

Rapid Fire 1 - Basic Science

5

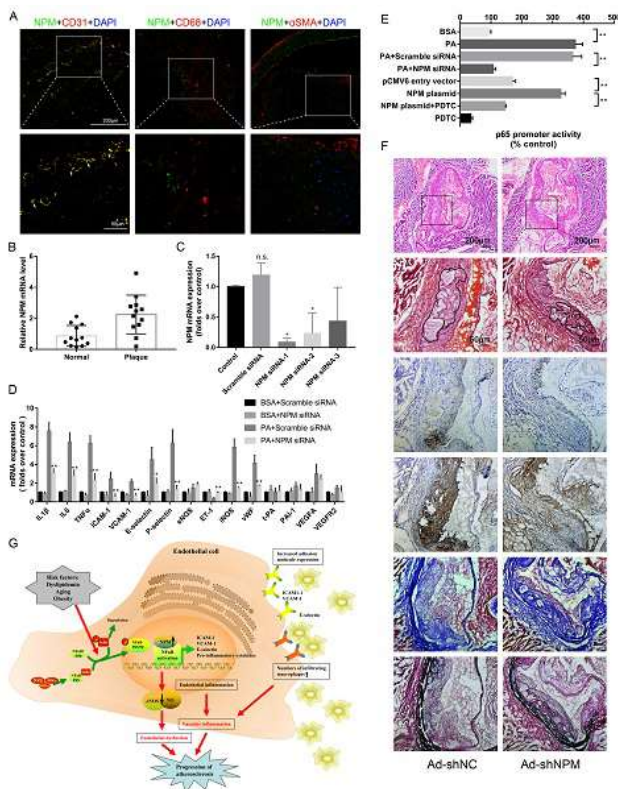
NPM accelerated vascular inflammation and endothelial dysfunction in atherosclerosis progression through NF-kappaB pathway

C Caijun Rao¹; B Liu²; F Li²; D Huang¹; K Huang¹; N Dong²

¹Wuhan Union Hospital, Department of Cardiology, Wuhan, China; ²Wuhan Union Hospital, Department of Cardiovascular Surgery, Wuhan, China

Purpose: It was uncertain whether Nucleophosmin (NPM) participated in cardiovascular disease. The present study aims to investigate the role and underlying mechanisms of NPM in exacerbating vascular inflammation and endothelial dysfunction in atherosclerosis progression.

Methods: Levels and location of NPM in human carotid atherosclerotic plaques and healthy controls were detected by RNA-Seq and immunohistochemistry. Human primary umbilical vein endothelial cells (HUVECs) were used as in vitro model. Atherosclerotic prone ApoE^{-/-} mice was fed with western diet for 24 weeks as in vivo model.



Results: Compared with controls, we found increased levels of NPM in atherosclerotic plaques, which mainly located in endothelial cells. In cultured HUVECs, palmitic acid induced NPM upregulation, the expression of inflammatory cytokines and monocyte adhesion, while NPM knockdown attenuated this effect. In vivo, adenovirus containing shNPM attenuated atherosclerotic lesion and promoted plaque stabilization in western diet-fed ApoE^{-/-} mice by reducing vascular inflammation, maintaining endothelial function and decreasing macrophage

infiltration in atheromatous plaques. Furthermore, NPM knockdown decreased NF-κB p65 phosphorylation. In HUVECs, NPM protein physically bind with Nuclear factor-κB (NF-κB) p65 subunits and promotes its nuclear transposition. NPM could also increase the transcriptional activity of NF-κB p65 promoter and enhance its binding to target genes including TNF-α, IL-1β, IL-6, ICAM-1 and E-selectin.

Conclusion: These data provided novel evidence that NPM promoted atherosclerosis by inducing vascular inflammation and endothelial dysfunction through NF-κB pathway, and suggested that NPM may be a novel target for atherosclerosis prevention and treatment.

6

Dual Regulation of SUMO2 and STAT1 by HectD3 Protects Heart from Hypertrophy and Inflammation

A Ashraf Rangrez¹; A Borlepawar¹; N Schmiedel¹; L Christen¹; A Bernt¹; A Helbig²; A Jungmann³; S Sossalla⁴; A Tholey²; O Mueller¹; D Frank¹; N Frey¹

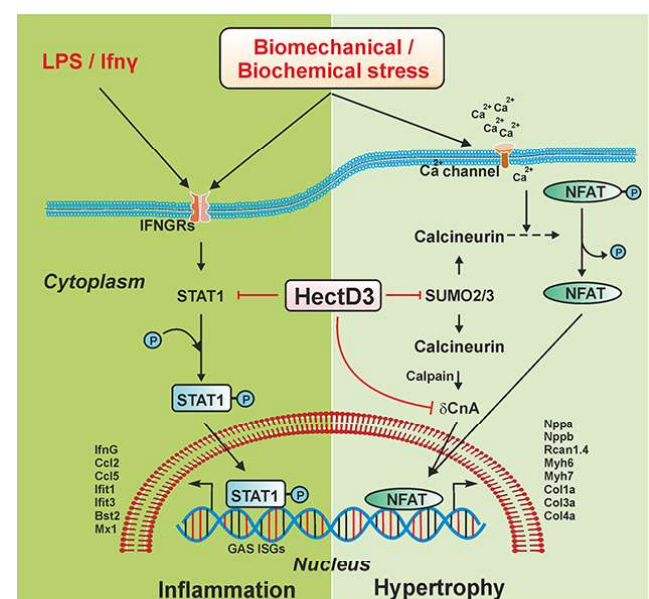
¹University Medical Center of Schleswig-Holstein, Kiel, Germany;

²Christian-Albrechts-University Kiel, Kiel, Germany; ³University Hospital of Heidelberg, Heidelberg, Germany; ⁴University Hospital Regensburg, Regensburg, Germany

Funding Acknowledgements: This work is supported by the grants received from medical faculty of Christian-Albrechts University of Kiel to AYR and from DZHK to AYR and NF

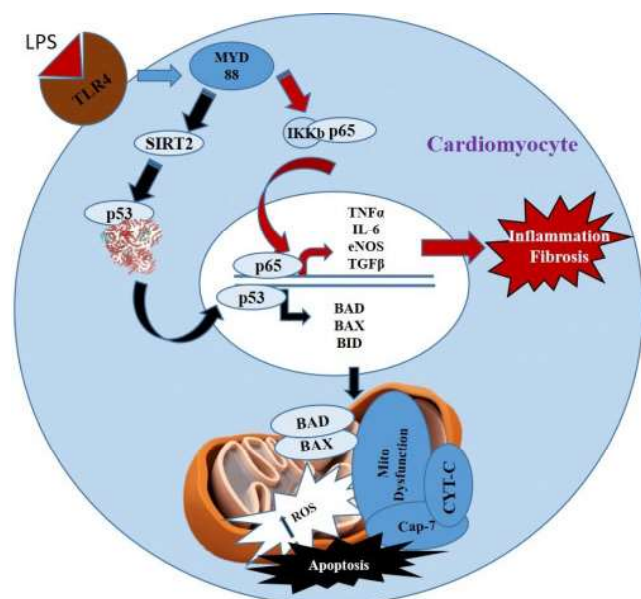
Background: We recently identified SUMO2 as a sumoylation independent inducer of cardiomyocyte hypertrophy through activation of Calcineurin-NFAT signaling via direct interaction and increased nuclear localization of calcineurin.

Purpose: In this study, we aimed at identifying cardiac-specific interactome of SUMO2 to decipher its cardiac function in depth.



Graphical abstract

important role TLR4 mediated apoptosis. Reducing TLR4 mediated fibrosis and apoptosis could be a novel approach in the treatment of heart failure, where TLR4 mediated inflammation plays a major role.



Graphical Abstract

P1248

Inhibition of myeloperoxidase in an obese/hypertensive mouse model attenuates obesity and liver damage, but not cardiac remodeling

A Arnold Plek¹; W Du¹; Z Wang²; DPY Koonen²; E Lindstedt³; E Michaelsson³; RA De Boer¹; HHW Sillje¹

¹University Medical Center Groningen, Cardiology, Groningen, Netherlands (The);

²University Medical Center Groningen, Pediatrics, Section Molecular Genetics, Groningen, Netherlands (The); ³AstraZeneca, Heart Failure Bioscience,

Cardiovascular and Metabolic Diseases, IMED Biotech Unit, Gothenburg, Sweden

Funding Acknowledgements: This work was supported by a grant from AstraZeneca.

Background: Heart failure with preserved ejection fraction (HFpEF) is a major health problem for which no proven therapy exists. Low-grade systemic inflammation caused by obesity, diabetes and hypertension is believed to contribute to HFpEF development and progression. The enzyme myeloperoxidase (MPO), involved in inflammation, has been linked to HFpEF and obesity.

Purpose: In this study, the effect of a novel MPO inhibitor, AZM198, on cardiac remodeling was investigated in an obesity/hypertension mouse model with HFpEF characteristics.

Methods: Male C57BL/6J mice aged 8 weeks were subjected for 16 weeks to either low fat diet (LFD) or high fat diet (HFD) with or without AZM198. During the last 4 weeks this was combined with angiotensin II (AngII) or saline (control) infusion. Just before sacrifice, body mass composition was determined, and cardiac magnetic resonance imaging (MRI) measurements and left ventricular (LV) pressures were recorded. The heart and other tissues were investigated at the molecular and histological level.

Results: A combination of HFD and AngII infusion did not reduce left ventricular ejection fraction (LVEF%), but did result in mild, but significant, elevated pathological cardiac hypertrophy and fibrosis and in diminished LV relaxation, all characteristics of HFpEF. MPO plasma levels were significantly elevated in this HFpEF model and this was driven by the HFD. AZM198 treatment significantly reduced the elevated MPO levels to control, LFD, levels. No adverse AZM198 effects were observed in any of the AZM198 mouse groups and AZM198 treatment had no significant effect on any of the measured cardiac parameters, including fibrosis, hypertrophy and relaxation (dP/dtmin; Tau). AZM198, however, significantly attenuated adipose tissue accumulation and reduced inflammatory crown-like structures and inflammatory

gene expression in adipose tissue. Liver ballooning degeneration was also significantly less prominent in AZM198 treated HFD groups.

Conclusions: AZM198 treatment normalized MPO levels in obese/hypertensive mice, but did not improve functional and structural cardiac parameters. However, AZM198 did reduce adipose inflammation, fat deposition and liver degeneration. These positive effects could be important for the obese human HFpEF population.

P1249

Correlation between myofilament Ca²⁺ sensitivity and left ventricular contractility parameters during the progression of pressure overload-induced left ventricular myocardial hypertrophy

M Mihaly Ruppert¹; B Bodi²; S Korkmaz-Icoz³; S Loganathan³; L Lehmann⁴; A Olah¹; BA Barta¹; A Sayour¹; B Merkely¹; M Karck³; Z Papp²; G Szabo²; T Radovits¹

¹Semmelweis University Heart Center, Budapest, Hungary; ²University of

Debrecen, Division of Clinical Physiology, Faculty of Medicine, Debrecen, Hungary;

³University of Heidelberg, Department of Cardiac Surgery, Heidelberg, Germany;

⁴University Hospital of Heidelberg, Department of Cardiology, Angiology and Pulmonology, Heidelberg, Germany

Funding Acknowledgements: ÚNKP-18-3-I-SE-9 (MR), ÚNKP-18-3-III-DE-387 (BB), NVKP-16-1-2016-0017

Background: During the development of pressure overload (PO)-induced pathological left ventricular (LV) myocardial hypertrophy (LVH) and its progression to heart failure distinct alterations could be observed both in LV contractility and myofilament function. However, whether the dynamic alterations on the two levels (contractility on the global ventricular level and myofilament function on the cellular level) correspond to each other has been not studied.

Purpose: Therefore, we aimed at investigating the relation between LV contractility and myofilament function in PO-induced LVH.

Methods: PO was evoked by abdominal aortic banding (AB) in male, Sprague-Dawley rats for 6, 12 and 18 weeks. Control animals underwent the same surgery without constricting the aorta (Sham). Characteristic PO-induced alterations were investigated by serial echocardiography, histology, quantitative real-time PCR and western blot. LV function was assessed by pressure-volume analysis. Force measurement was carried out in permeabilized cardiomyocytes.

Results: Sustained PO resulted in the development of pathological LVH in the AB groups as indicated by macroscopic (increased heart weight-to-tibial length ratio and LV mass index), microscopic (increased cardiomyocyte diameter) and molecular markers (reactivated fetal gene program: increased atrial natriuretic peptide and β -to- α myosin heavy chain expression). These alterations were already present at early stage of LVH (AB-week6). Furthermore, at more advanced stages (AB-week12, AB-week18), interstitial fibrosis and chamber dilatation were also observed. The detailed analysis of the pressure-volume loops revealed that the AB-wk6 group was associated with increased LV contractility (as indicated by increased end-systolic elastance [ESPVR]: 1.74 ± 0.22 vs. 3.28 ± 0.36 mmHg/ μ l, preload-recruitable stroke work [PRSW]: 104 ± 8 vs. 140 ± 8 mmHg and preload-adjusted maximal slope of systolic pressure increment [dPdt-EDV]: 33 ± 2 vs. 53 ± 6 (mmHg/s)/ μ l Sham-week6 vs. AB-week6, $P < 0.05$), maintained ventriculo-arterial coupling (VAC) and preserved systolic function. In the same experimental group, increased myofilament Ca²⁺ sensitivity (pCa50) and hyperphosphorylation of cardiac troponin-I (cTnI) at Threonin-144 was detected. In contrast, in the AB-wk12 and AB-wk18 groups, the initial augmentation of LV contractility, as well as the increased myofilament Ca²⁺ sensitivity and cTnI (Threonin-144) hyperphosphorylation diminished, resulting in impaired VAC and reduced systolic performance. Strong correlation was found between LV contractility parameters (ESPVR, PRSW and dP/dtmax-EDV) and myofilament Ca²⁺-sensitivity (pCa50) among the study groups.

Conclusion: Changes in myofilament Ca²⁺ sensitivity might underlie the alterations in LV contractility during the development and progression of PO-induced LVH.

P1250

HFWM: Circulating relaxin-1 is a surrogate marker of myocardial fibrosis and left ventricular diastolic function in HFREF

E Edit Gara¹; J Simon¹; GY Csiko¹; T Radovits¹; G Foldes¹; A Nemes¹; M Husveth-Toth¹; J Skopal¹; B Merkely¹

¹Semmelweis University, Heart Center, Budapest, Hungary

Recently relaxin-1 (RLX-1) has emerged as a possible therapeutic tool or target in myocardial fibrosis due to its anti-fibrotic effect on the failing myocardium. Previous randomised clinical trials investigated the therapeutic role of exogenous relaxin in patients with acute-on-chronic heart failure with reduced ejection fraction (HFREF) and failed to meet clinical endpoints. Here we aimed to assess endogenous, circulating RLX-1 levels in patients with HFREF of ischemic origin. Furthermore, we analyse the relation of RLX-1 levels and left the ventricular diastolic function, left