superior to other established antioxidants such as vitamin E, vitamin C and glutathione peroxidase (6). Thus, melatonin may protect tissues from damage to the nucleus, radiation-induced cytotoxicity and lipid peroxidation, and may prove particularly effective in defending cells against specific poisons, such as CCl4 and the herbicide paraquat (6).

From a clinical point of view, many speculations have been advanced for future treatment of immune-mediated diseases that have become refractory to standard therapy, such as severe progressive autoimmune diseases, acquired immunodeficiency syndrome and advanced stages of cancer. However, prospective, controlled clinical studies will be required to evaluate the perspectives of melatonin as an immunotherapeutic agent, and to safeguard both the scientific community and the public against undue and overwhelming euphoria.

References

Lorenz Hofbauer, Medizinische Klinik, Klinikum Innenstadt, Ludwig-Maximilians-Universität, Ziemssenstraße 1, 80336 München, Germany.

Intercellular chatter: osteoblasts, osteoclasts and interleukin 6

Lorenz C Hofbauer and Armin E Heufelder
Medizinische Klinik, Klinikum Innenstadt, Ludwig-Maximilians-Universität München, Germany

Homeostasis of bone metabolism and function depends upon bone remodeling, a coordinated, closely coupled process of resorption and formation of new bone. A variety of cell types and functions, hormones (steroid, polypeptide and thyroid hormones), as well as autocrine and paracrine growth factors and cytokines, act in concert to rebuild the skeleton while maintaining its structural and biomechanical properties (1). The two major players involved in bone remodeling, osteoblasts and osteoclasts, are of different origin: osteoblasts derive from pluripotent mesenchymal stem cells of the bone marrow, whereas osteoclasts originate from the hematopoietic granulocyte-macrophage colony-forming units (GM-CFU) (1). Thus, their differentiation to mature bone cells differs substantially with respect to their cytokine requirements and subsequent events of signal transduction.

In addition to their phenotypic markers, collagen type I and alkaline phosphatase, osteoblasts produce a variety of cytokines that are crucial for their maturation, including interleukin 6 (IL-6), IL-11, granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF). Cytokines involved in osteoclastogenesis include IL-1, IL-3, IL-6, IL-11, tumor necrosis factor, GM-CSF and M-CSF (1). Several recent studies have suggested a crucial role for IL-6 in conditions characterized by inappropriate bone resorption such as multiple myeloma, Paget's disease of bone, Gorham–Stout disease ("vanishing-bone disease") and rheumatoid arthritis (1, 2). In addition, IL-6 has been implicated in the pathogenesis of osteopenia associated with female and male hypogonadism (1). Owing to its role in both osteoblast and osteoclast evolution and its involvement in resorptive bone disorders, IL-6 has recently received much attention among osteologists. Interleukin 6, a pleiotropic cytokine, acts upon many cell types through their IL-6 receptors (IL-6R). Binding of IL-6 to the extracellular region of IL-6R activates intracellular signal transduction and induces tyrosine-specific phosphorylation of glycoprotein 130 (gp130), a 130-kD nonbinding signal transducer in various cell types, including bone cells (2).

The observation that osteoblasts, but not osteoclasts, express receptors for bone-resorbing agents such as parathyroid hormone, vitamin D and prostaglandins led to the hypothesis that hormones mediating bone resorption must first bind to osteoblastic lineage cells before stimulating osteoclastogenesis. Studies by Udagawa and colleagues (3) now demonstrate that similar mechanisms also apply to IL-6-mediated bone cell differentiation. In a recent study published in the Journal of Experimental Medicine they report the intriguing observation that induction of osteoclast differentiation by IL-6 depends on IL-6 receptor expression by osteoblasts, rather than osteoclast progenitors. In their experiments they used co-cultures of osteoclast progenitors and osteoblasts derived from transgenic mice over-expressing the human IL-6R. Osteoclast differentiation
Insulin-like growth factor binding protein 3 (IGFBP-3): a novel target of the tumor suppressor p53 inhibiting cell growth

Jérôme Bertherat

Service d’Endocrinologie and INSERM CJF 92-08, CHU Cochin, Paris, France

The insulin-like growth factors (IGFs) have been known for a long time to play an important stimulatory role in cell growth. Their bioavailability is regulated by at least six IGF binding proteins. More recently, an inhibition of cell proliferation by one of these IGF binding proteins (IGFBP-3) has been observed. The growth inhibitory effect of IGFBP-3 could be mediated by inhibition of IGF-I. Nevertheless, experiments performed using fibroblasts devoid of IGF-I receptor (derived from IGF-I receptor knockout embryos) suggest that growth inhibition by IGFBP-3 could be independent of the IGF-I receptor (1). The human tumor suppressor protein p53 is critical for the regulation of the cell cycle in response to genotoxic stress. Deleterious mutations or loss of the p53 gene are observed in over half of all human tumors. It is also speculated that the upstream or downstream components of the p53 pathway could be altered in some of the remaining tumors harboring a wild-type p53 gene. The identification of downstream targets of p53 is important for the understanding of oncogenesis. Protein p53 is a transcription factor that binds specific DNA sequences (p53-responsive elements). The tumor suppressor function of the wild-type p53 involves activation of the transcription of various growth regulatory genes. Some