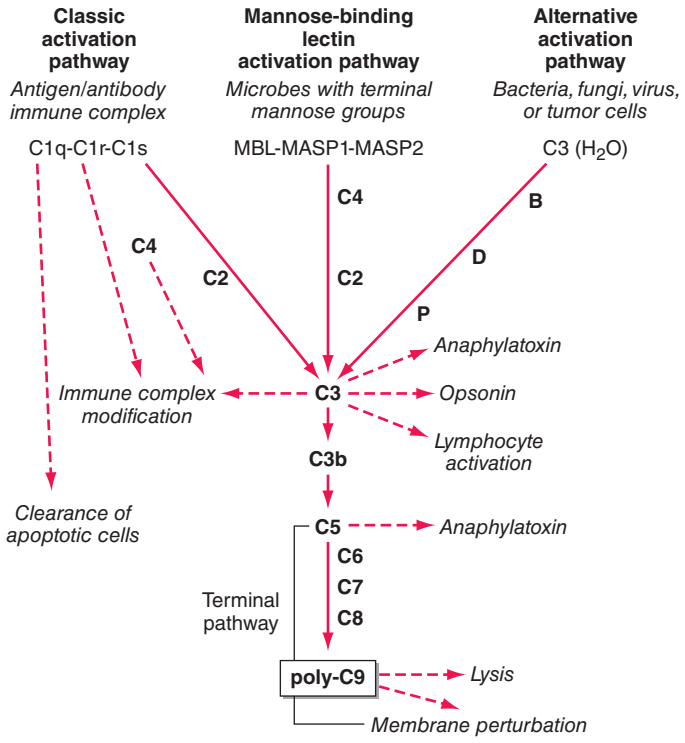

FIGURE 372e-5 The four pathways and the effector mechanisms of the complement system. *Dashed arrows* indicate the functions of pathway components. *(After BJ Morley, MJ Walport: The Complement Facts Books. London, Academic Press, 2000, Chap. 2; with permission. Copyright Academic Press, London, 2000.)*

tryptophan-serine-X-tryptophan-serine (WSXWS). This family can be grouped on the basis of the number of receptor subunits they have and on the utilization of shared subunits. A number of cytokine receptors, i.e., IL-6, IL-11, IL-12, and leukemia inhibitory factor, are paired with gp130. There is also a common 150-kDa subunit shared by IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors. The gamma chain (γ_c) of the IL-2 receptor is common to the IL-2, IL-4, IL-7, IL-9, and IL-15 receptors. Thus, the specific cytokine receptor is responsible for ligand-specific binding, whereas the subunits such as gp130, the 150-kDa subunit, and γ_c are important in signal transduction. The γ_c gene is on the X chromosome, and mutations in the γ_c protein result in the *X-linked form of severe combined immune deficiency syndrome (X-SCID)* **(Chap. 374)**.

The members of the *interferon (type II) receptor* family include the receptors for IFN-γ and -β, which share a similar 210-amino-acid binding domain with conserved cysteine pairs at both the amino and carboxy termini. The members of the *TNF (type III) receptor family* share a common binding domain composed of repeated cysteine-rich regions. Members of this family include the p55 and p75 receptors for TNF (TNF-R1 and TNF-R2, respectively); CD40 antigen, which is an important B cell-surface marker involved in immunoglobulin isotype switching; fas/Apo-1, whose triggering induces apoptosis; CD27 and CD30, which are found on activated T cells and B cells; and nerve growth factor receptor.

The common motif for the *seven transmembrane helix family* was originally found in receptors linked to GTP-binding proteins. This family includes receptors for chemokines (Table 372e-8), β-adrenergic receptors, and retinal rhodopsin. It is important to note that two members of the chemokine receptor family, CXC chemokine receptor type 4 (CXCR4) and β chemokine receptor type 5 (CCR5), have been found to serve as the two major co-receptors for binding and entry of HIV into CD4-expressing host cells **(Chap. 226)**.

Significant advances have been made in defining the signaling pathways through which cytokines exert their intracellular effects. The Janus family of protein tyrosine kinases (JAK) is a critical element involved in signaling via the hematopoietin receptors. Four JAK kinases, JAK1, JAK2, JAK3, and Tyk2, preferentially bind different cytokine receptor subunits. Cytokine binding to its receptor brings the cytokine receptor subunits into apposition and allows a pair of JAKs to transphosphorylate and activate one another. The JAKs then phosphorylate the receptor on the tyrosine residues and allow signaling molecules to bind to the receptor, whereby the signaling molecules become phosphorylated. Signaling molecules bind the receptor because they have domains (SH2, or src homology 2 domains) that can bind phosphorylated tyrosine residues. There are a number of these important signaling molecules that bind the receptor, such as the adapter molecule SHC, which can couple the receptor to the activation of the mitogen-activated protein kinase pathway. In addition, an important class of substrate of the JAKs is the signal transducers and activators of transcription (STAT) family of transcription factors. STATs have SH2 domains that enable them to bind to phosphorylated receptors, where they are then phosphorylated by the JAKs. It appears that different STATs have specificity for different receptor subunits. The STATs then dissociate from the receptor and translocate to the nucleus, bind to DNA motifs that they recognize, and regulate gene expression. The STATs preferentially bind DNA motifs that are slightly different from one another and thereby control transcription of specific genes. The importance of this pathway is particularly relevant to lymphoid development. Mutations of JAK3 itself also result in a disorder identical to X-SCID; however, because JAK3 is found on chromosome 19 and not on the X chromosome, JAK3 deficiency occurs in boys and girls **(Chap. 374)**.

THE ADAPTIVE IMMUNE SYSTEM

Adaptive immunity is characterized by antigen-specific responses to a foreign antigen or pathogen. A key feature of adaptive immunity is that following the initial contact with antigen (*immunologic priming*), subsequent antigen exposure leads to more rapid and vigorous immune responses (*immunologic memory*). The adaptive immune system consists of dual limbs of cellular and humoral immunity. The principal effectors of cellular immunity are T lymphocytes, whereas the principal effectors of humoral immunity are B lymphocytes. Both B and T lymphocytes derive from a common stem cell **(Fig. 372e-6)**.

The proportion and distribution of immunocompetent cells in various tissues reflect cell traffic, homing patterns, and functional capabilities. Bone marrow is the major site of maturation of B cells, monocytes-macrophages, DCs, and granulocytes and contains pluripotent stem cells that, under the influence of various colony-stimulating factors, are capable of giving rise to all hematopoietic cell types. T cell precursors also arise from hematopoietic stem cells and home to the thymus for maturation. Mature T lymphocytes, B lymphocytes, monocytes, and DCs enter the circulation and home to peripheral lymphoid organs (lymph nodes, spleen) and mucosal surface-associated lymphoid tissue (gut, genitourinary, and respiratory tracts) as well as the skin and mucous membranes and await activation by foreign antigen.

T Cells The pool of effector T cells is established in the thymus early in life and is maintained throughout life both by new T cell production in the thymus and by antigen-driven expansion of virgin peripheral T cells into "memory" T cells that reside in peripheral lymphoid organs. The thymus exports ~2% of the total number of thymocytes per day throughout life, with the total number of daily thymic emigrants decreasing by ~3% per year during the first four decades of life.

Mature T lymphocytes constitute 70–80% of normal peripheral blood lymphocytes (only 2% of the total-body lymphocytes are contained in peripheral blood), 90% of thoracic duct lymphocytes, 30–40% of lymph node cells, and 20–30% of spleen lymphoid cells. In lymph nodes, T cells occupy deep paracortical areas around B cell germinal centers, and in the spleen, they are located in periarteriolar areas of white pulp **(Chap. 79)**. T cells are the primary effectors of cell-mediated immunity, with subsets of T cells maturing into CD8+ cytotoxic T cells capable of lysis of virus-infected or foreign cells (short-lived effector T cells) and CD4+ T cells capable of T cell help for CD8+ T cell and B cell development. Two populations of long-lived memory T cells are triggered by infections: effector memory and central memory T cells.