Project description in English

Cardio-oncology: The effect of clinically used MEK1/2 inhibitors (INH) on oncostatin M (OSM)-activated signaling cascades and on OSM-induced cancer- and heart failure-promoting secretome

Heart failure caused by cancer drugs is one of the most important causes of long-term morbidity and mortality in cancer survivors. Specific biomarkers for the early detection of cardiotoxicity are not yet well known, and effective cardioprotective drugs are lacking. Therefore, it is absolutely necessary, especially in order to be able to offer the affected patients an optimal therapy in the sense of personalized medicine, to find biomarkers for the early detection of the cardiotoxicity of cancer drugs, as well as to develop effective drugs to protect heart function. In this project, the effects of cardiomyocyte secretions on tumor cells and vice versa the influences of already clinically used cancer therapeutics on heart muscle cells are investigated. Through comprehensive analyses in cell cultures and the use of state-of-the-art analytical techniques, such as transcriptome and proteome studies, we aim to gain crucial insights that can point the way for the development of heart-sparing therapies against cancer. We believe it is essential to identify the specific secreted proteins and intracellular protein phosphorylation patterns influenced by OSM and pharmacological inhibitors on muscle and cancer cells. [Project partners: Prof. Dr. Hakan Akintürk, JLU Giessen (Head of Pediatric Cardiac Surgery), Dr. Ayse Cetinkaya, Senior Physician, Kerckhoff Clinic, Bad Nauheim, Prof. Dr. Rajkumar Savai, Institute for Lung Health (ILH), JLU Giessen and Dr. Andre Schneider, Max-Planck-Institute, Bad Nauheim.]

Cardiac sarcoidosis: Identification of biomarkers that indicate disease progression and clarification of the complex interactions between different immune cell subtypes, cytokines and signaling pathways involved in the development of cardiac sarcoidosis.

Cardiac sarcoidosis is an inflammatory disease that affects the heart and can even lead to heart failure in the final stages. The focus of this project is the research and characterization of cardiac sarcoidosis in the human heart. Through the analysis of transcriptomes, the application of immunostaining techniques and protein biochemical methods, we strive to identify key genes within the granulomas. These genes could provide insights into dysfunctional signaling pathways and molecular patterns specific to cardiac sarcoidosis. Our goal is to discover biomarkers that could not only indicate disease progression, but also provide potential signs of a positive response to therapeutic interventions. In addition, we explore the complex interactions between different subgroups of immune cells, cytokines and signaling pathways to gain a better understanding of the mechanisms that contribute to the development of this rare disease.

Functional characterization of the role of mast and immune cells in the development of heart failure in pediatric patients

Immune cell infiltration plays a decisive role both in the regeneration of the myocardium after acute damage and in the development of heart failure in the context of chronic inflammation. In experimental animal models of myocarditis and dilated cardiomyopathy (DCM), we were able to demonstrate that oncostatin M (OSM), which belongs to the interleukin-6 cytokine family, strongly promotes the development of heart failure by degrading the O2-consuming contractile apparatus. Furthermore, OSM enhances immune cell infiltration by stimulating the release of various chemokines from cardiomyocytes (Reg3β). Among the attracted immune cells, mast cells are of particular interest in addition to macrophages, as they release highly cardioactive cytokines such as OSM, TGFβ and interleukin 4/13 (IL4/13) when activated. While TGFβ induces fibroblasts to secrete extracellular matrix proteins, which contributes to fibrosis, IL-4/13 enhances the degenerative effect of OSM on the contractile apparatus in the inflamed myocardium. In addition, activated mast cells in the heart muscle tissue can release multipotent molecules that control the functions of different cardiac cell types.

Initial results show that myocardial infiltration of mast cells and macrophages plays a greater role in heart disease in pediatric patients than in adult patients. Therefore, the aim of this project is to clarify the role of this "multifunctional master cell" in the context of macrophage infiltration using state-of-the-art microscopy and omics technologies to elucidate the extent and function of mast cell infiltration and other immune cells in the development of heart failure in pediatric patients.

[Project partners: Prof. Dr. Hakan Akintürk, JLU Giessen (Head of Pediatric Cardiac Surgery) and Dr. Ayse Cetinkaya, Senior Physician, Kerckhoff Clinic, Bad Nauheim]

Influence of the lipopeptide MALP-2 on myocardial function, inflammation and remodeling after experimental myocardial infarction

The role of macrophage-activating lipopeptide (MALP-2) as a ligand of toll-like receptors (TLR) in different models of vascular regeneration has been extensively investigated. TLRs are not only known for regulating inflammatory processes, but also for their involvement in regenerative processes, such as the formation of new blood vessels (angiogenesis). Dr. Grote from the Philipps-Universität Marburg has been researching the adaptive and regenerative effects mediated by MALP-2 for many years. This bacterial lipopeptide, originally discovered in Mycoplasma species, is recognized by a heterodimer of TLR2 and TLR6 on the cell membrane. It has been shown that even a single administration of MALP-2 promotes angiogenesis, endothelial regeneration after vascular injury and the vascular regeneration potential of mesenchymal stem cells. Studies have shown that the growth factors from endothelial cells released by MALP-2, in particular the granulocyte-macrophage colony-stimulating factor (GM-CSF), are largely responsible for these regenerative effects. The release of GM-CSF from endothelial cells is regulated redox-sensitively. Because MALP-2 promotes angiogenesis and endothelial regeneration, it could play an important role in restoring heart function and improving healing after a heart attack. In addition, research into the molecular mechanisms by which MALP-2 works can help to develop targeted treatments after a myocardial infarction.

[Project partners: Prof. Dr. Kerstin Troidl, TH Bingen & Max Planck Institute, Bad Nauheim and PD Dr. Karsten Grote, Philipps-Universität Marburg]

The function of the interleukin-4 receptor (IL-4R) signaling cascade in the oncostatin M-controlled protection and degeneration of cardiomyocytes

IL-4R is considered a key regulator between humoral and adaptive immunity. Its protective properties after myocardial infarction are attributed to the activation and proliferation of tissue macrophages triggered by it. However, our studies clearly show that the effects of IL-4R are not limited to macrophages. The IL-4R not only mediates anti-inflammatory signals from its ligands IL-4 and IL-13, but is also involved in the oncostatin M receptor signaling cascade and cardiomyocyte remodeling. Furthermore, a much broader range of activities than expected was shown in heart muscle cell cultures after IL4-R stimulation, so that this receptor is directly at the regulatory center of myocardial diseases. In order to determine the structural, metabolic and inflammatory remodeling capacity of IL-4R activation, we aim to study cardiomyocyte cell cultures with and without receptor or signal components (e.g. JAK/Stat; Ras/Raf/MEK/Erk) by siRNA knock-downs. Our research project aims to clarify in cell culture whether targeting the IL-4R cascade has the potential to improve regeneration after an acute heart attack and to reduce the extent of degeneration of heart muscle cells in chronic heart disease.