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タイトル: **Inflammatory processes and bone metabolism**
(炎症過程と骨代謝)

Willy Hofstetter 先生はビスフォスフォネートの生みの親である **H.A. Fleisch** 先生のお弟子さんのお 1 人で、現在スイスベルン大学の骨代謝グループのリーダーとして、さまざまな研究を行っています。特に、炎症性サイトカインと骨代謝の研究で著名な研究者です。今回は、サバティカル休暇を松本歯科大学での研究にあてることができるかを調べる目的で来学されました。多くの大学院生ならびに先生方のご参加をお願いいたします。

担当:硬組織疾患制御再建学　高橋　直之

INFLAMMATORY PROCESSES AND BONE METABOLISM

It has become increasingly evident that the immune system and bone are forming a close anatomical and functional relationship. Inflammatory processes are found to profoundly affect bone metabolism by creating a local environment favoring osteoclastogenesis and bone resorption. A limited set of cytokines, including interleukin-1 (IL1) and tumor necrosis factor alpha (TNFα), as well as IL6 or IL17 are released by immune cells upon activation in diseases and surgical complications such as Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), osteoporosis or loosening of permanent implants. We have focused on the role of TNFα in bone metabolism and we found that the cytokine, depending on the target cell populations, can exert pro- as well as anti-osteoclastogenic effects.

A feature in inflammatory joint diseases like RA and AS is the development of osteolytic lesions in the subchondral bone. In contrast to earlier days, when the use of anti-inflammatory steroids was the major therapy, more sophisticated biological drugs, such as antibodies against TNFα or IL6 receptor antagonists, are available today. To investigate the mechanisms of action of TNFα in RA and AS patients that were subjected to a therapeutic protocol with inactivating anti-TNFα antibodies, peripheral blood mononuclear cells (PBMC) were isolated at pre-determined time points. The cells were culture on dentin slices in media containing macrophage-colony stimulating factor (MCSF) and receptor activator of NF-κB ligand (RANKL) and the resorptive activity of the cells was determined. The ability of the cells to develop into bone resorbing osteoclasts was greatly reduced within days after the onset of the therapeutic protocol. Further studies revealed changes in the cellular composition within PBMC of the patients that may at least partially account for the observed reduction in bone resorption *in vitro*.

Even though TNFα has been been described as a potent mediator of bone loss by inducing resorption, while inhibiting formation, the actions of the cytokine may be more complex. When added to a co-culture of primary murine osteoblasts with osteoclast progenitor cells (OPC), TNFα was found to inhibit the development of osteoclast in dependence of its dose. Two effects were found to overlay each other, a stimulation of osteoclastogenesis through a direct action on OPC and an inhibition of the process via osteoblast lineage cells. Expression analysis, which was complemented by experimental evidence, suggested that the haematopoietic growth factor granulocyte-macrophage colony stimulating factor (GMCSF), which is known to inhibit osteoclastogenesis, was released upon treatment of osteoblast lineage cells with TNF.

The TNFα-induced release of GMCSF was attenuated by anti-inflammatory compounds, and thereby, development of osteoclasts was restored.

Thus, TNFα can be described as a growth factor that exerts opposite effects on developing osteoclast lineage cells. Through a direct action on these cells, in the presence of limiting levels of RANKL, TNFα potently stimulates development and activity of osteoclasts. Indirectly, through the release of GMCSF, however, TNFα profoundly inhibits osteoclastogenesis by blocking RANK expression and rendering the cells unresponsive to RANKL. Combining the *in vivo* and *in vitro* data, a model is postulated in which GMCSF acts on osteoclast lineage cells in separate physiological compartments. In circulation, the growth factor may act as a proliferation factor for monocyte lineage cells, increasing the pool of potential osteoclast progenitors. Upon migration to the bone marrow, the progenitors are exposed to a local osteoclastogenic environment that directs osteoclastic differentiation and increased bone resorption that is responsible for bone loss frequently associated with inflammatory diseases.