



Institute of Orthopedic Research and Biomechanics, Center of Musculoskeletal Research

Work Group: Cellular and Molecular Regulation of Bone Remodeling and Regeneration

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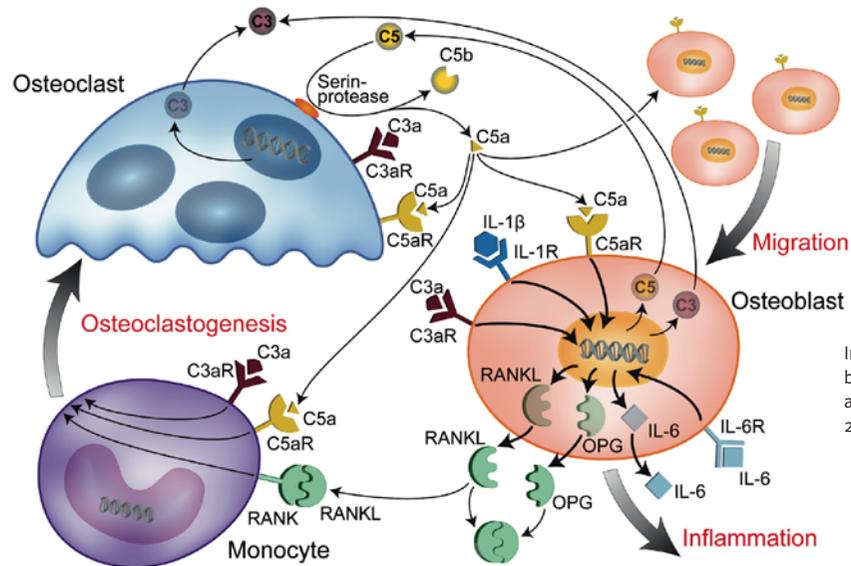
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The overall goal of the research activities at this interdisciplinary research institute is to better understand the reasons for degeneration and diseases of the musculoskeletal system and to develop improved therapeutical strategies. The various research groups of the institute deal with basic and applied research projects which are related to bone metabolism and regeneration in healthy, diseased and injured patients, mechanotransduction in bone, intervertebral disc regeneration and biomechanics of the spine and joints.

One of our research teams focuses on fracture healing in osteoporotic bone. Osteoporosis is one of the most prevalent diseases in the aged population. It predominantly affects postmenopausal women, but also older men, and is characterized by an imbalance between bone formation and resorption. The resulting bone loss leads to fragility fractures. Fracture healing is often associated with complications due to the reduced regenerative capacity of the osteoporotic bone. The underlying



Influence of complement on bone cells (Schöngraf P. et al. Immunobiology, 2013, 218:1-9)

pathomechanisms might be complex and are poorly understood so far. Important factors might be sex hormone deficiency, advanced age, immobilization, altered mechanotransduction, and deficiencies in important regulatory pathways, such as Wnt signaling. Wnt signaling is a key pathway controlling bone formation. Polymorphisms in Wnt-related genes are associated with osteoporosis. We therefore investigate in particular the role of Wnt signaling in bone regeneration and fracture healing using a broad spectrum of methods (specific mouse models with modifications in the Wnt pathway, histology, micro computed tomography, cell culture, molecular biology). Furthermore, we are interested in the role of estrogen in bone regeneration, the interaction of estrogen receptor signaling and the Wnt pathway in mechanotransduction in bone. Our current results indicate that both pathways are important for bone regeneration and mechanically induced bone formation, and interact both in vitro as well as in vivo. The results of these studies might help to identify crucial pathomechanisms of impaired bone regeneration in osteoporotic patients.

Another focus of our research is the investigation of the influence of systemic inflammatory conditions, such as posttraumatic systemic inflammation, on bone regeneration. A severe tissue trauma is associated with an extensive activation of the complement system, a crucial part of the innate immunity. Our present data suggest an important role of complement in delayed bone healing. We investigated the effects of activated complement on osteoblasts and osteoclasts and found that the complement anaphylatoxins could modulate important bone cell functions, such as osteoblast migration, cytokine release and osteoclast formation and activity. These data help to understand the interaction of posttraumatic inflammatory conditions on bone regeneration.

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Selected Publications:

- Recknagel S, Bindl R, Kurz J, Wehner T, Schoengraf P, Ehrnhaller C, Qu H, Gebhard F, Huber-Lang M, Lambris JD, Claes L, Ignatius A (2012): C5aR-antagonist significantly reduces the deleterious effect of a blunt chest trauma on fracture healing. *J Orthop Res.* 30:581-6.
- Ignatius A, Ehrnhaller C, Brenner RE, Kreja L, Schoengraf P, Lisson P, Blakytyn R, Recknagel S, Claes L, Gebhard F, Lambris JD, Huber-Lang M (2011): The Anaphylatoxin Receptor C5aR Is Present During Fracture Healing in Rats and Mediates Osteoblast Migration In Vitro. *J Trauma.* 71:952-960.
- Ignatius A, Schoengraf P, Kreja L, Liedert A, Recknagel S, Kandert S, Brenner RE, Schneider M, Lambris JD, Huber-Lang M (2011): Complement C3a and C5a modulate osteoclast formation and inflammatory response of osteoblasts in synergism with IL-1β. *J Cell Biochem.* 112:2594-2605.
- Recknagel S, Bindl R, Kurz J, Wehner T, Ehrnhaller C, Knoferl MW, Gebhard F, Huber-Lang M, Claes L, Ignatius A (2011): Experimental blunt chest trauma impairs fracture healing in rats. *J Orthop Res.* 29:734-739.
- Liedert A, Mattausch L, Rontgen V, Blakytyn R, Vogele D, Pahl M, Bindl R, Neunaber C, Schinke T, Harroch S, Amling M, Ignatius A (2011): Midkine-deficiency increases the anabolic response of cortical bone to mechanical loading. *Bone.* 48:945-951
- Liedert A, Wagner L, Seefried L, Ebert R, Jakob F, Ignatius A (2010): Estrogen receptor and Wnt signaling interact to regulate early gene expression in response to mechanical strain in osteoblastic cells. *Biochemical and biophysical research communications.* 394:755-759.