UNIVERSITY HOSPITAL

Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

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Research focus
- Tissue and Bone Destruction
- Autoimmunity
- Metabolism
- Tissue Homeostasis
- Innate Immunity
- Fibrosis Research
- Clinical Research
- COVID-19 and Inflammation

Structure of the Chair

Professorships: 8
Personnel: 246
- Doctors (of Medicine): 31
- Scientists: 52
  (thereof funded externally: 22)
- Graduate students: 36

Clinical focus areas
- Rheumatology (In- and outpatient department)
- Immunology (In- and outpatient department)

Research

The Department of Medicine 3 focuses on translational and clinical inflammation research to decipher the mechanisms that are responsible for pathogenesis and perpetuation of rheumatic inflammatory and autoimmune diseases. The emphasis of the experimental research is on the interaction between immune cells and cells of affected organs. The main focus of the clinical research is innovative drug trial studies and early recognition of rheumatic diseases, e.g. by imaging methods.

Tissue and Bone Destruction
Chronic inflammation often leads to bone loss. Responsible for this are mediators released by inflammation that have a destructive effect on the joints and the bone.

PI: Prof. Dr. A. Bozec
We delineate that macrophages are skewed into an anti-inflammatory and bone protective phenotype by Fra-1 expression via the induction of L-arginine. We have also shown that HIF1a is essential in regulating B cells, which influences autoimmune responses and bone homeostasis. Recently, we have uncovered a new crosstalk between osteocyte death and the induction of bone loss by increasing osteoclastogenesis via activation of the c-type lectin receptor Mincle.

PI: Dr. U. Steffen
The group investigates the interplay between antibodies and bone loss in rheumatic diseases. We showed the regulation of bone resorption by Siglec-9 and the effects of IgA subclasses on immune cells and bone. For instance, the IgA subclass IgA2 acts proinflammatory and aggravates rheumatoid arthritis.

PI: Dr. S. Frey
The group showed that JAK inhibitors relieve pathological bone loss and promote the repair of affected bone substance. In addition, the group could decipher the mechanism that is responsible for osteoblast differentiation allowing bone repair during arthritis.

Autoimmunity
The origin of autoimmunity leading to chronic inflammation is essential for developing strategies that allow to prevent autoimmune disease.

PI: Prof. Dr. G. Krönke
A new mechanism and function has been discovered that allows the joint cavities remain cell free: Using light sheet fluorescence microscope, we were able to visualize a closed mantle of resident macrophages along the synovium, which isolates the joint from the surrounding tissue and is a protective membrane against inflammatory reactions.

Metabolism
Misdirected metabolic processes such as in obesity, diabetes and chronic intestinal diseases appear to have a major influence on inflammatory activity in joint and bone diseases.

PI: Prof. Dr. M. Zaiss
Interactions between intestinal and bone cells play an important role in the pathogenesis and progression of rheumatoid arthritis. In this context, metabolic products of the intestinal bacteria such as short chain fatty acids influence the immune system and therefore have an effect on autoimmune diseases such as rheumatoid arthritis. We were able to show that a diet rich in fibres has an anti-inflammatory effect. Also the immunomodulatory effect of moderate alcohol consumption was described by the group.

Tissue Homeostasis
Inflammation leads to fast tissue responses that can either prevent or promote inflammation.

PI: Prof. Dr. S. Uderhardt
The use of intravital imaging and multiplex microscopy enabled us to demonstrate that tissue-resident macrophages can actively protect stromal tissue damage and prevent the activation of inflammatory effector cells. This "cloaking" mechanism prevents inflammatory collateral damage and maintains tissue homeostasis during local stromal injury.

PI: PD Dr. M. Hoffmann
We could show that the so-called "inflammatory tissue priming" is based on a metabolic reprogramming of tissue-derived synovial fibroblasts (SF). Inflammatory tissue priming develops following activation of intracellular complement C3 and the complement C3a receptor, which initiates the mTOR/HIF1α pathway, resulting in increased glycolysis and oxidative phosphorylation and activation of the NLRP3 inflammasome in SF. This new concept may be a basis for new therapeutic approaches that seek to reset tissue priming and would thus allow suspension of anti-inflammatory therapies at low risk of relapse.

Innate Immunity
Neutrophil extracellular traps (NETs) play a crucial role in the pathogenesis of autoimmune diseases and are essential for the immune system.

PI: Prof. Dr. Dr. M. Herrmann, PD Dr. L. Munoz
Neutrophils, NETs and aggregated NETs (aggNETs) are double-edged swords that orchestrate the innate immune response but also carry the risk of causing autoimmunity, epithelial damage and vascular blockages. We showed that gallstone formation essentially requires NETs. In accordance with the physicochemical process of crystal formation, NETs promote their aggregation into larger aggregates and eventually into gallstones. Similarly, they promote calcium crystal aggregation in the salivary gland ducts and trigger concrement formation. They are particularly important for patrolling and monitoring the external and internal body surfaces and exhibit anti-inflammatory characteristics in the oral cavity and eye. In contrast, excessive aggNET formation can directly block vessels and ducts, causing thrombi, like those observed in COVID-19 or duct obstruction such as gallstones. We describe how NET formation influences diseases and how NET formation can be therapeutically inhibited.

Fibrosis Research
Fibrotic diseases are characterized by aberrant activation of fibroblasts with progressive deposition of extracellular matrix.

PI: Prof. Dr. J. Distler
We demonstrated that fibroblast growth factor receptor 3 (FGFR3) and its ligand FGF9 are induced by the profibrotic cytokine transforming growth factor β (TGF-β) in patients with systemic sclerosis (SSc) with a corresponding FGFR3 signature in SSc skin. Activation of FGFR3 induces a profibrotic phenotype in fibroblasts by inducing multiple profibrotic signals, while inhibition of FGF9/FGFR3 shows antifibrotic effects in different models. We also demonstrated that activation of DNA

methyltransferase 3A (DNMT3A) and DNMT1 in fibroblasts turns off the expression of the antifibrotic factor Suppressor of Cytokine Signaling 3 by promoter hypermethylation in the sense of tissue memory, and the resulting hyperactivation of the JAK/STAT signaling cascade promotes fibrotic tissue remodeling.

PI: PD Dr. A. Ramming
In fibrotic diseases, fibroblasts synthesize large amounts of extracellular matrix. However, fibroblasts in arthritis are also characterized by the degradation of the extracellular matrix. We identified the transcription factor PU.1 as an essential regulator of the pro-fibrotic gene expression program. The interplay between transcriptional and post-transcriptional mechanisms that normally control PU.1 expression is disrupted in several fibrotic diseases, leading to upregulation of PU.1, induction of fibrosis-associated gene sets and a phenotypic switch to extracellular matrix-producing pro-fibrotic fibroblasts.

Clinical Research
In order to transfer innovative diagnostic and monitoring methods as well as targeted therapies into routine practice, we conduct phase Ib-IV therapy studies as well as phase II studies on the safety and efficacy of drugs.

PI: PD Dr. A. Kleyer, PD Dr. D. Simon, PD Dr. M. Pachowsky
Structural changes in the joints result from chronic inflammatory arthritis. By using state-of-the-art imaging techniques such as MRI or high-resolution peripheral quantitative computed tomography (HR-pQCT), we are able to identify early bone changes associated with the onset of arthritis. Hereby, we combine advanced imaging with computer technology (cinematic rendering). Furthermore, we showed that certain bone changes in the finger joints, such as erosions and osteophytes, are age-dependent and that the biomechanical properties of the peripheral bone are relevantly reduced in patients with hand osteoarthritis. In addition to bony changes, we investigated whether sequences in MRI, such as T2 mapping, detect cartilage damage in patients with RA. These innovative diagnostic and monitoring methods as well as targeted therapies are being investigated in ongoing studies (Phase II-IV) to evaluate disease progression and treatment response in patients with rheumatoid arthritis or psoriatic arthritis and to transfer them into clinical routine.

COVID-19 and Inflammation
We identify factors influencing the humoral immune response to SARS-CoV-2 in patients with immune-mediated inflammatory diseases.

PI: Prof. Dr. Dr. M. Herrmann
We showed that severe COVID-19 is characterized by pronounced formation of NETs within the micro-vessels. The intravascular aggregation of NETs leads to rapid occlusion of the affected vessels, impaired microcirculation and organ damage. In severe COVID-19 infections, the neutrophil granulocytes are highly activated and adopt a so-called low-density phenotype, which tends to spontaneously form NETs.

PI: Prof. Dr. G. Schett, Prof. Dr. B. Manger, PD Dr. D. Simon
SARS-CoV-2 antibody testing showed that patients with inflammatory diseases, including rheumatoid arthritis, Crohn´s disease and psoriasis receiving cytokine inhibitor therapy have a low risk for COVID-19 infection. This finding has been surprising and indicated that immune modulatory treatment of such patients should not be stopped but maintained during the pandemics.

Teaching

The Department of Medicine 3 is embedded into the curriculum-based teaching of Medicine. In the course of interdisciplinary teaching, the lecture “Dr. House in Erlangen – surgical and internal differential diagnosis” for first-year students is to highlight particularly.
Furthermore, master’s theses as well as medical and scientific doctorates are supervised.

Selected publications

Simon D, et al. Patients with immune-mediated inflammatory diseases receiving cytokine inhibitors have low prevalence of SARS-CoV-2 seroconversion. Nat Commun. 2020 Jul 24;11(1):3774.

Schett G, et al. COVID-19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol. 2020 Aug;16(8):465.

Tajik N, et al. Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis. Nat Commun. 2020 Apr 24;11(1):1995.

Simon D, et al. Bone Mass, Bone Microstructure and Biomechanics in Patients with Hand Osteoarthritis. JBMR. 2020b. 35, 1695-1702.

Leppkes M, et al. Vascular occlusion by neutrophil extracellular traps in COVID-19. EBioMedicine. 2020 Aug;58:102925.

Steffen U, et al. IgA subclasses have different effector functions associated with distinct glycosylation profiles. Nat Commun. 2020 Jan 8;11(1):120.

Distler JHW, et al. Shared and distinct mechanisms of fibrosis. Nat Rev Rheumatol. 2019 Dec;15(12):705.

Daniel C, et al. Extracellular DNA traps in inflammation, injury and healing. Nat Rev Nephrol. 2019 Sep;15(9):559.

Muñoz LE, et al. Neutrophil Extracellular Traps Initiate Gallstone Formation. Immunity. 2019 Sep 17;51(3):443.

Culemann S, et al. Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature. 2019 Aug;572(7771):670.

Wohlfahrt T, et al. PU.1 controls fibroblast polarization and tissue fibrosis. Nature. 2019 Feb;566(7744):344.

International cooperations
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