UniversitätsKlinikum Heidelberg

External Seminar Speaker

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Place: **Analysezentrum 3, 2. OG, Room 02.332**
Date: **Monday, November 4th**
Time: **12 am**
1 pm Get together

"Igniting the Flame of Inflammation through Cardiomyocyte CaMKII and Inflammasome Activation"

Inflammation is associated with cardiac remodeling and heart failure, but how it is initiated in response to non-ischemic interventions in the absence of cell death is not known. I will discuss evidence that the activation of CaMKIIδ in cardiomyocytes initiates inflammatory responses that lead to adverse remodeling. Our conclusions are based on studies with CaMKIIδ transgenic mice, and cardiac specific knockout (CKO) mice. We show that Angiotensin II (AngII) or transverse aortic constriction (TAC) induces rapid and robust increases in pro-inflammatory chemokine and cytokine gene expression resulting from activation of NFkB. In CKO mice the ability of AngII and TAC to induce NFkB activation and pro-inflammatory gene expression is markedly attenuated. Inflammatory gene expression occurs within the cardiomyocyte (CM) compartment since isolated CMs from TAC hearts show robust CaMKδ dependent increases in gene expression at early times whereas inflammatory gene mRNAs are not increased in the non-myocyte fraction containing immune cells and fibroblasts. Priming of the NLRP3 inflammasome, assessed by measuring IL-1β, IL-18 and NLRP3 mRNA levels and inflammasome activation assessed via caspase-1 activity and IL-18 cleavage, are also increased in CM at 3 dayTAC in CTL and diminished in CaMKII KO hearts. NLRP3 activation is mediated in part through increased mitochondrial ROS. Macrophages (CD68+) accumulate in the heart in response to AngII or TAC treatment and this is diminished in CKO and inhibited in CTL mice by blocking MCP-1 signaling or inflammasome activation. Fibrosis is also attenuated by these interventions and in the CKO heart. Ventricular dilation and contractile dysfunction

assessed by echocardiography at day 42 post TAC are diminished in the CKO as well as by pharmacological inhibition of CaMKII, NFkB or inflammasome signaling in the first one or two weeks after TAC. Systemic inflammation assessed as serum amyloid is also increased by TAC and diminished when cardiomyocyte CaMKIIδ is deleted. We conclude that CaMKIIδ transduces hormonal and other non-ischemic signals to initiate inflammatory responses within cardiomyocytes which then drive subsequent immune cell recruitment, fibrosis and adverse remodeling.

Host: **Prof. Dr. med. Johannes Backs**
Director of the Institute of Experimental Cardiology
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