INTRODUCTION

Considering the anatomical localization of bone and bone marrow it is not surprising that both tissues are composed of cells from hematopoietic as well as from stromal origin. Indeed, apart from the stroma-derived osteoblasts and osteocytes, which are characterized by their ability to produce a mineralized matrix, bone also contains osteoclasts. Osteoclasts belong to the hematopoietic lineage and have a lot in common with macrophages and characteristically resorb bone. The hematopoietic compartment of the bone marrow on the other hand, is functionally and structurally supported by a microenvironment of stromal elements including adipocytes, fibroblasts, endothelial cells and undifferentiated mesenchymal cells. These mesenchymal cells represent a reservoir of “uncommitted”, self-renewing cells which differentiate into various stromal elements, including bone. Under normal conditions, hematopoiesis and stromal differentiation require complex sequences of cellular events that are modulated by site-specific and cell-specific signals capable of initializing and promoting the recruitment and proliferation of the appropriate cells at the right time. These signals are mediated by hormones, prostaglandins, growth factors and cytokines which either reside in the bone matrix or in the bone marrow. The goal of this chapter is to review the effects of interleukin-10 (IL-10) on bone formation and hematopoiesis. IL-10 was initially described as cytokine synthesis inhibiting factor (CSIF) based on its potential to block the synthesis of cytokines produced by type 2 helper T cells.

IL-10 AND BONE FORMATION

THE ORIGIN AND CHARACTERISTICS OF OSTEOGENITOR CELLS

Bone marrow stroma forms a network of fibroblasts, adipocytes, endothelial cells and mesenchymal cells that supports and regulates hematopoiesis.
poiesis and harbors cells that give rise to the osteogenic lineage. The presence of osteoprogenitor cells in the marrow stroma is illustrated by the fact that bone marrow differentiates into bone ossicles when transplanted under the kidney or when cultured in intraperitoneally implanted diffusion chambers. In addition, a number of immortalized and transfected cell lines were generated from bone marrow stroma, which elicit osteogenic characteristics when cultured in vitro or when transplanted in vivo. Recent studies in the mouse showed that osteoprogenitor cells are low density cells (1.066-1.067 g/ml), which represent 0.00045% of the cells in normal bone marrow and 0.0057% in marrow treated with the chemotoxic drug 5-fluorouracil (5-FU). Moreover, these cells form bone nodules in culture and bind to both wheat germ and soybean agglutinin. Since 5-FU treatment depletes more than 95% of the circulating cells in vivo without reducing the frequency of osteoprogenitor cells, it is fair to say that the latter cells reside in the bone marrow in a quiescent state. Immunohistochemistry and in situ hybridization showed that mesenchymal cells of the bone marrow are uncommitted to the bone lineage since they do not produce or express bone related proteins. However, when cultured in the presence of β-glycerophosphate and vitamin C, mesenchymal cells quickly differentiate into bone. During this process they sequentially secrete alkaline phosphatase (ALP), collagen type I and osteocalcin, and finally form a mineralized matrix which contains the bone specific mineral, hydroxyapatite. Immunoanomaly analysis in combination with cell sorting revealed that uncommitted murine mesenchymal cells display a high forward and perpendicular light scatter profile. In addition, these cells bind wheat germ agglutinin and the monoclonal antibodies Sca-1, KM16, Sab-1 and Sab-2. Whereas, Sca-1 is commonly expressed on hematopoietic stem cells, KM16, Sab-1 and Sab-2 are specific for the stromal lineage. On the other hand, osteoprogenitor cells do not express the hematopoietic lineage markers Gr-1, B220, L3T4, Lyt2, Thy-1, Mac-1, Mac-2 and Mac-3. A comparable observation was made in the human bone marrow where osteoprogenitor cells express the hematopoietic and stromal marker CD34 and STRO-1 respectively, but none of the lineage markers (unpublished observation). Hence, it appears that mesenchymal cells express markers that are co-expressed by cells of the hematopoietic lineage. This indicates that hematopoietic and stromal cells may originate from a common precursor. Recent data revealed that at least the fetal human bone marrow contains a CD34+ CD38-DR- cell type, which gives progeny to both hematopoietic and stromal cells. However, personal observations showed that Sca-1*WGA* and CD34*CD38* cells from mature murine and human bone marrow are unable to differentiate into either hematopoietic or stromal cells respectively (unpublished observation).

In conclusion, a vast amount of data indicate that osteoprogenitor cells originate from uncommitted, pluripotent mesenchymal cells which represent a minor population in the bone marrow.

IL-10 REGULATES BONE PROTEIN SYNTHESIS AND EXTRACELLULAR MATRIX FORMATION

In vitro and in vivo bone formation is characterized by an increased proliferation of osteogenic cells, followed by subsequent synthesis of ALP, collagen type I and osteocalcin which finally leads to the formation of a mineralized matrix. We developed an in vitro model for bone formation to screen the effect of different cytokines on the sequential events, which govern osteogenic differentiation. When IL-10 was administered to this culture system, it significantly decreased the synthesis of ALP, collagen type I and osteocalcin (Fig. 7.1). Surprisingly, this effect was not preceded by an overall suppression of DNA synthesis or by a reduction of the growth, or the colony size, of the fibroblast colony forming cells (CFU-F), which are believed