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IMPROVEMENT OF CARDIAC FUNCTION BY TRANSPLANTED MESENCHYMAL STEM CELLS WITH DOWN-REGULATION OF PHD2 VIA PARACRINE FACTORS IN MYOCARDIAL INFARCTED MICE

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Objectives Transplantation of stem cell has emerged as a promising therapeutic intervention for cardiac repair. However, the survival rate of post-transplanted stem cell in the harsh microenvironment is very low. Prolyl hydroxylase domain protein 2 (PHD2) is an important cellular oxygen sensing molecules, which regulate the cellular response to the alteration of oxygen concentration. Knockout of PHD2 is protective for ischaemic cardiac disease. We hypothesise that transplantation of ADSCs genetically modified with PHD2 inhibition promotes the stem cell survival and cardiac function. In present study, adipose derived mesenchymal stem cell

(ADSCs) were isolated and cultured from healthy human subcutaneous adipose tissue. ADSCs were transfected with lentiviral shPHD2-GFP to knockdown PHD2. ADSCs were intramyocardially transplanted after acute myocardial infarction in mice. It resulted that ADSCs with PHD knockdown significantly reduced infarction size and promoted cardiac function. Inhibition of PHD2 by shRNA induced greater ADSC survival both in vivo and in vitro. Pretreatment with conditioned medium from ADSCs with PHD2 inhibition further decreased myocyte apoptosis. IGF-1 and Sfrp2 levels in the conditioned medium were significant higher than that in control cells and blockade of these two cytokines attenuated the cardioprotective effect of ADSCs with PHD2 inhibition. Those results indicate that transplantation of ADSCs, with inhition of PHD2 expression, into infarcted heart, improve cardiac function by reducing the apoptosis of ADSCs and cardiac myocytes, mainly due to the improved stem cell paracrine function in the post-MI heart. Inhibition of PHD2 in stem cells might be a novel strategy for stem cell therapy of cardiac regeneration.

Methods

Results:

Conclusions