Projects

Project A - Prof. Stephan Baldus, Cardiology

**Full Title:**
Myeloperoxidase (MPO)-mediated microvascular dysfunction in heart failure – impact of MPO-derived macrophage activation

**Aim**
This project will decipher the mechanistic role of macrophage polarization as a stress response pathway in heart failure. The significance of myeloperoxidase (MPO) as a modulator of the macrophage’s phenotype and as a central disruptive factor for the resolution of inflammation will be explored. Ultimately, results from this project will help to better understand the potential of MPO as a novel therapeutic target in heart failure.

**Description**
Current concepts for the treatment of heart failure center around augmenting cardiac contractility. However, progression of heart failure is critically propagated by dysfunction of resistance vessels, thereby impairing coronary perfusion and yielding increased peripheral vascular tone. Inflammation is recognized as a key factor in vascular dysfunction, with macrophages being a major component of vessel wall infiltrates. There is accumulating evidence that – apart from macrophages – activation of polymorphonuclear neutrophils (PMN) also importantly contributes to vascular dysfunction. However, little is known about the interplay of macrophages and PMN in this context as well as about their mechanistic role in the regulation of vascular resistance. The PMN- and macrophage-derived heme enzyme myeloperoxidase (MPO), which catalyzes the generation of reactive pro-inflammatory species, emerges as an important mediator of inflammatory vascular diseases. Given that MPO release is increased in heart failure patients, that MPO promotes activation and recruitment of leukocytes, and that the enzyme via nitric oxide-scavenging is causally linked to endothelial dysfunction, the current project intends to investigate the significance of MPO-induced macrophage activation for vascular dysfunction in heart failure.

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Project B - Prof. Thomas Benzing, Nephrology
**Full Title**
Role of stress signaling in podocytes in progressive damage of the glomerular microcirculation

**Aim**
An overarching aim of this study is to identify the underlying molecular mechanisms of injury that are amenable to potential therapeutic interventions to combat the increasingly prevalent progressive chronic kidney disease. It is expected that interventions that target the inflammatory and stress signaling process per se will provide a promising new approach to attack a large group of overlapping disorders through an innovative intervention.

**Description**
Chronic kidney disease (CKD) is an increasingly prevalent condition and associated with cardiovascular morbidity and mortality. Microvascular dysfunction of the glomerular circulation is of major importance in the pathogenesis of CKD, as the majority of kidney diseases start in the glomerular microcirculation of the kidney filter. Loss of podocytes, pericyte-like cells of the glomerular capillaries, is now being viewed as the culprit of progressive glomerular disease as postmitotic podocytes display a very limited capacity of selfrenewal. Research over the past decade has revealed that activation of pathogenic pathways in podocytes is both sufficient and required for the development of progressive glomerular disease and damage to the glomerular microcirculation.

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**Lab Link**
Project C - Prof. Jens Brüning, Max Planck Insitute for Metabolic Research

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**Full Title**
Role of distinct ceramide species in the development of atherosclerosis

**Aim**
Ceramides have been classically viewed as a homogeneous group of sphingolipids that have also been linked to metabolic and vascular disease, respectively. However, ectopic accumulation of ceramides has evolved a major risk factor for the development of obesity-associated insulin resistance and has also been linked to vascular inflammatory disease such as atherosclerosis.

**Description**
In the proposed study, we aim to delineate the specific underlying molecular and cellular mechanisms through which CerS6-derived C16-ceramides promote atherosclerotic lesion formation. To this end, we will identify the subcellular localization of CerS5- and CerS6-dependently generated C16 ceramides in endothelial cells and atherosclerotic plaque using LDLR-/- mice. Finally, we will study the specific contribution of the thereby identified signaling network(s) in control of lipid-induced ER-stress activation in endothelial and smooth muscle cells – key events during dysregulated stress signaling in vascular dysfunction and functionally validate the contribution of CerS6-dependently formed C16 ceramides in the progression of
atherosclerosis through analysis of conventional as well as myeloid lineage, vascular smooth muscle as well as endothelial-specific CerS6-deficient mice. Collectively, these experiments will unravel novel molecular effector networks and pathways of critical importance for the pathogenesis of atherosclerosis associated with obesity.

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Project D - Prof. Argyris Papantonis, Center for Molecular Medicine

**Full Title**
Cell-to-cell transcriptional remodeling: a nuclear role for myeloperoxidase in endothelial inflammation

**Aim**
The identification and mechanistic validation of direct MPO targets will add valuable information that will help us to establish pharmacological inhibition of the MPO regulatory pathway as a specific therapeutic strategy in cardiovascular disease.

**Description**
MPO is a known inflammatory mediator severely affecting vascular and myocardial function. MPO is secreted by activated neutrophils and monocytes, accumulates in the plasma, and is taken up by endothelial cells (ECs) in the microenvironment. This leads to the remodeling of EC gene expression both in vitro and in vivo. Yet, how this is achieved remains unknown. We offer preliminary evidence in support of the hypothesis that MPO function is a result of its translocation into cell nuclei where, given its predicted capacity to bind chromatin, it may modulate transcription. If this holds true, MPO will constitute a unique example of cell-to-cell crosstalk via a secreted enzyme directly acting to regulate gene expression. We propose probing the molecular function of MPO in ECs, using a combination of cutting-edge genomics and cell biology technologies, along with animal models. Such an approach should expand our current understanding of MPO’s impact on vascular inflammation and will help to establish MPO-directed specific pharmacological therapies in cardiovascular disease.

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Project E - Prof. Manolis Pasparakis, CECAD Research Center, Institute for Genetics

**Full Title**
RIP kinase 1 signaling in atherosclerosis

**Aim**
This project bears the potential to identify targetable proteins as important contributors to the progression of atherosclerotic plaques. Specifically, our studies aiming to address the role of RIPK1 kinase activity in the pathogenesis of atherosclerosis may identify RIPK1 as a therapeutic target in this disease. Considering that RIPK1 inhibitors are currently in phase II clinical trials for the treatment of different inflammatory diseases, our studies have strong therapeutic potential.

**Description**
Atherosclerosis remains the number one cause for morbidity and mortality in western countries. The development and growth of atherosclerotic plaques is the result of a chronic non-resolving inflammatory response involving the activation of endothelial cells to express cytokines, chemokines, and adhesion molecules, thereby resulting in the recruitment and entrapment of monocytes in the subendothelial space. Here, monocytes mature into macrophages that take up lipids to become foam cells. The death of lipid-laden macrophages is believed to critically affect the progression of atherosclerosis. The aim of this project is to experimentally address the role of apoptosis and necroptosis in atherogenesis.

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Project F - Prof. Stephan Rosenkranz, Cardiology

**Full Title**
Role of IL-6 signaling and macrophage polarization in pulmonary hypertension

**Aim**
We anticipate that this study may potentially provide the molecular basis for novel, disease-modifying pharmacological interventions. Immune-modulatory therapies represent an exciting opportunity to further improve the treatment options of this deadly disease.

**Description**
Pulmonary hypertension (PH) is a devastating vascular disease characterized by a high mortality and limited treatment options. In addition to adverse regulation of vascular tone and remodeling, inflammation is increasingly recognized as a key pathogenic factor. However, the precise inflammatory mechanisms and their specific contribution to the pathobiology of PH remain elusive. In this project, we aim to evaluate the pathogenic relevance of interleukin (IL)-dependent macrophage and T-cell activation for vascular dysfunction in PH.

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Full Title
Effect of nitrated fatty acids on the nitric oxide-response in heart failure with preserved ejection fraction

Aim
Given the potent anti-inflammatory and anti-fibrotic effects of nitroalkenes, administration of the purified compound as well as dietary supplementation might evolve as attractive therapeutic options for cardiovascular disorders like HFpEF. Of note is that nitrated conjugated linoleic acid is currently being tested in phase 1 clinical studies.

Description
Vascular inflammation and depletion of nitric oxide (NO) with ensuing microvascular dysfunction is critical in HF with preserved ejection fraction (HFPEF) [1,2]. Nitrated fatty acids (NO$_2$-FA) are endogenously occurring termination products of inflammatory, oxidant-induced nitration reactions. By reversible electrophilic adduction to biological targets via their NO$_2$-group, these molecules increase vascular NO, and resolve inflammation. Previously, our group has demonstrated protective effects of NO$_2$-FA in myocardial ischemia/reperfusion [3] and angiotensin II-(ang II) induced atrial fibrotic remodeling [4]. Given the central role of vascular inflammation and impaired NO signaling in HFPEF, we aim to unravel the role of NO$_2$-FA in this disorder.

PI
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Full Title
Innate immune response to DNA damage in ageing-associated vascular disease

Aim
Our project will open new opportunities for therapeutic targeting of DNA damage driven inflammatory signaling with the aim to prevent aging-associated vascular dysfunction.

Description
DNA damage accumulation causally contributes to the functional decline associated with aging. Congenital defects in nucleotide excision repair (NER) lead to highly skin cancer prone Xeroderma pigmentosum (XP) or accelerated aging in Cockayne syndrome (CS) patients when global-genome (GG-) NER or transcription-coupled (TC-) NER is affected, respectively (Edifizi & Schumacher, 2015). CS patients display growth retardation and premature aging, and typically die between the ages of 12 and 16 from atherosclerosis.

In C. elegans, persistent CpG-rich DNA induces an innate immune response that, when chronic, causes loss of proteostasis in the endoplasmic reticulum. This dysfunction ultimately leads to
tissue degeneration, similar to the outcomes of chronic inflammation in higher organisms. Treatment with low doses of tunicamycin and N-acetylglucosamine (box – Therapeutic Interventions), both of which promote proteostasis, alleviate the stress on the endoplasmic reticulum leading to tissue maintenance – even during the ongoing immune response.

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Project I - Prof. Aleksandra Trifunovic, CECAD Research Center, Mitochondria in Ageing

Full Title
Endothelial mitochondrial dysfunction in the development of heart failure

Aim
Strong mitochondrial dilated cardiomyopathy and diminished respiration can be alleviated by the loss of mitochondrial matrix protease CLPP, opening a new avenue for novel therapeutic intervention in mitochondrial diseases.

Description
Endothelial cell (EC) dysfunction crucially contributes to the development of impaired coronary and systemic perfusion as well as reduced exercise capacity in patients with HF. The key determinants in endothelial dysfunction are reduced levels of NO and abundant formation of ROS within the vascular wall. Recent studies have suggested that endothelial mitochondria are centrally involved in maintaining the fine regulatory balance between mitochondrial calcium concentration, ROS production, and NO availability. In comparison with other cell types with higher energy requirements, mitochondria content in ECs is modest, making up only 2-6% of total cell volume. The low content of mitochondria indicates that they are likely to serve as critical signaling organelles in the endothelium. The role of mitochondria in vascular smooth muscle cells (VSMCs) is even less understood. Similar to ECs, mitochondria contribute only modestly to the VSMC bioenergetics. Nevertheless, mitochondrial dysfunction, and particularly mitochondrial DNA damage, has recently been associated to atherosclerosis. The historical view that in atherosclerosis, aberrant proliferation of VSMCs promotes plaque formation, but that VSMCs in advanced plaques are beneficial by, e.g. preventing rupture of the fibrous cap, has recently also been challenged. This project aims to determine the role of endothelial mitochondria in the development of HF.

Model of endothelial cell Dars2-deficiency and experimental approach to assess the role of mitochondrial dysfunction in heart failure.

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