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Cardiac Stem Cell Transplantation Improve Electrophysiological Stability in Rats with Myocardial Infarction via Inhibition of TGF-β1 Pathway

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Objectives: Whether cardiac stem cells (CSCs) and mesenchymal stem cells (MSCs) transplantation improved electrophysiological stability in rats with myocardial infarction (MI) is still unclear. We sought to compare the effects of the CSCs and MSCs transplantation on the electrophysiological characteristics in rats with MI, and explore the mechanisms.
Methods: MI was induced in 30 male Sprague-Dawley rats. 2 weeks later, animals were randomized to receive 5×10^6 CSCs labeled with PKH26 in PBS, 5×10^6 MSCs labeled with PKH26 in phosphate buffer solution (PBS) or PBS alone injection into the infarcted anterior ventricular free wall (10 rats for each group). 2 weeks after the injection, electrophysiological characteristics were measured. Angiotensin II (ANG II), ANG II type I receptor (AT1), ANG II type II receptor (AT2) and Connexin-43 (Cx43) levels in left ventricular tissues were detected. Finally, we examined Transforming growth factor-β1 (TGF-β1) as well as its downstream signaling molecules in left ventricular tissues. Labeled CSCs and MSCs were observed in 5 μm cryostat sections from each heart.
Results: Comparison of MSCs group and PBS group, the electrophysiological stability was improved in CSCs group (Correct activation recovery time dispersion: CSCs group vs. MSCs group vs. PBS group: 32.4±8.8ms vs. 31.7±31.5ms vs. 63.9±34.6ms P=0.0209. ventricular arrhythmias induced rate: CSCs group vs. MSCs group vs. PBS group: 14/85 vs. 16/41 vs. 22/63 P<0.05. ventricular fibrillation threshold: CSCs group vs. MSCs group vs. PBS group: 8.9±1.9mA vs. 3.0±0.9mA vs. 3.6±1.6mA P=0.0000). CSCs transplantation exhibited reduction of ANG II, and increase of AT2 and Cx43 in left ventricular tissues. TGF-β1 was decreased in left ventricular tissues after CSCs transplantation. To the downstream signaling molecules of TGF-β1, Smad2, Smad3, ERK1/2 and p38 were all decreased, genetically in left ventricular in CSCs group, while Smad7, in contrary to the above factors, presented a converse alteration.
Conclusions: CSCs transplantation is superior to MSCs transplantation in modulating the electrophysiological abnormality in rats with MI. CSCs transplantation provoked up-regulation of Cx43. However, MSCs rarely provoked Cx43 expression. Inhibition of TGF-β1 mediated signaling pathway might be involved in the process.

GW25-e1166

High density lipoprotein prevents tunicamycin-induced down-regulation of LOX-1 expression and lipid uptake function in hepatic cells via inhibiting IRE1/XBP-1 pathway

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Objectives: High density lipoprotein (HDL) and endoplasmic reticulum (ER) stress both regulate lipid metabolism in hepatocytes. Nevertheless, the impact of HDL on ER stress-mediated alternation of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) level remains unclear. Here, we aim to investigate impact on LOX-1 expression by tunicamycin (TM) -induced ER stress and to determine effect of HDL on TM-affected LOX-1 expression in hepatic L02 cells.
Methods: L02 cells were treated with 0.1-2 μg/ml TM and/or 1-100 μg/ml HDL. Overexpression or silence of related cellular genes were conducted in TM treated cells. mRNA expression was evaluated using real time RT-PCR. Protein expression was analyzed by western blot and immunocytochemistry. Lipid uptake was examined by oil red O staining and DiI-Ac-LDL labeling followed by flow cytometric analysis.
Results: TM induced upregulation of ER chaperone glucose-regulated protein (GRP) 78, downregulation of LOX-1 expression and lipid uptake. Knocking down of inositol-requiring kinase/endonuclease-1 (IRE1) or X-box-binding protein-1 (XBP-1) effectively restored LOX-1 expression and improved lipid uptake in TM treated cells. HDL treatment blunted the negative impact on LOX-1 expression and lipid uptake induced by TM. Additionally, HDL at concentration 1-10 μg/ml significantly reduced the GRP78, IRE1 and XBP-1 expressions in TM-treated cells (P<0.01 compared with TM treatment alone).
Conclusions: Our findings reveal that HDL could prevent TM-induced reduction of LOX-1 expression and lipid uptake function via inhibiting IRE1/XBP-1 pathway, suggesting a new mechanism for beneficial roles of HDL in improving lipid metabolism.

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Remote limb ischemic postconditioning-induced expression of microRNAs and its mechanisms in myocardial ischemic/reperfusion injury

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Objectives: Remote limb ischemic post-conditioning (RIPostC) represents a novel and potentially promising cardioprotective strategy for preventing from myocardial ischemia/reperfusion (I/R) injury due to the high feasibility and safety. Previous research had showed that RIPostC could reduce the myocardial infarction size through the activation of TRPV1 and its neurotransmitter substance P (SP). Recent studies showed that microRNA-1 and microRNA-133a play an important role in protecting heart from I/R injury through their target genes CASP9. Whether microRNA-1 and microRNA-133 participate in the molecular biological regulation after SP acted on heart was never been reported. The present study was undertaken to investigate: (1) RIPostC can regulate the expression of microRNA-1 and microRNA-133a; (2) TRPV1 receptor and its neurotransmitter SP were responsible for the RIPost-induced expression of microRNA-1 and microRNA-133a; (3) MicroRNA-1 and microRNA-133a were involved in myocardial protective effect by regulating apoptosis-related genes CASP9.
Methods: 1. SD rats were divided into five groups: Sham-operated group, which the rats underwent thoracotomy without ligation; I/R group, which the rats were treated with ischemia for 30 min and reperfusion for 180 min; RIPostC group, which 3 cycles of transient limb I/R (ischemia 5 min/reperfusion 5 min) were given just after myocardial reperfusion; RIPostC+ capsazepine (TRPV1 receptor antagonist) group, which capsazepine (3 mg/kg) was injected into the rats through caudal vein before myocardial infarction, then 3 cycles of transient limb I/R (ischemia 5 min/reperfusion 5 min) were given just after myocardial reperfusion; RIPostC+ RP67580 (SP receptor antagonist) group, which RP67580 (5 mg/kg) was injected into the rats through caudal vein before myocardial infarction, then 3 cycles of transient limb I/R (ischemia 5 min/reperfusion 5 min) were given just after myocardial reperfusion. 2. The expression of microRNA-1and microRNA-133a of myocardial tissue in the five groups was validated by quantitative real-time RT-PCR. 3. The expression of apoptosis-related genes CASP9 mRNA of myocardial tissue in the five groups was validated by quantitative real-time RT-PCR.
Results: (1) I/R injury could down-regulate the expression of microRNA-1 and microRNA-133a and up-regulate the expression of CASP9 mRNA; compared with I/R injury group, RIPostC up-regulated the expression of microRNA-1 and microRNA-133a and down-regulate the expression of CASP9 mRNA; (2) Compared with RIPostC only, down-regulated the function of TRPV1 receptor or SP receptor could down-regulated the expression of microRNA-1 and microRNA-133a and up-regulated the expression of CASP9 mRNA.
Conclusions: RIPostC could regulate the expression of microRNA-1 and microRNA-133a by TRPV1 receptor and its neurotransmitter SP. MicroRNA-1 and microRNA-133a may play an important role in RIPostC protection by regulating apoptosis-related genes CASP9.

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Apelin Treatment Enhances ACE2 expression and Attenuates Angiotensin II-Mediated Aortic Fibrosis in Apolipoprotein E-Deficient Mice

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Objectives: Apelin is a second catalytic substrate for angiotensin-converting enzyme 2 (ACE2). Apelin and its cognate receptor APJ are essential for diverse biological processes. However, the function of Apelin signaling in the vasculature remains to be identified. We evaluated the effectiveness of apelin treatment to inhibit the progression of angiotensin II (Ang II) -mediated vascular fibrosis in apolipoprotein E-knockout (KO) mice.
Methods: 3-month wild-type (WT) and ApoEKO mice received with mini-osmotic pumps with Ang II (1.5 mg/kg/d) or saline for 2 weeks. The Ang II-infused ApoEKO mice were treated with apelin (200 μg/kg/d) or placebo for 2 weeks. We examined changes in matrix metalloproteinases (MMP), aortic ultrastructure, and pathological signaling assessed by real-time PCR, Western blotting, Masson trichrome staining and transmission electron microscope analysis, respectively.
Results: Chronic Ang II infusion resulted in marked increases in systolic blood pressure (SBP) levels and aortic expression of TGF-β1, osteopontin (OPN), collagen I, MMP2 and MMP9 in both WT and ApoE-mutant mice (n=5-8; P<0.01, respectively). Intriguingly, Ang II treatment led to greater increase in aortic fibrosis in the ApoEKO mice with exacerbation of aortic ultrastructure injury when compared with the Ang II-infused WT mice. Downregulation of aortic expression of ACE2 and APJ receptor was observed in the Ang II-treated ApoEKO mice with activation of phosphorylated levels of P-ERK1/2 and P-Smad2 (n=5-6; P<0.01, respectively). More importantly, treatment with apelin significantly reduced SBP levels and prevented Ang II-mediated increases in aortic expression of TGF-β1, OPN, collagen I, MMP2, MMP9, P-ERK1/2 and P-Smad2 in the ApoEKO mice in response to Ang II (n=4-5; P<0.05 or P<0.01, respectively). Finally, apelin treatment blunted aortic fibrosis and enhanced ACE2 level in aortas of the Ang II-infused ApoE-mutant mice (n=4-5; P<0.05, respectively), associated with marked attenuation in aortic ultrastructure injury. However, there were no changes in aortic expression of collagen III and Mas receptor among groups (n=4-8; P>0.05; respectively).
Conclusions: Ang II triggers increased aortic fibrosis and severe aortic ultrastructure injury in the ApoE-deficient mice linked with activation of the TGF-β/Smad/ERK and MMP signaling. Apelin treatment prevents Ang II-mediated aortic fibrosis and