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Intramyocardial delivery of FGF-21 by a novel thermosensitive hydrogel attenuates cardiac remodeling and improves cardiac function post myocardial infarction

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OBJECTIVES Fibroblast growth factor-21 (FGF-21) has been discovered as a strong hormone, plays an important role in lipid metabolism, glucose metabolism, associated with several diseases such as obesity, metabolic syndrome, diabetes mellitus and cardiovascular events. And it has been recently reported to attenuate cardiac function following myocardial infarction (MI). This study was designed to investigate whether this effect could be strengthened by local intramyocardial injection of FGF-21 along with a novel Dex-PCL-HEMA/PNIPAAm hydrogel and ascertain its possible mechanism of action.

METHODS MI models were induced in rats by coronary artery ligation. Phosphate-buffered saline (PBS group), Dex-PCL-HEMA/PNIPAAm hydrogel (Gel group), phosphatebuffered saline containing FGF-21 (FGF-21 group), and hydrogel containing FGF-21 (Gel+FGF-21 group) were injected into the peri-infarcted myocardium immediately after myocardial infarction, respectively. The sham group was thoracic but without coronary artery ligation.

RESULTS The injection of FGF-21 along with hydrogel reduced MI area, inhibited inflammatory response and cell apoptosis, restrained collagen accumulation and improved cardiac function. Additionally, activation of PI3K-Akt1 signaling pathway was remarkably increased compared with the injection of either agent alone post MI in rats.

CONCLUSIONS These findings indicate that FGF-21 injection along with Dex-PCL-HEMA/PNIPAAm hydrogel acquires more cardioprotective effects than either alone in rat post MI via activation of PI3K-Akt1 signaling pathway.

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Negative effects of diabetic duration on Myocardial Infarction in Diabetic Mice

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OBJECTIVES Acute myocardial infarction (AMI) is one of the most serious diseases that threaten human's health. It indicates that there are 114 million diabetics and 148.2 million prediabetics in China. China has become a diabetes capital all over the world. About 65 percent of people with diabetes die from heart disease. Strong evidence exists that diabetics suffer from increased incidence and severity of myocardial infarction (MI) and are much more likely to suffer from heart failure following MI. It is still controversial about the sensitivity of myocardium for the MI injury in diabetic. It is not verified that diabetic duration maybe a factor in the sensitivity of myocardium for the MI injury in diabetic. The aim of this study was to investigate the effects of diabetic duration on left ventricular dysfunction and heart failure after AMI and its mechenism.

METHODS The non-diabetic (group1, n=20) and age-matched non-diabetic (group2, n=50) mice were subjected to myocardial infarction at 1 day (n=10), 7 days (n=10), 14 days (n=10), 30 days (n=10) after the establishment of diabetes, respectively. Mouse were rendered diabetic by 5 days of daily intraperitoneal injection with 40mg/kg STZ (Sigma) in 0. 05 M sodium citrate, pH 4.5. Blood glucose was measured 2 days after the final injection, and diabetic condition was confirmed by markedly elevated fasting -blood glucose levels (>11.1umol/L). Mouse underwent myocardial infarction by ligating the left anterior descending coronary artery with injection of saline. Sham-operated mouse underwent the same surgical procedures except that the suture placed under the left anterior descending coronary artery was not ligated. Myocardial tissue sections were traced and stained with immunofluorescence to find cells which glowing red fluorescent and alpha sarcomeric actin positive under fluorescence microscope. Cardiac functionwas monitored using echocardiography after 4 weeks in half mouse of every subgroup.

RESULTS The fasting-blood glucose level was elevated with diabetic duration increasing. Compare with the control group 1, there were lower left ventricular ejection fraction ($p < 0.001$), longer fraction ($p < 0.001$) and larger left ventricular end-diastolic volume ($p < 0.001$) in the experimental group 2. In addition, there were lowest left ventricular ejection fraction, longest fraction and largest left ventricular end-diastolic volume in the 30-day diabetic mouse sub-group of group 2. Diabetic duration may decrease the sensitivity of myocardium for the MI injury in diabetic mice.

CONCLUSIONS The MI injury is time-dependently increased in diabetic mice. The longer diabetes duration mice may have less sensitivity for MI injury.

GW27-e0398

Mitogen-activated protein kinase interacting kinase 1 (Mnk1) Deficiency Aggravates Cardiac Remodeling via Regulation of Sprouty2-dependent ERK1/2 pathway

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OBJECTIVES Identifying the key factor involved in cardiac remodeling is critically important for developing novel strategies to protect against heart failure. Studies have shown that the phosphorylation of sprouty2 by Mnk1 protects sprouty2 from degradation, and sprouty2 inhibits the Ras/ERK pathway through binding to growth factor receptor bound protein 2. We now hypothesize that Mnk1 may mediate beneficial effects through its ability to keep the stability of sprouty2. In this study, we investigated one knockout mouse line lacking Mnk1 (Mnk1-KO) and neonatal rat ventricular myocytes (NRVMs) lacking or overexpressing Mnk1, and further aimed to discriminate the role of Mnk1 in cardiac remodeling.

METHODS Cardiac remodeling was induced by transverse aortic constriction (TAC) in Mnk1-KO mice and their wild-type (WT) littermates. The effect of Mnk1 deficiency on TAC-induced cardiac remodeling was evaluated using echocardiography, hemodynamics, histology, and molecular analyses. For the in vitro studies, cardiomyocyte hypertrophy model was established using neonatal rat ventricular myocytes (NRVMs) treated by Angiotensin II (Ang II) (1 μM). Using siRNA- or adenovirus-mediated loss-of-function and gain-of-function Mnk1, the role of Mnk1 in cardiomyocyte hypertrophy was identified.

RESULTS After 4 weeks of TAC, Mnk1-KO mice developed exaggerated cardiac hypertrophy, fibrosis, apoptosis, and cardiac dysfunction and showed increased ERK1/2 activation along with reduced sprouty2 expression. In line with the in vivo studies, Mnk1 knockdown by Mnk1 siRNA transfection resulted in exaggerated cardiomyocyte hypertrophy in Ang II-treated NRVMs. Moreover, adenovirus-mediated overexpression of Mnk1 in NRVMs protected cardiomyocytes from Ang II-induced hypertrophy. In addition, overexpression of sprouty2 rescued NRVMs with Mnk1 knockdown from Ang II-induced hypertrophy. In accordance with the in vivo studies, as compared with the control group, Mnk1 knockdown led to hyper-phosphorylation of ERK1/2 and suppression of the sprouty2 expression in Ang II-treated NRVMs, furthermore, Mnk1 overexpression led to hypo-phosphorylation of ERK1/2 in Ang II-treated NRVMs. In addition, sprouty2 overexpression suppressed the activation of ERK1/2 in Ang II-treated NRVMs with Mnk1 knockdown.

CONCLUSIONS Mnk1 carries out a suppressive function in cardiac remodeling via regulating sprouty2-dependent ERK1/2 pathway.

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Study on atractylodin mediated apoptosis in mouse vascular smooth muscle cells

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OBJECTIVES To investigate the effects of atractylodin in mouse primary vascular smooth muscle cells(VSMCs).

METHODS Observe different concentrations (5,10,20,40,60 mg/l) of atractylodin dilutions impact in VSMCs at different time points, observe changes in cell morphology by microscope, cell proliferation assay by MTT, detected the changes in cell cycle and apoptosis percentage by flow cytometry, detect the changes in several specific proteins by Western blotting, and examine changes in cytokine secretion by liquid chip.