9. Therapeutic use of hematopoietic growth factors in bone marrow transplantation

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The proliferation, differentiation, and function of hematopoietic cells is tightly regulated by a complex family of glycoprotein hormones, collectively described as hematopoietic growth factors [1–6]. Advances in molecular biological and protein purification techniques have made it possible to purify and subsequently clone the genes for an increasing number of these factors. These include the colony-stimulating factors (CSFs), first identified in mice by their ability to stimulate hematopoietic colony formation in semisolid medium, and the interleukins, so named because of their important role in cell-cell communication. In this review we briefly discuss the basic properties of these factors and outline their potential clinical uses, particularly in the setting of bone marrow transplantation. The in-vivo effects of several of these factors have already been studied in animals and in humans, and initial data indicate that these agents will be useful in a variety of clinical settings.

The mature elements of the blood and immune system are derived from a hierarchy of bone marrow progenitor cells [7,8]. Stem cells have the capability for self-renewal or differentiation along several cell lineages. Pluripotent and multipotent stem cells give rise to all or multiple cell lineages, respectively, and produce more differentiated progenitor cells committed to a single lineage (see Figure 1). Progenitors for granulocytes (colony-forming unit-granulocyte, CFU-G), macrophages (CFU-M), erythrocytes (CFU-E), or megakaryocytes (CFU-Mega) have been described [8] and growth of these committed progenitors in culture requires the presence of specific colony-stimulating factors. Differentiation and subsequent lineage restriction of these progenitors is associated with sequential expression of cell surface receptors for specific hematopoietic growth factors [1]. The particular growth factors present in the bone marrow microenvironment may influence the path that any one cell takes, thus a combination of intrinsic and external factors likely affect the proliferation and differentiation of hematopoietic cells.

The signals controlling erythropoiesis have been partially characterized. When the oxygen-sensing mechanism of the kidney detects hypoxia, erythropoietin production is increased. Erythropoietin binds to its receptor on committed erythroid progenitors, stimulating their proliferation and resulting in an expansion of erythropoiesis and an increase in red cell mass [9,10].
Additional factors control erythrocyte differentiation in vivo, and the signals controlling the day-to-day production of erythrocytes are also incompletely defined.

Positive and negative feedback mechanisms probably exist for myeloid cells, and the colony-stimulating factors, which have potent effects on myeloid progenitors, are likely to be involved in stimulating their proliferation and supporting, if not influencing, their differentiation. A common progenitor cell for neutrophils and macrophages, the colony-forming unit granulocyte-macrophage (CFU-GM), has been identified that responds to granulocyte-macrophage colony-stimulating factor (GM-CSF) [5,11], interleukin-3 (multi-CSF) [11], granulocyte CSF [12], and macrophage CSF [13]. The specific colonies formed are determined by which CSFs are present, although other factors, including IL-1, can influence the growth of CFU-GM. In-vitro CSF production can be stimulated by a variety of inflammatory mediators, but the in-vivo signals controlling CSF expression and the precise role of CSFs in the control of myelopoiesis are poorly understood.

In adults, normal hematopoiesis occurs only within the specialized microenvironment of the bone marrow. In-vitro culture studies suggest that stromal cells are critical to support hematopoiesis [14–16]. Endothelial cells and fibroblasts are rich sources of hematopoietic growth factors [17–20] and produce extracellular matrix (proteoglycans, etc.), which bind GM-CSF and IL-3 in the marrow microenvironment [21,22]. Complex cellular interactions probably localize growth factor activities to certain areas in the marrow, creating optimal conditions for cell growth and possibly leading to positive and negative feedback loops. For example, monocytes produce both IL-1 and tumor necrosis factor (TNF), which can induce production of GM-CSF by stromal cells [18]. The GM-CSF produced could further activate monocytes, increasing the release of IL-1, TNF, and M-CSF [23]. A variety of synergistic interactions have been described among hematopoietic growth factors, as they act at different stages of development and via different mechanisms. Exposure of cells to one factor may alter the expression of receptors for another factor, either downregulating or increasing their numbers. The