BMBF-Research Network Musculoskeletal Disorders: METARTHROS – metabolic impact on joint and bone diseases

Speaker
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Aims and structure

METARTHROS is one of nine national consortium projects in the course of the BMBF research network "Musculoskeletal diseases", investigating clinically relevant key factors in the interaction between inflammation and metabolic diseases. The consortium has been funded by the BMBF for a period of 3.5 years with 4.1 million euros. It aims to define the pathophysiological processes and the clinical impact of disturbed glucose and energy homeostasis, such as obesity and diabetes on arthritis. METARTHROS consists of eight subprojects and one clinical trial, represented by a strongly interdisciplinary consortium of rheumatologists, diabetologists, epidemiologists, geneticists, imaging physicists, and orthopedics, bridging translational, clinical, and health care sciences in the field of arthritis. Furthermore, the consortium combines aspects of medical care, translational and clinical research in the field of arthritis. Due to the cooperation of eight different centers, including the German Diabetes Center Düsseldorf (DDZ) and the German Rheumatism Research Centre Berlin (DRFZ), the consortiums disposes of well-characterized patient cohorts, biobanks as well as a range of technical skills, reaching from disease modeling, outcome, research, and trial design.

Research

The main focus of the METARTHROS consortium is the evaluation of the interplay of different molecular mechanisms and factors which are responsible for the development and progress of musculoskeletal disorders and connected to metabolic diseases. It is not known how glucose metabolism affects mechanistically musculoskeletal diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (PsA), and osteoarthrosis (OA). Thereby, regulation of inflammation mediated by the adipose tissue might be a key factor affecting the joint-bone-unit.

Preliminary results of prior collaboration „A Network on Clinics and Pathophysiology of Osteophytes and Ankylosis" (ANCYLOSS) have shown that diabetes is an independent predictor for severe joint diseases. Furthermore, we were able to investigate adipokines – pro-inflammatory mediators originating in adipose tissue – and could show that they are tightly connected to joint inflammation and bone architecture. Diabetes is associated to severe osteoarthrosis that could lead to endoprosthetic surgeries. Thus, it seems that arthritis, overweight, and diabetes form an alliance, affecting joint and bone structures destructively. Hallmarks of RA and diabetes include the detection of an increase of markers of inflammation before the actual onset of the disease, which indicates subclinical inflammation as a common mechanism. In particular, resistance against insulin is intensified in inflammation. Intriguingly, resistance against insulin is not only present in patients with RA, but observed early in the course of the disease.
The METHARTHROS subprojects (TP) 1-3 are investigating pathophysiological aspects that are clinically relevant in arthritis and energy metabolism. TP 4-6 are developing instruments and methods concerning genetic, serological factors and imaging modalities in order to observe the impact of metabolism on musculoskeletal disorders. TP 7 and 8 analyze the effects of diabetes and overweight on the clinical presentation, changes in bone structure as well as the therapeutic response of patients with arthritis. Additionally, the importance of musculoskeletal diseases in patients with diabetes will be defined. All results will be incorporated into the clinical study in order to establish a strategy for intervention that aims to limit inflammation and improves the resistance against insulin.
Experimental studies revealed a molecular mechanism that substantiates the close alliance of adiposity, resistance against insulin and inflammation. Here, high fat diet led to a specific alteration in the microbacterial flora of the gut. This alteration induced the activation of the peroxisome proliferator-activated receptor PPAR-γ which plays an important role in bone formation. It was shown that there was an increase in adipose tissue in the bone marrow replacing stem and immune cell niches. Another group was able to detect the release of adiponectin from cells involved in the bone reconstruction in arthritic bone tissue. Adiponectin changes the gene expression and cytokine release in osteoblasts and elevates the IL-8 release in osteoclasts. These results support the pro-inflammatory role of adiponectin and indicate that adiponectin is influencing bone remodeling in RA via osteoblasts and osteoclasts.
Analysis of synovial fluids of patients with RA revealed that lack of sialic acid in glycosylation of immunoglobulin G 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 – as e.g. RA – 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 addition, it has been demonstrated that obesity has an overall negative effect on the efficacy of cytokine therapies TNFi and TOC, whereas this cannot be demonstrated for the cell-directed therapies RTX and ABA. The strength of the influence depends on the endpoint considered as well as on gender.
The findings mentioned here represent only a small part of the more than 50 results already published by the METARTHROS consortium.

Teaching

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

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