

Bone remodeling

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This lecture is dedicated to Professor Herbert A. Fleisch, former Head of the Laboratory for Experimental Surgery, Swiss Research Institute, Davos (1963-1967) and former Head of the Department of Pathophysiology, University of Bern (1967-1997).

Bone is a living tissue which is constantly remodeled to remove microfractures, to adapt to changing mechanical strains and to fulfill its role in calcium and phosphate homeostasis. The remodeling process is based on a concerted action of bone forming and bone resorbing cell populations replacing old bone by new bone. This sequence of events is tightly regulated, deviations from a neutral balance between bone resorption and formation will result in changes in bone mass, causing osteosclerosis or osteopenia.

The close proximity of the haematopoietic compartment (origin of osteoclast lineage cells), the marrow stroma (harbouring the precursors of the osteoblast lineage cells) and of vasculature suggests not only an anatomical but also a functional relationship between the different cell systems. Indeed, the communication between the different cell lineages has been suggested to occur through cell-cell contacts, through soluble factors, or through constituents of the extracellular matrix (ECM) that are liberated during bone resorption.

The coupling of bone resorption and formation was demonstrated by blocking the resorptive process with bisphosphonates. While bone loss can be stopped with bisphosphonates, virtually no increase in bone mass is observed due to a slowdown of bone turnover. The molecular entities accomplishing this connection, however, have not yet been elucidated.

Further information on the regulation of bone mass and the interaction between bone forming and resorbing cells could be gained through the investigation of various osteopetrotic animal strains. Osteopetrosis is a common phenotype with a multitude of underlying causes, and two types of the disease can be distinguished. In some cases, osteopetrosis can be cured by marrow transplantation, suggesting an inherent

defect in the haematopoietic compartment, others. In other cases, marrow transplantation does not reverse the osteopetrotic phenotype, suggesting a defective haematopoietic microenvironment. Indeed the first osteopetrotic mouse whose defect was characterized, the *op* strain, was found to be deficient in the growth factor for cells of the monocyte/macrophage lineages, macrophage colony-stimulating factor, M-CSF (1,2). Later, receptor activator of NF- κ B ligand (RANKL) was found as a second bone cell derived factor governing the development and activity of osteoclasts (3).

A most relevant aspect in bone remodeling is represented by pathophysiological conditions with a dysregulation of bone formation and resorption, as is the case in diseases like osteoporosis, osteoarthritis or in clinical complications such as the aseptic loosening of prosthetic implants. In each of these conditions, the common denominator is the cytokine repertoire that is mediating the bone wasting. Inflammatory processes, initiated by cytokines such as tumor necrosis factor- α (TNF α) and interleukin-1 (IL1) are crucially involved (4).

The mechanisms of the communication among the different cell types that is essential for the maintenance of physiological bone metabolism and turnover are as of yet not fully elucidated. Cell-cell contact will be required for the full function of membrane-bound growth factors (M-CSF, RANKL), but histological evidence does not support an immediate vicinity of bone resorbing and bone forming cell lineages. Other means of compartmentalization in the bone multicellular unit (BMU), in which the coupling of resorption and formation takes place, must take effect (5).

References

- 1) Felix R *et al.* (1990), J Bone Miner Res 5:781-5
- 2) Felix R *et al.* (1990), Endocrinology 127:2592-4
- 3) Kong YY *et al.* (1989), Nature 397:315-23
- 4) Balga R *et al.* (2006), Bone 39:325-35
- 5) Eriksen EF *et al.* (2007) J Bone Miner Res 22:1-6