

Rapid Fire 1 - Basic Science

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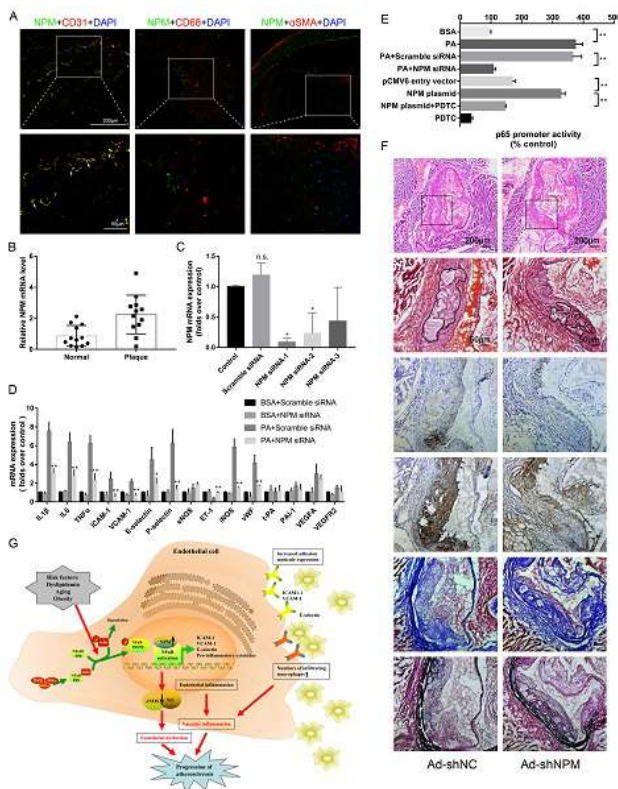
NPM accelerated vascular inflammation and endothelial dysfunction in atherosclerosis progression through NF-kappaB pathway

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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.

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

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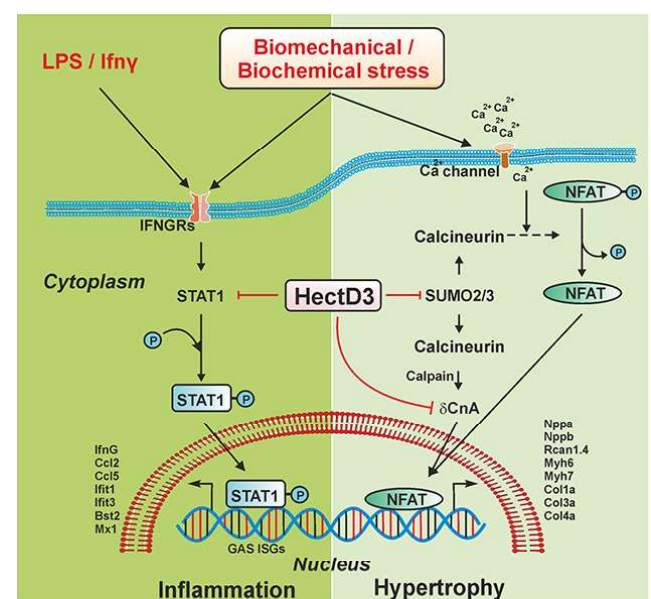
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Background: We recently identified SUMO2 as a sumoylation independent inducer of cardiomyocyte hypertrophy through activation of Calcineurin-NFAT signaling via direct interaction and increased nuclear localization of calcineurin.

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



Graphical abstract

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HFWM: Inhibition of the pro-inflammatory neutrophil mediator S100A8/A9 alleviates heart failure development post-myocardial infarction

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Background: The potent immune and inflammatory response to myocardial infarction (MI) aggravates myocardial damage and precipitates the development of heart failure (HF). The pro-inflammatory alarmin S100A8/9 rises rapidly in blood and myocardium after MI and has been linked with increased risk for recurrent MI and CV death in these patients.

Purpose: In MI patients, we studied whether S100A8/A9 at the time of the MI is associated with impaired cardiac function and incident HF. Further, we assessed whether inhibition of S100A8/A9 activity in the acute phase can improve cardiac function post-MI in mice.

Methods: In a cohort of 524 MI patients, we studied the associations between S100A8/A9 and incident HF during a 2-year follow-up. In a subgroup of 114 of these patients we also examined the correlations between S100A8/A9 and left ventricular function at 1 year after MI, measured by echocardiography. To assess the role of S100A8/A9 in HF development, we induced MI by permanent left coronary artery ligation in C57BL/6 mice. The mice were subsequently treated with the S100A8/A9 blocker ABR-238901 (30mg/kg) or PBS for 3 days. ABR-238901 inhibits the binding of S100A8/A9 to its receptors RAGE and TLR4. Immune cell populations in blood and myocardium were analyzed by flow cytometry, and cardiac function was assessed by magnetic resonance on days 3, 7 and 21 post-MI.

Results: In a Cox proportional regression analysis adjusted for age and sex, patients with acute S100A8/A9 values in the highest tertile had a 1.3 (95%CI 1.0 – 1.7) higher risk to develop HF compared to the lowest tertile (P=0.026). Higher acute S100A8/A9 also correlated with lower left-ventricular ejection fraction (r=-0.332, P=0.001) and larger end-systolic volume (r = 0.201, P=0.037) at 1 year. In mice, S100A8/A9 blockade post-MI had potent local and systemic anti-inflammatory effects, leading to significantly reduced numbers of neutrophils and inflammatory Ly6C(hi) monocytes in blood and myocardium on days 3 and 7 post-MI. Left ventricular ejection fraction was significantly higher on day 7 (25% vs 16%, P<0.01) and on day 21 (26% vs 12%, P<0.001) in mice treated with ABR-238901 compared to the PBS control. We recorded a remarkable hemodynamic recovery in the ABR-238901-treated mice, with an approximately 40% increase in cardiac output from 6.4mL/min on day 3 to 8.9 mL/min on day 21. On day 21 post-MI, the average cardiac output in the ABR-238901-treated group reached 83% of the baseline pre-MI value, compared to 51% in the control mice.

Conclusions: Our study identifies a deleterious role of S100A8/A9 in the immediate post-ischemic phase, mediating the development of cardiac dysfunction and chronic HF. We identify S100A8/A9 as an important target for immunomodulatory therapies aiming to ameliorate the development of post-ischemic HF, as S100A8/A9 blockade led to significant gains in cardiac function and hemodynamic parameters.

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Sleep-disordered breathing is associated with ventricular arrhythmias in postmenopausal women with hypertension and coronary artery disease.

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Background: Arterial hypertension (AH) and coronary artery disease (CAD) hold leading position in the structure of cardiovascular morbidity. High risk of developing AH and CAD becomes clinically significant after a woman enters menopause. The problem of sleep-disordered breathing is also being actively studied recently, as more and more information is accumulating about the negative effect of sleep apnea on the cardiovascular system.

Purpose: To study the role of sleep-disordered breathing on ventricular arrhythmias (VA) in postmenopausal women with AH and CAD

Methods: 144 postmenopausal women with AH 1–2 degrees and chronic forms of CAD (mean age 66.6 ± 7.5 years) were examined. 27.1% of women had heart failure (NYHA I-II). The first group included 96 patients with VA. The second group consisted of 48 women without VA. The groups were divided into subgroups: A - index of apnea / hypopnea (AHI) <5 per hour of sleep; B - AHI ≥ 5 per hour of sleep. Patients

underwent holter monitoring of ECG and respiratory monitoring. To characterize the VA, the Low and Wolf classification was used in the Ryan modification, VA 3 and higher gradations were taken to arrhythmias of high gradations.

Results: Patients with sleep-disordered breathing (AHI ≥ 5 per hour of sleep) were found in the I (36.5%) and II (22.9%) groups, but in the group with VA of such patients there was a 13.6% increase (χ^2 with the Yates correction = 1.9 p> 0.05). Patient didn't significantly differ in the frequency of detection of VA I, III, IV and V grades (> 0.05). Frequent ventricular extrasystole (VE) by 22.2% (p < 0.01 in the Fisher test) was more often recorded in patients in the IA subgroup (29.9% and 5.7% accordingly). Polymorphic pair VE more often (by 20.8%; p < 0.01 by Fisher test) was detected in women of the IB subgroup. In patients with IB subgroups, arrhythmias of high gradations (51.4%) were more frequent (21.9% χ^2 = 4.56 p < 0.05) compared with the IA subgroup. Using the method of calculating the odds ratio, it was found that the AHI ≥ 5 episodes per hour of sleep increases the chance of development of high-grade VA by 2.5 times, polymorphic pair VE by 7 times.

Conclusions: Sleep-disordered breathing (AHI ≥ 5 per hour of sleep) is associated with high-gradations VA and polymorphic paired VE.

Odds ratio of developing VA

Indicator	index of apnea / hypopnea		
OR	95%CI	P criteria χ^2	
High gradations ventricular arrhythmias	2,52	1,16 - 5,92	<0,05
Polymorphic pair ventricular extrasystole	7,0	1,75 - 28,22	<0,01

OR - odds ratio; CI - confidence interval

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Effects of early vs. late initiated pressure unloading on myocardial reverse remodeling and recovery of cardiac dysfunction in a rat model of left ventricular hypertrophy induced by pressure overload

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Background: Left ventricular hypertrophy (LVH) induced by pressure overload (PO) regresses after pressure unloading. However, distinct structural alterations become irreversible during the progression of LVH, which might influence the recovery of cardiac function.

Purpose: Here, we investigated how an early- versus late initiated pressure unloading affects reverse remodeling and different aspects of LV function.

Methods: PO was induced by abdominal aortic banding (AB) of rats for 6, 12 and 18 weeks. Sham-operated animals served as controls. Pressure unloading was evoked by removing the aortic constriction at week 6 (early-debanded) and week 12 (late-debanded). Echocardiography and histology were carried out to detect structural alterations. Pressure-volume analysis was performed to assess LV function. Molecular alterations were analyzed by qRT-PCR and western blot.

Results: LV hypertrophy regressed to a similar degree in early- and late-debanded groups (similar regression regarding LV mass, cardiomyocyte diameter, heart weight - to - tibial length ratio and beta-to-alpha myosin heavy chain expression). In contrast, resorption of myocardial fibrosis was only detected in the early-debanded group (LV collagen fraction: 7.7±0.7 vs. 5.4±0.3% ABw12 vs. early-debanded; p<0.05, while it persisted in the late-debanded group (7.4±0.9 vs. 6.9±0.6% ABw18 vs. late-debanded; ns.). Debanded normalized ventriculo-arterial coupling and increased systolic performance in both groups. However, the residual dysfunction in active relaxation (Tau normalized to control: 18±5 vs. 38±8% early-debanded vs. late-debanded; p<0.05) and increased stiffness was more severe in the late- compared to the early-debanded group.

Conclusion: Early debanding led to complete structural reverse remodeling and full restoration of LV function. In contrast, late debanding resulted in partial regression of PO-induced structural alterations, which impeded the normalization of diastolic but not systolic function.