Haematopoiesis, the production of blood cells, is a dynamic process that reflects a balanced response to competing stimulatory, enhancing, and suppressing influences. Mature blood cells are derived in a hierarchical fashion from relatively immature cells, referred to as stem and progenitor cells. The ultimate marrow and blood repopulating cell is a pluripotential hematopoietic stem cell which has the capacity to self-renew, differentiate into early cells of multiple lineages as well as reconstitute the myelo-lymphopoietic system in a lethally irradiated host. Stem cells give rise to multipotential progenitors which in turn give rise to more lineage-restricted progenitors. Progenitor cells appear to have little or no self-renewal capacity, but they give rise to precursor cells, the first morphologically recognizable cells in a given cell lineage. Stem and progenitor cells express the CD34 antigen, which identifies a transmembrane glycoproteic structure. On the basis of CD34 expression and low or high expression of non lineage specific antigens, including Thy1, CD38, HLA-DR, CD45RA, CD71, hematopoietic cells can be fractionated into primitive, intermediate and late progenitors.

After two decades of in vitro studies, it is apparent that much of the regulation of hematopoiesis at the level of stem, progenitor, precursor and mature cells is mediated by a group of glycoproteic molecules termed colony-stimulating factors (CSFs). CSFs can be classified on the basis of their target cell population as early- and late-acting growth factors. The known regulators with proliferative effects on one or another hematopoietic population already exceed 20 in number, and added to these are a variety of inhibitory factors and a number of factors allowing selective cell-cell adhesion. The relevance of CSFs to hematopoietic regulation is supported by the presence of specific CSF receptors on stem and progenitor cells. Environmental components have also been described which can affect hematopoietic proliferation and differentiation at several levels, including direct cell-to-cell interactions, interactions of cells with extracellular matrix molecules, and interaction of cells with soluble growth regulatory molecules.

So far, the majority of clinically available CSFs, such as granulocyte CSF (G-CSF) or erythropoietin (Epo) affect late, lineage-specific progenitors. And even the more primitive factors interleukin-3 (IL-3) or granulocyte-macrophage CSF (GM-CSF) are unlikely to act on self-renewing progenitors. Therefore, the search for early-acting growth factors allowing selective manipulation of stem cell self-renewal and commitment is of particular biological and clinical relevance.

Among early-acting cytokines is a factor that has been referred to as stem cell factor (SCF), mast cell growth factor (MGF), Kit ligand (KL), and Steel factor (SF). SCF is the ligand for the receptor encoded by the c-kit proto-oncogene. Kit receptor, similarly to the CSF-1 receptor encoded by the c-fms proto-oncogene, has an extracellular ligand-binding domain, a hydrophobic transmembrane domain, and an intracellular domain with protein-tyrosine kinase (TK) activity.

Several receptor TKs have been shown to be important in the differentiation and proliferation of hematopoietic cells. Recently, as a step in a strategy to isolate and clone growth factors for human stem cells, the cDNA for stem cell TK-1 (STK-1), a human homologue of the
murine Flk2/Flt3 receptor which is expressed on normal human CD34+ marrow cells has been cloned. The human homologue of the murine Flt3 ligand (Flt3-L), an additional early-acting growth factor, has also been cloned and characterized.

SCF and Flt3-L have several characteristics in common. By themselves, both compounds only weakly stimulate the differentiation of stem cells and progenitor blood cells, though both compounds synergize with lineage-restricted growth factors. Both compounds are biologically active in soluble and membrane-bound forms, and both are transmembrane proteins that undergo proteolytic cleavage to generate their soluble forms. Both have four cysteine residues that form intramolecular disulfide bonds to stabilize their three-dimensional structure. And both bind to a subfamily of tyrosine kinase receptors that have five immunoglobulin-like segments in their extracellular domains. Flt3-L and SCF have one very distinguishing characteristic: the absence of any mast cell stimulatory activity by Flt3-L.

By itself, SCF has little proliferative activity on hematopoietic progenitor cells in terms of number and size of colonies. However, SCF is a potent co-stimulator and in most cases is a synergistic factor when used with a number of other CSFs to stimulate the growth of hematopoietic progenitors in vitro and blood cell production in vivo. SCF synergizes with interleukin-3 (IL-3), interleukin-6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), erythropoietin (Epo) to stimulate myeloid, erythroid as well as megakaryocytic progenitors. In this issue of Haematologica, Grossi et al. show that SCF administration enhances both the proliferation and maturation of murine megakaryopoiesis in vivo. SCF synergizes with interleukin-7 (IL-7) to stimulate pre-B lymphocyte colony formation, directly acts on a highly immature population of CD34+ progenitors and supports the growth of multipotential progenitors with high replating potential.

SCF could find use in a number of clinical settings ranging from chemotherapy recovery to gene therapy. Following high-dose chemotherapy and autologous stem cell transplantation, SCF could accelerate hematopoietic recovery. However, as may be anticipated on the basis of in vitro studies, the target of SCF is a very early cell population and there is no reason to assume that following stem cell transplantation SCF alone can accelerate hematopoietic recovery, as has been shown for IL-3, GM-CSF, PIXY321 or G-CSF. Indeed, in the context of allo- or autografting, SCF can be expected to synergize with more lineage-restricted blood-cell growth factors such as EPO and G-CSF. Patients with engraftment failure or severe aplastic anemia could benefit from in vivo SCF-induced stem cell proliferation and expansion. In addition, SCF as well as Flt3-L could allow further escalation of the concentration of chemical agents used for marrow purging, paving the way for hyper-purging strategies in an attempt to improve the clinical efficacy of marrow decontamination.

SCF has been shown to be very efficient in stem and progenitor cell mobilization. The combined use of low-dose SCF and G-CSF could efficiently influence both the quality and the quantity of mobilized cells. In fact, SCF could enhance the mobilizing effect of G-CSF, permitting collection of large amounts of early progenitors with in vivo repopulating potential. This would result in an overmobilization of stem and progenitor cells that could eventually reduce the 4-7 days of aplasia following high-dose therapy and autologous stem cell rescue.

SCF stimulates mast-cell proliferation, whereas Flt3-L does not. In early phase I trials of SCF, mast-cell-induced inflammation was observed at doses of SCF >10 μg/kg/d and, subsequently, in phase I/II trials premedicating patients with an antihistamine was a mandatory step. All in vivo uses of SCF will be limited by mast cell activation and in all future clinical trials SCF should be used at low doses in combination with lineage-restricted cytokines.

The recent cloning of cDNAs for both human and murine thrombopoietin (c-Mpl ligand) will probably lead to strategies based on the combined use of low-dose SCF and c-Mpl ligand in order to achieve a significant and long-lasting
stimulation of megakaryocyte maturation.29,30

SCF might be of relevant clinical value in two ex vivo applications that would overcome all problems related to mass cell activation. SCF, once again in combination with other CSFs, has been shown to be a factor essential to the amplification of progenitor cells as well as the maintenance, or even slight amplification, of stem cells.31 The ex vivo amplification of stem and progenitor cells is now considered an essential step in the context of therapeutic strategies based on high-dose sequential chemotherapy and double autografting procedures.32 In gene therapy, SCF could help multiply a patient’s stem cells, which make up less than 0.01 percent of bone marrow cells, thereby making them easier to isolate. Self-renewing stem cells would be the ideal cells to genetically engineer since the goal of gene therapy is to produce a permanent genetic alteration.33

In conclusion, early-acting factors are now available for clinical use. By definition, these factors exert pleiotropic effects, some of which could be clinically dangerous. However, the possibility of manipulating stem cells is now a reality and opens fascinating scenarios.

References

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