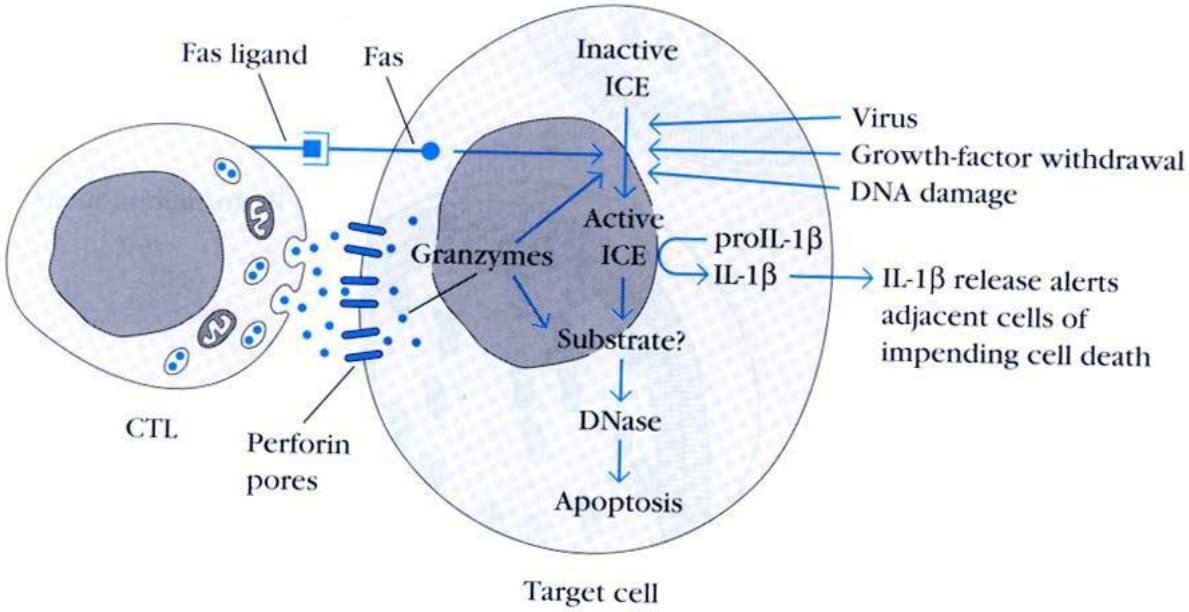


FIGURE 16-8

Proposed model of target-cell apoptosis stimulated by CTLs. Activation of interleukin 1β converting enzyme (ICE) leads to apoptosis. Granzymes released from some CTLs may activate ICE or act directly in the apoptotic pathway. In some cases, a signal induced by interaction of the Fas ligand and Fas, a TNF-type cytokine receptor on the target cell, also is thought to activate ICE. [Adapted from M. J. Smyth and J. A. Trapani, 1995, *Immunol. Today* **16**(4):202.]

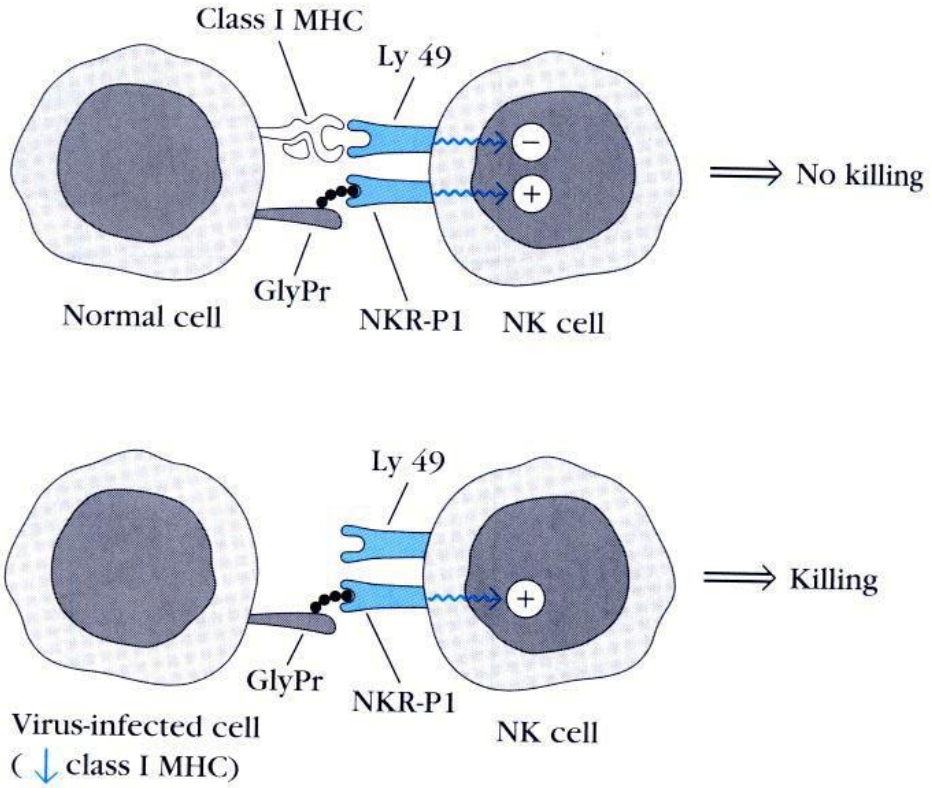


FIGURE 16-11

Two-receptor model of how cytotoxic activity of NK cells is restricted to altered self-cells. The NKR-P1 receptor on NK cells interacts with carbohydrate moieties (black circles) on membrane glycoproteins (GlyPr) of normal and altered self-cells, inducing a killing signal (+). Engagement of a second NK receptor called Ly49 with class I MHC molecules delivers another signal (–) that counteracts the killing signal. Expression of class I molecules on normal cells thus prevents their destruction by NK cells. Because class I expression is decreased on altered self-cells, the killing signal predominates, leading to their destruction.

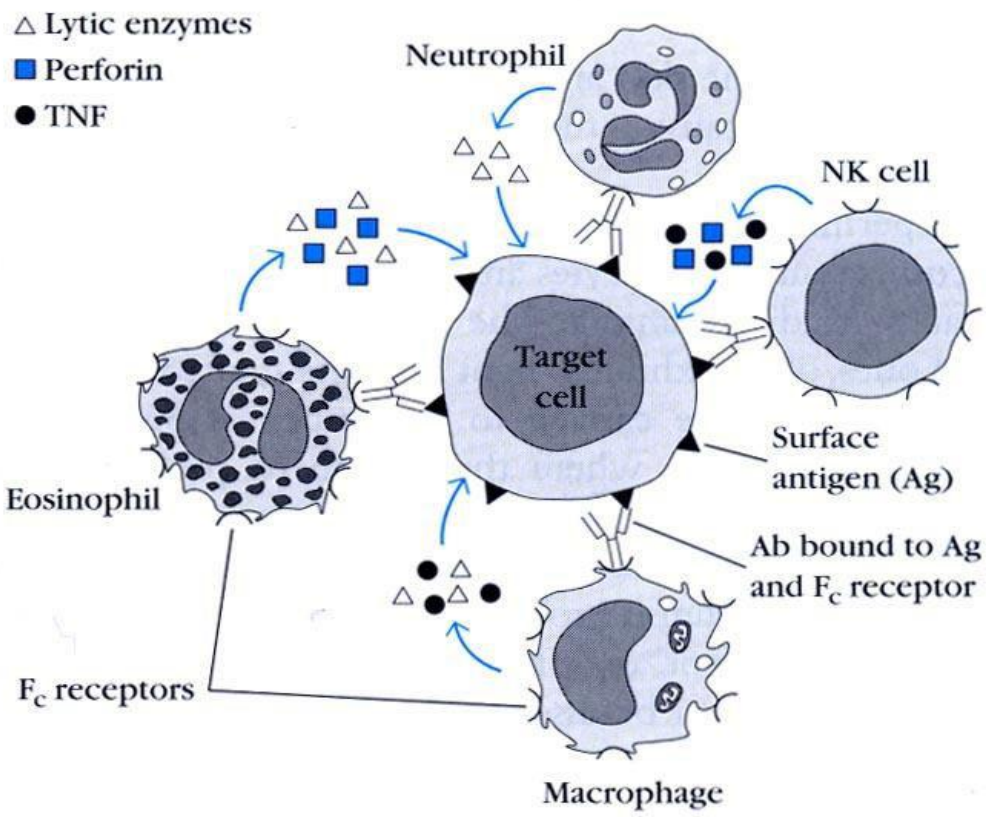


FIGURE 16-12

Antibody-dependent cell-mediated cytotoxicity (ADCC). Nonspecific cytotoxic cells are directed to specific target cells by binding to the Fc region of antibody bound to surface antigens on the target cells. Various substances (e.g., lytic enzymes, TNF, perforin) secreted by the nonspecific cytotoxic cells then mediate target-cell destruction.

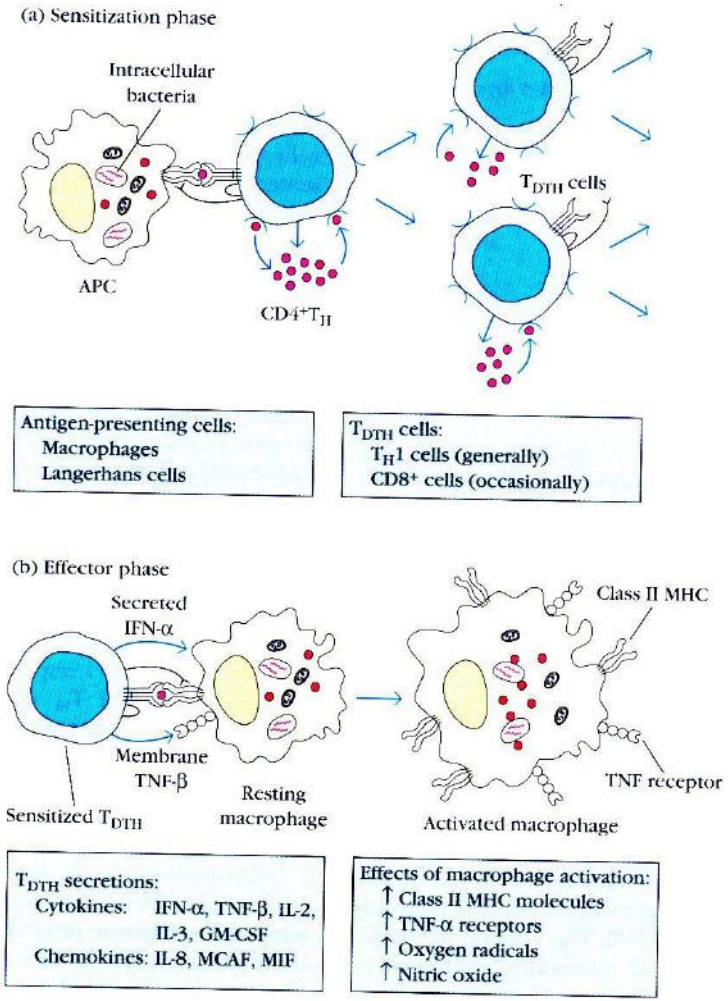


FIGURE 16-15

Overview of the DTH response. (a) In the sensitization phase following initial contact with antigen (e.g., peptides derived from intracellular bacteria), T_H cells proliferate and differentiate into T_{DTH} cells. (b) In the effector phase following subsequent exposure of sensitized T_{DTH} cells to antigen, the T_{DTH} cells secrete a variety of cytokines and chemokines. These factors attract and activate macrophages and other nonspecific inflammatory cells. Activated macrophages are more effective in presenting antigen, thus perpetuating the DTH response, and function as the primary effector cells in this reaction. MCAF = macrophage chemotactic and activating factor; MIF = macrophage-inhibition factor.

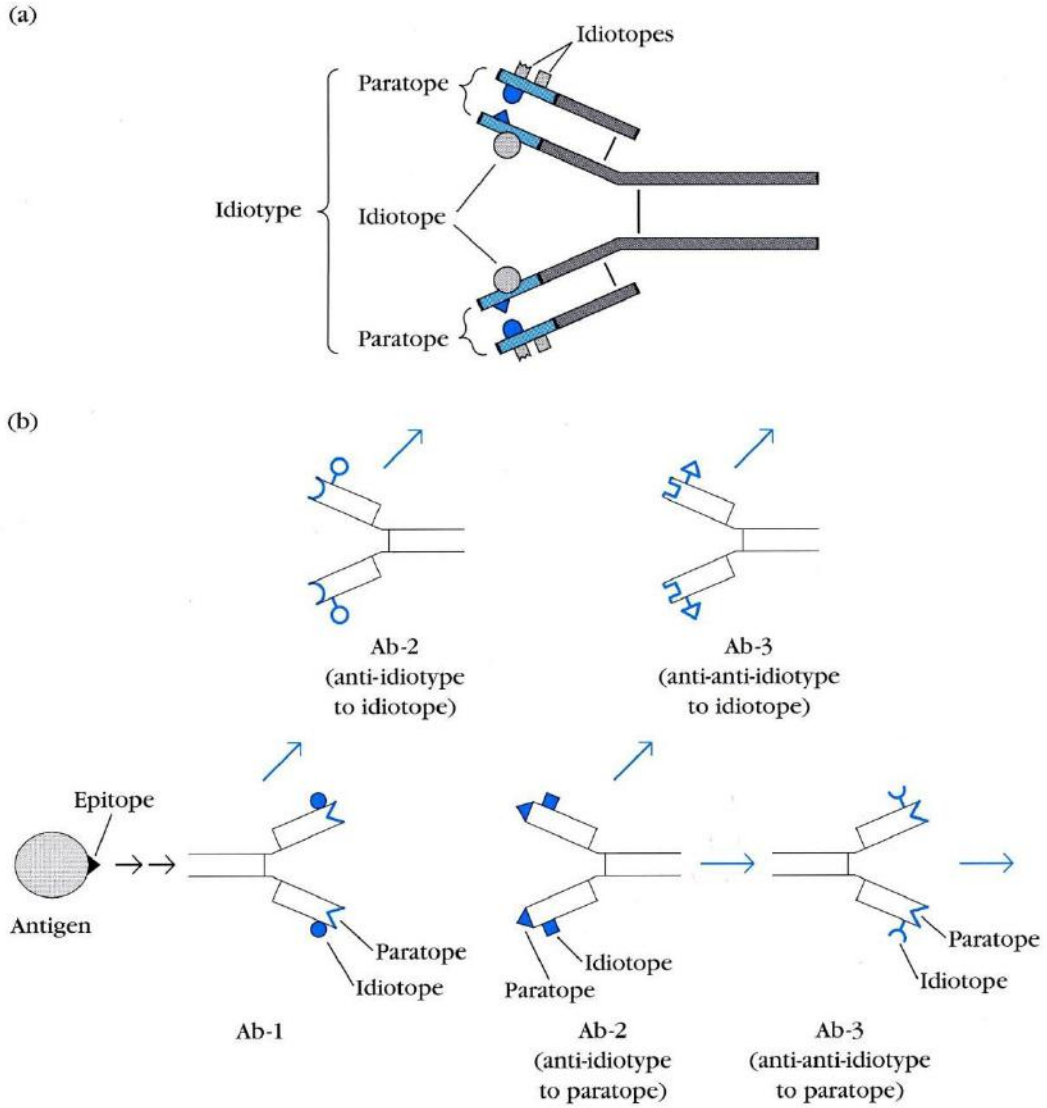
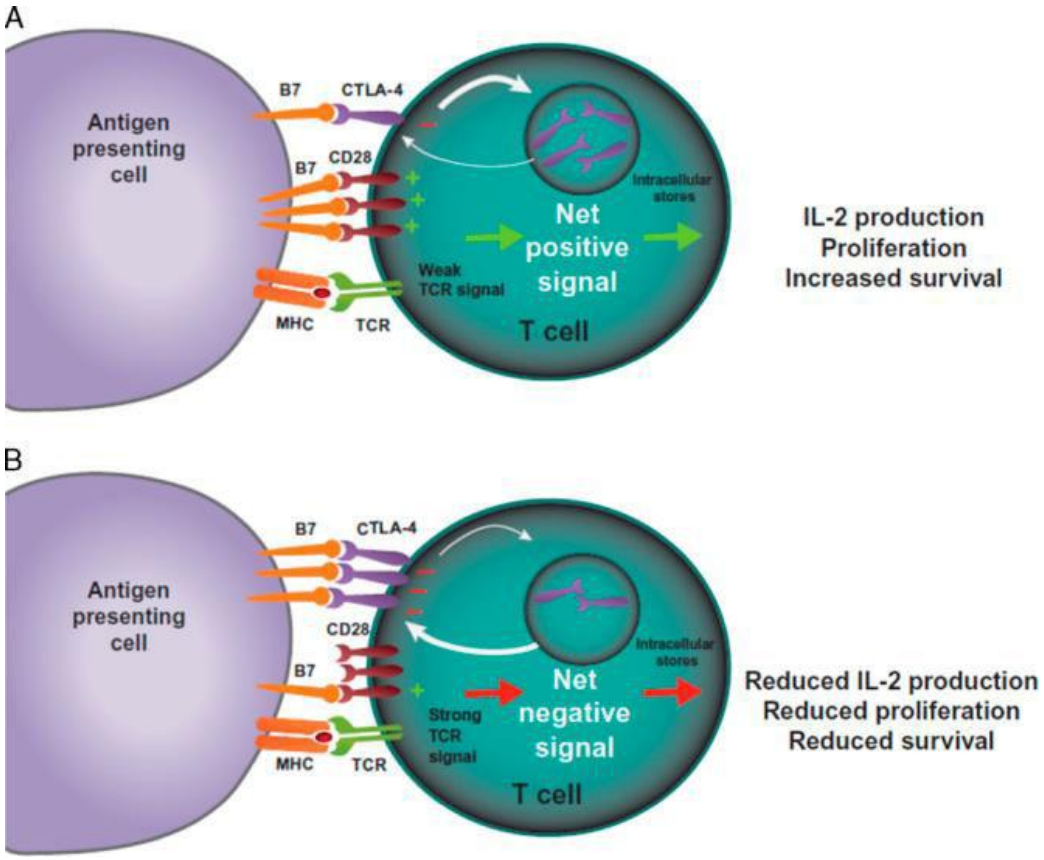
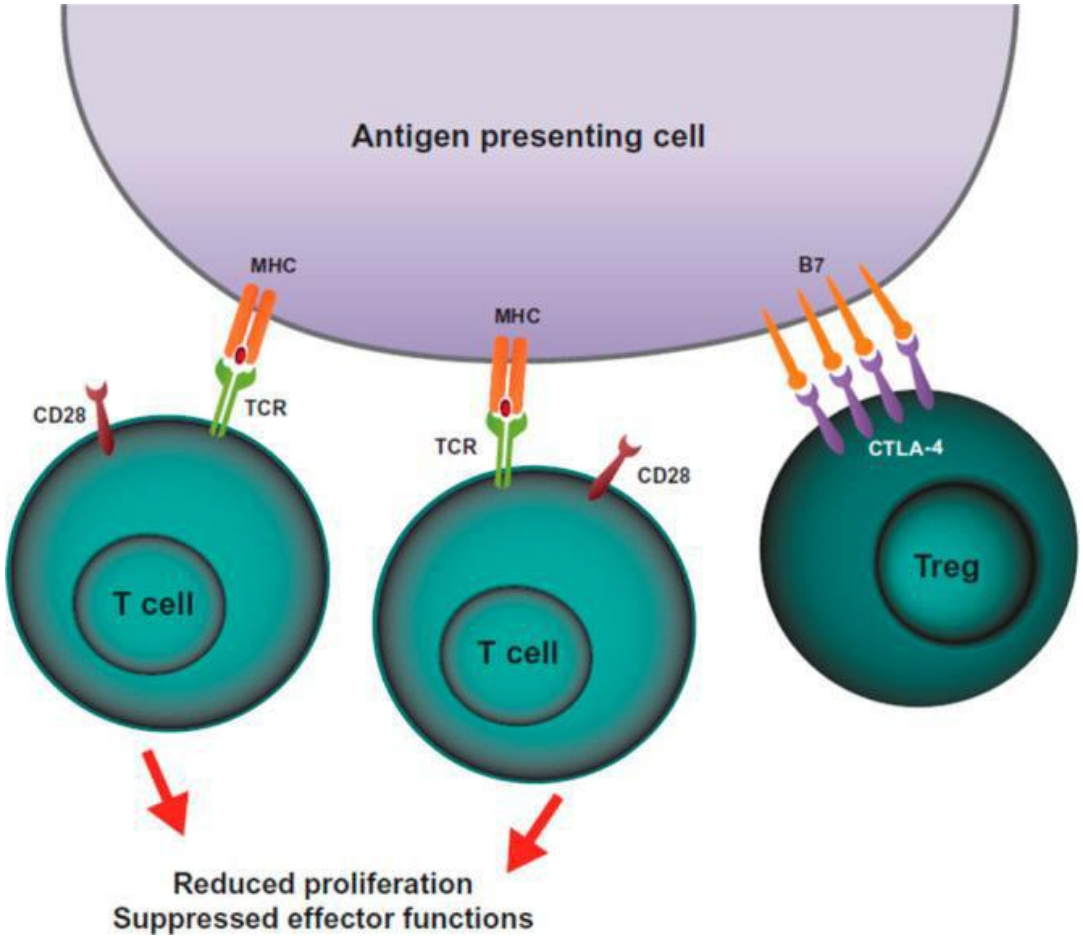


FIGURE 16-23

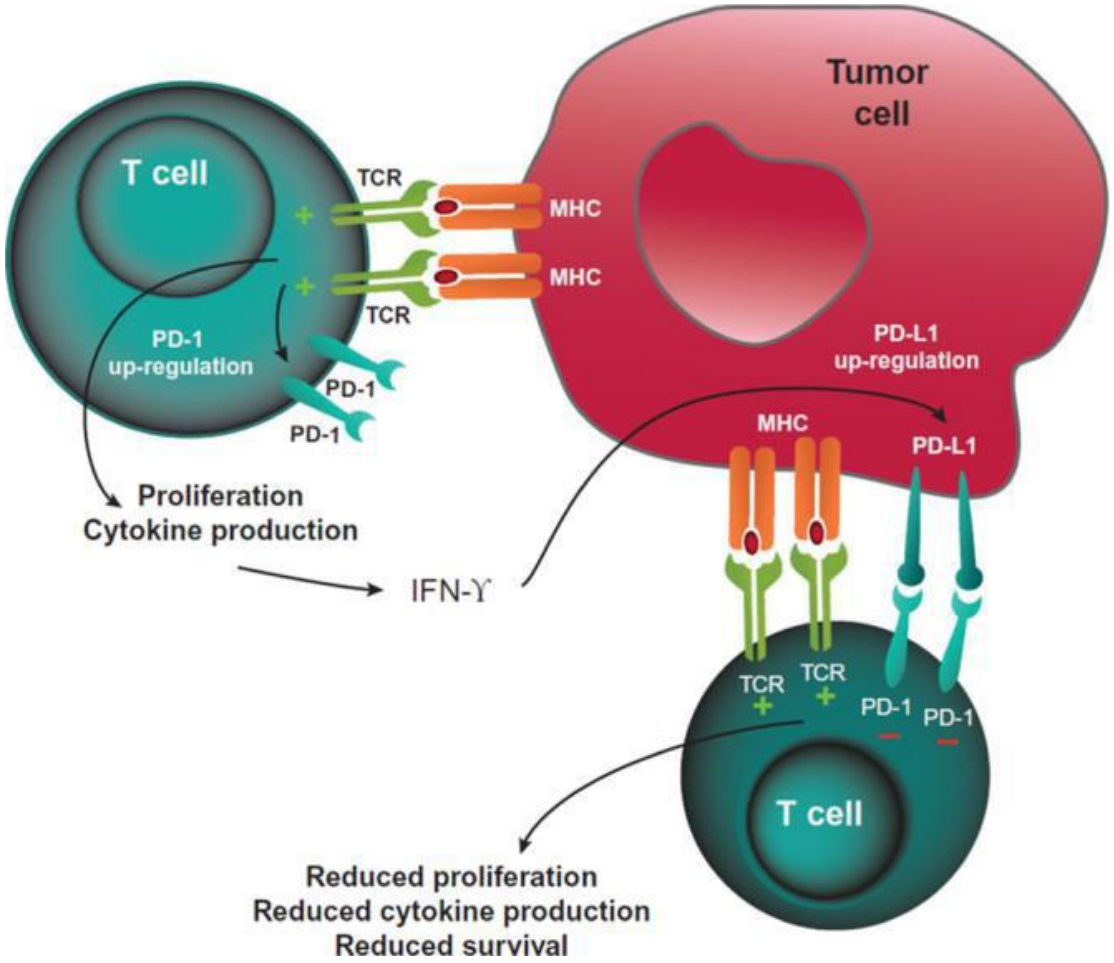
Network theory proposed by Niels Jerne. (a) Each antibody molecule expresses unique variable-region epitopes called idiotopes; the sum of the idiotopes is its idiotype. Idiotopes may coincide with the antigen-binding site, or paratope. (b) According to the network theory, the immune response to an antigen results in the formation of anti-idiotype antibodies specific for the individual idiotopes of the primary antibody (Ab-1). These anti-idiotype antibodies (Ab-2) in turn induce the formation of anti-anti-idiotype antibodies (Ab-3). A network of interacting antibodies is thus formed that serves to regulate the immune response. Note that the anti-idiotype antibody to the paratope of Ab-1 is an internal image of the original epitope on the antigen.



CTLA-4-mediated inhibition of T cells. T cells are activated when TCRs bind antigen displayed in the MHC on antigen-presenting cells in concert with CD28:B7-mediated costimulation. A, In the case of a weak TCR stimulus, CD28:B7 binding predominates, resulting in a net positive activating signal and IL-2 production, proliferation, and increased survival. B, In the case of a strong TCR stimulus, CTLA-4 expression is upregulated by increased transport to the cell surface from intracellular stores and decreased internalization. CTLA-4 competes with CD28 for binding of B7 molecules. Increased CTLA-4:B7 binding can result in a net negative signal, which limits IL-2 production and proliferation, and limits survival of the T cell. CTLA-4 indicates cytotoxic T-lymphocyte–associated antigen 4; IL-2, interleukin-2; MHC, major histocompatibility complex; TCR, T-cell receptor.



CTLA-4-mediated inhibition of Tregs. One hypothesis of how CTLA-4 expression on Tregs can inhibit T-cell activation is depicted. Constitutive expression of CTLA-4 on Tregs can sequester or cause internalization (not depicted) of B7 molecules on antigen-presenting cells. The lack of CD28:B7-mediated costimulation leads to reduced T-cell proliferation and reduced effector functions. CTLA-4 indicates cytotoxic T-lymphocyte–associated antigen 4; MHC, major histocompatibility complex; TCR, T-cell receptor; Tregs, regulatory T cells



PD-1-mediated inhibition of T cells. T cells recognizing tumor antigens can be activated to proliferate, secrete inflammatory cytokines, and resist cell death. Prolonged TCR stimulation during an ongoing immune response can cause upregulated PD-1 expression. Tumor cells can express PD-L1 (and PD-L2, not shown) as a consequence of inflammatory cytokines and/or oncogenic signaling pathways. PD-1:PD-L1 binding inhibits TCR-mediated positive signaling, leading to reduced proliferation, reduced cytokine secretion, and reduced survival. IFN-γ indicates interferon-γ; MHC, major histocompatibility complex; PD-1, programmed death protein 1; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; TCR, T-cell receptor.