miR-19a-3p containing exosomes improve function of ischemic myocardium upon shock wave therapy

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1. Introduction

As many current approaches for heart regeneration exert unfavorable side effects, the induction of endogenous repair mechanisms in ischemic heart disease is of particular interest. Recently, exosomes carrying angiogenic miRNAs have been described to improve heart function. However, it remains challenging to stimulate specific release of reparative exosomes in ischemic myocardium. In the present study, we sought to test the hypothesis that the physical stimulus of SWT causes the release of exosomes. We aimed to substantiate the pro-angiogenic impact of the released factors, to identify the nature of their cargo, and to test their efficacy in vivo supporting regeneration and recovery after myocardial ischemia.

2. Material & Method

Ischemic muscle and human umbilical vein endothelial cells underwent SWT. Exosomes were isolated subsequently from the supernatant and characterized by transmission electron microscopy, nanoparticle tracking analysis and flow cytometry. Exosome content was evaluated via a miRNA sequencing array. To investigate a potential effect of SWT in chronic ischemic heart failure, SWT was applied to chronic ischemic myocardium. Heart function was analyzed via transthoracic echocardiography and pressure/volume measurements and myocardial scar was quantified.

3. Results

Mechanical stimulation of ischemic muscle via SWT caused extracellular vesicle (EV) release from endothelial cells both in vitro and in vivo. Characterization of EVs via electron microscopy, nanoparticle tracking analysis and flow cytometry revealed specific exosome morphology and size with presence of exosome markers CD 9, CD81 and CD63. Exosomes exhibited angiogenic properties activating protein kinase b (Akt) and extracellular-signal regulated kinase (ERK) resulting in enhanced endothelial tube formation and proliferation. A miRNA array and transcriptome analysis via next-generation sequencing were performed to specify exosome content. miR-19a-3p was identified as responsible cargo, antimir-19a-3p antagonized angiogenic exosome effects. Exosomes and target miRNA were injected intramyocardially in mice after left anterior descending artery (LAD) ligation. Exosomes resulted in improved vascularization, decreased myocardial fibrosis and increased left ventricular ejection fraction.

4. Discussion

The mechanical stimulus of SWT causes release of angiogenic exosomes. miR-19a-3p is the vesicular cargo responsible for the observed effects. Released exosomes induce angiogenesis, decrease myocardial fibrosis and improve left ventricular function after myocardial ischemia.