inside blood

as the explanation for the characteristic osteolytic lesions found in myeloma patients. But despite many suggested candidates, the activating factors involved have resisted definitive identification. In this issue 2 elegant studies together convincingly pin the blame for the osteolysis on an imbalance of 2 molecules, osteoprotegerin ligand (OPGL, aka TRANCE and RANKL) and osteoprotegerin (OPG). Both of these molecules are involved together in the regulation of bone resorption: OPGL, a member of the tumor necrosis factor superfamily, causes activation and differentiation of osteoclasts by binding to the receptor RANK on osteoclast precursors, and OPG is a decoy receptor and inhibitor of OPGL.

In the in vitro study by Giuliani and colleagues (page 3527), OPG and OPGL were shown to be expressed by osteoblast precursors and bone marrow stromal cells in myeloma marrow and not by the myeloma cells themselves. But culturing human myeloma cells in contact with stromal cells resulted in increased expression of OPGL mRNA. Conditioned medium from the myeloma cells did not stimulate OPGL expression, and the availability of the integrin VLA-4 was required for the increased expression. On the other hand, cocultures of myeloma cells and osteoblast precursors resulted in a decrease in OPG mRNA. Immunohistochemistry also revealed increased $OPGL^+$ stromal cells and decreased OPG^+ osteoblastic cells associated with myeloma cell infiltrates in marrow biopsies from patients with osteolytic lesions, as compared with those without bone lesions or to healthy controls, further supporting the authors' conclusion that an imbalance in the OPG/OPGL system induced by the myeloma tumor leads to osteolysis.

In the second study Croucher and colleagues (page 3534) examined the effect of recombinant human OPG on a mouse model of myeloma in which the mice develop severe osteolytic bone disease by 12 weeks after intravenous transfer of myeloma cells. Treatment with OPG was initiated once myeloma was established, as evidenced by detection of a serum paraprotein. Four weeks later, the OPG-treated mice had markedly reduced numbers of lytic bone lesions, decreased numbers of osteoclasts and increased bone density, as compared with the untreated myeloma mice. Unlike Giuliani and colleagues, Croucher and colleagues found that the mouse myeloma cells expressed RANKL (OPGL) mRNA and that the protein could be demonstrated on the cell membrane by flow cytometry. They leave open the possibility that stromal cell synthesis of RANKL (OPGL) may also be stimulated by the myeloma cells, as described by others. Clearly, these studies raise promising therapeutic possiblities for recombinant OPG and other approaches targeting RANKL (OPGL) to prevent and treat the devastating bone disease of multiple myeloma.

—Geraldine P. Schechter
Washington VA Medical Center

Some signals are more equal than others

We take it for granted that administering growth factors such as EPO or GM-CSF causes a selective increase in patients' hematocrit or granulocyte/monocyte counts, respectively. These selective effects of cytokines are in part due to lineage-restricted expression of their cognate receptors on late hematopoietic progenitors. But since multiple cytokine receptors are coexpressed on early committed progenitors and stem cells, it is conceivable that these cells can distinguish among specific incoming signals originating from different receptors and translate this information into activation of differentiation programs. If so, we would of course like to break the code in which this information is encrypted.

Although very attractive, the concept of specific instructive signaling by cytokine receptors has remained controversial. Hisakawa and colleagues (page 3618) provide evidence largely in support of an alternative permissive model. They examined the effects of a functional human GM-CSF receptor (hGM-CSFR) ectopically expressed on erythroid progenitors of transgenic mice. Due to species specificity, activation of the transgenic hGM-CSFR is entirely dependent on exogenous human ligand. Furthermore, to exclude the possibility of cross-talk with the endogenous mouse EPO receptor (EPOR), *hGM-CSFR* mice were crossed with *EPOR* knockout mice, and fetal liver cells deficient for *EPOR* but expressing the *hGM-CSFR* transgene were derived. Under these stringent conditions, hGM-CSF promoted fully differentiated CFU-Es and BFU-Es in vitro. Furthermore, increased expression of the same adult hemoglobins as in EPO-treated wild-type control cells was observed. These results argue that the EPO and hGM-CSF signals are equal and interchangeable. But detailed analysis of yolk sac cells at embryonic day 8 revealed subtle differences: only hGM-CSF was able to induce expression of adult hemoglobins in primitive erythropoietic cells, while both receptors promoted erythroid-colony formation. Thus specific signaling information may be detectable only within a particular cellular context, and hence both the instructive and permissive models may be partially correct. The next question is, What are the molecular features defining the cellular context?

—Radek C. Skoda
German Cancer Research Center