event; subsequent stages of maturation are hypothesized to occur under the influence of growth factors, or cytokines (Table 45-2). Cytokines act on different cells through specific cytokine receptors. Receptor activation induces signal-transduction pathways that lead to changes in gene transcription and eventual cell proliferation and differentiation. These growth factors also act as survival factors for the developing hematopoietic cells by preventing *apoptosis* (i.e., programmed cell death). This process occurs in the cellular milieu of the bone marrow, where hematopoiesis depends in part on the nonhematopoietic cells (i.e., fibroblasts, endothelial cells, osteoblasts, and fat cells) that make up that microenvironment. Research in HSC biology has focused on how the cells are regulated by growth factors in the bone marrow microenvironment and by unique cell surface ligand interactions between stem cells and the surrounding stromal cells in well-defined sites called *stem cell niches.*

Hematopoietic Differentiation Pathway

Hematopoiesis has been hypothesized to proceed along a tightly regulated hierarchy (Fig. 45-1) governed by effects of intrinsic transcription factors and cytokines in the bone marrow microenvironment. As more primitive cells mature under the influence of specific regulatory cytokines, they undergo several cell divisions and become *progenitor cells* committed to one lineage. They also lose their self-renewal capacity. Morphologically, these cells are transformed from nonspecific blastlike cells into cells that can be identified by their color, shape, and granular and nuclear content. Functionally, they acquire distinguishing cell surface receptors and responses to specific signals.

Maturing granulocytes and erythroid cells undergo several more cell divisions in the bone marrow, whereas lymphocytes travel to the thymus and lymph nodes for further development. Megakaryocytes cease cellular division but continue with nuclear replication. Eventually, these cells are released from the marrow as fully functional erythrocytes, mast cells, granulocytes, monocytes, eosinophils, macrophages, and platelets.

Pluripotent Stem Cells

The pluripotent HSC is morphologically indistinguishable and is best identified by its expression of the cell differentiation antigen, CD34, and by its ability to form pluripotent colonies in vitro. Under the influence of interleukin-1 (IL-1), IL-3, IL-6, FMS-like tyrosine kinase 3 (FLT3), and a specific stem cell factor (KIT ligand [KITLG], or steel factor), this cell matures into a myeloid-lineage stem cell (i.e., granulocyte-erythrocyte-macrophage-megakaryocyte colony-forming unit [CFU-GEMM] cell)

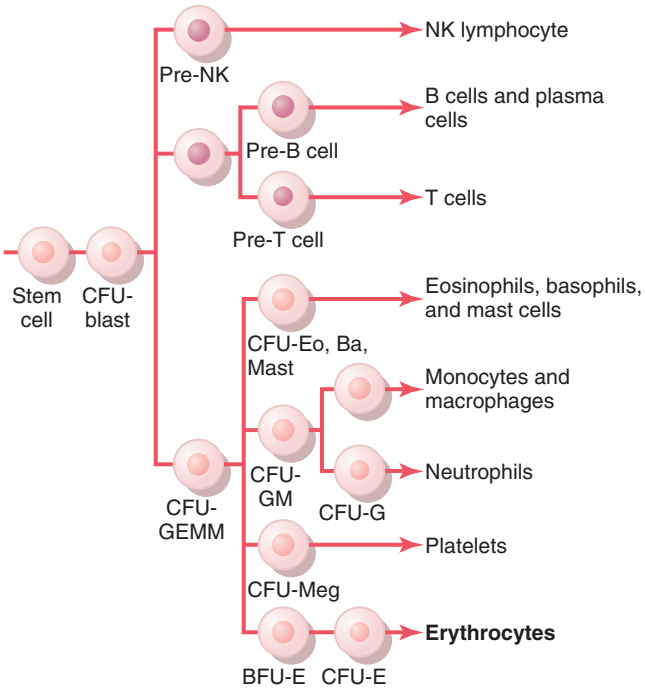

FIGURE 45-1 Development of bone marrow cells. Ba, Basophil; BFU, blast-forming unit; CFU, colony-forming unit; E, erythroid; Eo, eosinophil; G, granulocyte; GEMM, granulocyte-erythrocyte-macrophage-megakaryocyte; GM, granulocyte-macrophage; Meg, megakaryocyte; NK, natural killer.

TABLE 45-2 CYTOKINES AND THEIR ACTIVITIES

ACRONYM	NAME	EFFECTS ON HEMATOPOIESIS
EPO	Erythropoietin	Stimulation of proliferation and maturation of erythroid progenitors; produced by the kidney in response to anemia and hypoxia; important clinically for treatment of anemia associated with low EPO levels (e.g., renal failure, anemia of chronic disease)
G-CSF	Granulocyte colony-stimulating factor	Stimulation of proliferation and maturation of granulocytes; more broad-based effect because also increases release of stem cells in peripheral blood; clinically important for treatment of neutropenia and mobilization of stem cells for transplantation
GM-CSF	Granulocyte-monocyte colony-stimulating factor	Proliferation of granulocyte and monocyte precursors; role unclear in steady-state hematopoiesis because knockout has no hematopoietic phenotype
TPO	Thrombopoietin	Proliferation of megakaryocytes; results disappointing in clinical studies
M-CSF	Monocyte colony-stimulating factor	Proliferation of monocytes
IL-2	Interleukin-2	Proliferation of T cells
IL-3	Interleukin-3 (multi– colony-stimulating factor)	Proliferation of granulocytes, monocytes; broad-based effects, appearing to increase the proliferation of stem cells; not in use clinically
IL-4	Interleukin-4	Proliferation of B cells
IL-5	Interleukin-5	Proliferation of T cells, B cells; proliferation and differentiation of eosinophils
IL-11	Interleukin-11	Proliferation of megakaryocytes; undergoing clinical testing
LIF	Leukemia inhibitory factor	Proliferation of stem cells and megakaryocytes
SCF	Stem cell factor (kit ligand)	Proliferation of progenitor cells; broad-based effects on multiple lineages