Department of Medicine 3 – Rheumatology and Immunology

Chair of Internal Medicine III

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Research focus
- Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)
- Apoptosis, necrosis, and NETosis as immune modulators
- Activation of neutrophile granulocytes
- National and international clinical trials
- Immunogenetics and transplantimmunology
- Immunodeficiencies and infectious diseases
- Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)
- Molecular signaling pathways in RA
- Metabolic impact on inflammation
- Pathomechanisms of bone destruction in RA
- Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)
- Immunbiology and molecular mechanisms of inflammation
- Analysis of inflammatory mechanisms in adult onset Still's disease
- Molecular and cellular immunology in metabolism
- Epidemiology and experimental imaging

Structure of the Chair

Professorships: 6
Personnel: 163
- Doctors (of Medicine): 18
- Scientists: 28 (thereof funded externally: 24)
- Graduate students: 47

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 besides drug trial studies on interdisciplinary cooperations to optimize imaging methods.

Activation of synovial fibroblasts by microparticles in rheumatoid arthritis (RA)

PI: Prof. Dr. J. Distler
Microparticles are realized by activated and apoptotic leukocytes and accumulate in the involved joints in patients with RA. We demonstrated that microparticles represent a novel mechanism for inter-cellular communication and that they play a role in the pathogenesis of RA by triggering a vicious circle of inflammation and bone-erosion. The mechanisms by which microparticles activate synovial fibroblasts are currently in focus.

Apoptosis, necrosis, and NETosis as immune modulators

PI: Prof. Dr. Dr. M. Herrmann
We utilize controlled suicide systems to analyze generation and role of ROS (reactive oxygen species) and their intracellular accumulation. We employ the MSU (monosodium urate) driven inflammation to analyze recruitment of granulocytes to sites of inflammation, NET formation, and aggregation.

Activation of neutrophile granulocytes

PI: Dr. M. Hoffmann
Neutrophil granulocytes can either fuel or downregulate inflammation. We investigate the influence of neutrophils on inflammatory diseases and bone metabolism (gout, RA, or SLE). We focus on the formation of neutrophil extracellular traps (NET) and on chemical redox reactions. Finally, we are going to translate data from animal models and *in vitro*-findings to humans and develop new treatment strategies.

National and international clinical trials

PI: PD Dr. J. Rech, Dr. A. Kleyer
Various national and international phase Ib-IV studies are conducted to investigate new treatment approaches in rheumatic diseases. The major focus are on treatments with "biologicals and small molecules", e.g. blockade of the proinflammatory cytokine TNFα, IL-6, IL-17, IL12/23, JAK3-kinase. We initiated and conducted a multicenter phase II trial in patients with erosive finger osteoarthritis.

Immunogenetics and transplantimmunology

PI: Prof. Dr. B. Spriewald
One research area is the induction of transplantation tolerance and modulation of transplant arteriosclerosis through the application of donor alloantigen and co-stimulation blockade. An important contribution to clinical research is the detection and differentiation of anti-HLA alloantibodies.

Immunodeficiencies and infectious diseases

PI: Prof. Dr. T. Harrer
The major research interests of this group are aspects of HIV-infection, such as immunology, drug resistance, and research on new therapeutic and diagnostic procedures, like T cell receptor transfer and immunomonitoring using mRNA electroporation. We are developing immunotherapies, like vaccines and immunomodulators, and participate in clinical studies on therapeutics for HIV-infection. Other projects focus on further infectious and immunologic diseases and chronic fatigue syndrome.

Mechanisms for the activation of fibroblasts in systemic sclerosis (SSc)

PI: Prof. Dr. J. Distler
SSc is characterized by organ fibrosis, mediated by an uncontrolled production of ECM by fibroblasts. However, therapies to inhibit selectively the overproduction of ECM are lacking. We investigate novel signaling cascades that activate fibroblasts and study therapeutic approaches to inhibit the overproduction of ECM by SSc fibroblasts.

Molecular signaling pathways in RA

PI: Prof. Dr. G. Schett, PD Dr. M. Stock
RA is characterized by perpetuating synovial inflammation and progressive joint destruction based on cartilage damage and bone erosion as a result of an imbalance of formation and resorption of cartilage and bone. Wnt signals link inflammation to this structural damage in arthritis and may play a major role in the pathogenesis of RA. We focus on regulation of the Wnt signaling network in rheumatic diseases and evaluate the potentials to interfere with cartilage damage caused by dysregulated Wnt signaling.

Metabolic impact on inflammation

PI: Prof. Dr. A. Bozec
Arthritis, adipose, and diabetes appear to form an alliance that has a pro-inflammatory and destructive effect on joints and bones. We investi-

gate central transcription factors and signaling pathways relevant as checkpoints for differentiation and activation in osteoclast, osteoblasts, and adipozytes.

Pathomechanisms of bone destruction in RA

PI: Prof. Dr. G. Schett, Dr. U. Steffen

RA is one of the most common inflammatory rheumatic joint diseases with an estimated prevalence of 1 %. Chronic arthritis, if poorly controlled, typically provokes extensive joint damage with the emergence of bone destruction associated with significantly decreased functional capacities. Hence, the project group focuses on the pathophysiology of bone destruction by the use of experimental arthritis models. They investigate the mechanisms leading to increased synovial activation of osteoclasts and decreased ability to repair bone destruction with the help of osteoblasts.

Analysis of risk factors and long-term outcome in patients with systemic lupus erythematosus (SLE)

PI: Prof. Dr. B. Manger

In a cohort of 410 SLE patients, genetic, serological, and clinical predictors for long-term outcome are analyzed in retrospective and prospective studies. One focus is on the investigation of premature atherosclerosis and ovarian failure in SLE.

Immunbiology and molecular mechanisms of inflammation

PI: Prof. Dr. G. Krönke

Insights into basic principles of immunity are a key for the better understanding of autoimmunity and inflammation. Simultaneously, they allow the development of new therapeutic strategies for autoimmune and chronic inflammatory diseases. We investigate molecular mechanisms that link innate and adaptive immunity and thus influence inflammation, tolerance, and autoimmune responses. Our aim is to understand key decisions points that trigger a physiological immune response or cause autoimmunity (e.g. RA and systemic lupus).

Analysis of inflammatory mechanisms in adult onset Still's disease

PI: PD Dr. J. Rech, Prof. Dr. B. Manger

Inflammatory mechanisms and cytokine profiles in patients with adult onset Still's disease are analyzed with respect to clinical presentation and outcome to identify therapeutic strategies for this rare disease.

Molecular and cellular immunology in metabolism

PI: Dr. M. Zaiss

Different types of immune responses require alterations in metabolism – vice versa, are immunomedulators (e.g. cytokines) dictating direct alterations in metabolism, which highlight the interaction between these two aspects? Our aim is the investigation of the interplay of immunology, metabolism, and nutrition in order to prevent or resolve autoimmune diseases.

Epidemiology and experimental imaging

PI: Dr. A. Kleyer, Dr. D. Simon

Epidemiological research with well-defined patient cohorts is an essential element to understand the course of rheumatic diseases and to provide optimal targeted treatment. Our group is particularly interested in the early stages of RA and psoriatic arthritis (PsA). We are developing and establishing new outcome measures by using experimental imaging to study the transition from silent disease to clinical evident inflammation.

Teaching

The Department of Medicine 3 is embedded into the curriculum-based teaching of the Medicine and Dentistry. 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 as well as MD and PhD theses are supervised.

Selected publications

Kienhöfer D et al. Experimental lupus is aggravated in mouse strains with impaired induction of neutrophil extracellular traps. JCI Insight. 2017 May 18;2(10): pii: 92920

Pfeifle R et al. Regulation of autoantibody activity by the IL-23-TH17 axis determines the onset of autoimmune disease. Nat Immunol. 2017, 18(1):104–113

Rauber S et al. Resolution of inflammation by interleukin-9-producing type 2 innate lymphoid cells. Nat Med. 2017, 23(8):938-944

Meng X, Grötsch B, Luo Y, Knaup KX, Wiesener MS, Chen XX, Jantsch J, Fillatreau S, Schett G, Bozec A. Hypoxia-inducible factor-1α is a critical transcription factor for IL-10-producing B cells in autoimmune disease. Nat Commun. 2018 Jan 17;9(1):251

Lucas S, Omata Y, Hofmann J, Böttcher M, Iljazovic A, Sarter K, Albrecht O, Schulz O, Krishnacoumar B, Krönke G, Herrmann M, Mougiakakos D, Strowig T, Schett G, Zaiss MM. Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun. 2018 Jan 4;9(1):55

Zehender A, Huang J, Györfi AH, Matei AE, Trinh-Minh T, Xu X, Li YN, Chen CW, Lin J, Dees C, Beyer C, Gelse K, Zhang ZY, Bergmann C, Ramming A, Birchmeier W, Distler O, Schett G, Distler JHW. The tyrosine phosphatase SHP2 controls TGFβ-induced STAT3 signaling to regulate fibroblast activation and fibrosis. Nat Commun. 2018 Aug 14;9(1):3259

International cooperations

Prof. L. Klareskog, Karolinska Institute, Stockholm: Sweden

Prof. Dr. S. Kiechl, Medizinische Universität Innsbruck, Innsbruck: Austria

Prof. M. Hansson, Uppsala University, Uppsala: Sweden

Prof. Dr. E. Wagner, Spanish National Cancer Research Centre (CNIO), Madrid: Spain

Prof. I. McInnes/Dr. C. Goodyear, University of Glasgow, Glasgow: UK