Priority Program 1468: Osteoimmunology – IMMUNO BONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone

Speaker
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Aims and Structure
The interdisciplinary project “Osteoimmunology – IMMUNO BONE – A Program to Unravel the Mutual Interactions between the Immune System and Bone” (SPP 1468 – IMMUNO BONE) is a priority program that has been funded by the DFG for the first funding period of three years with a total volume of 6.8 million Euro. At the beginning of 2013, SPP 1468 – IMMUNO BONE has been positively evaluated for a second funding period for additional three years with a total volume of 7.1 million Euro. The interdisciplinary consortium consists of 20 groups of 15 different research institutions of osteologic orthopedics, rheumatology, and immunology.

Research
Osteoimmunology is an interdisciplinary research field investigating the interactions between immune and bone cells. It is assumed that both systems communicate with each other and that their interplay has an influence on diseases like osteoporosis and arthritis. Initial insights about the interaction between bone and the immune system were recognized 15 years ago by the discovery of a protein termed Receptor Activator of NF-κB Ligand (RANKL). It was shown that molecules on the surface of immune cells influence bone homeostasis. Within SPP 1468 – IMMUNO BONE, we identified several molecular mechanisms and essential cellular interactions between inflammatory cells, cytokines, and bone cells. The findings improved knowledge of the pathogenesis of bone diseases triggered by inflammatory processes. On the other hand these findings form the basis to develop innovative therapy approaches for treatment of rheumatic inflammatory diseases. Some significant results of the project groups in Erlangen can be highlighted as follows:

The findings of the different projects prove a close interaction between immune-, bone- and metabolic system. A connection between unhealthy nutrition and damage of the immune system was shown. This group identified that high-fat diet leads to specific alterations in the bacterial flora of the gut. They described how these alterations activate the metabolic checkpoint molecule PPAR-γ, leading to an increased production of adipose tissue in the bone marrow and displace the stem cell and bone marrow niche. It is known that if adipocytes store energy, this leads to inflammation and subsequent damage or destruction of joints and bones.

A group in Erlangen revealed that lack of sialic acid in the glycosylation of immunoglobulin G in synovial fluids of patients with rheumatoid arthritis (RA) leads to an activation of osteoclast formation. Therefore, IgG complexes are a key component of inflammatory bone loss. This mechanism is directly involved in the induction of an autoimmune disease – rheumatoid arthritis – and was recently described in more detail. The lack of sialic acid in the glycosylation of proteins involved in RA induction seemed to be the key element. The group was able to show the direct involvement of TH17 cells on the immunologic memory that, by a simple variation of the glycosylation structure of autoantibodies, led to the provocation of RA.

In all inflammatory and renewal processes immune cells interact with pathogens and endogenous cells. An IMMUNO BONE group discovered a new mechanism which is responsible for ongoing activation of renewal processes. They were able to reactivate the receptor Nr4a1 pharmacologically which inhibits TGF-beta leading to a block of excessive activation of fibrocytes. This reactivation can counteract excessive production or disturbed tissue necrosis of extracellular necrosis in fibrotic diseases. Neutrophil extracellular trap (NET) formation is a cell component of neutrophils. One of our groups was able to demonstrate the size dependent induction of NETosis with inert, non-polar nanoparticles – like nanodiamonds or uric acid crystals, with the latter appearing in acute gout attacks. This process not only leads to the immobilization of uric acid crystals in gout, but induces the resolution of the originally inflammatory response.

All these results show that diverse interactions between the immune and skeletal system exist which are clinically relevant. The results mentioned are just a part of the more than 90 scientific articles published within SPP 1468 – IMMUNO BONE.

Teaching
The heads of the research groups are involved in the traditional teaching program (lectures, seminars, internships) covering all subjects in the field of medicine and molecular medicine as well as in the PhD/MD programs for basic and translational research.