Effect of receptor activity-modifying protein-1 on vascular smooth muscle cells

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Although transplanting mesenchymal stem cells can improve cardiac function and contribute to endothelial recovery in a damaged artery, mesenchymal stem cells may induce neointimal hyperplasia by directly or indirectly acting on vascular smooth muscle cells. Receptor activity-modifying protein 1 is the specificity receptors of calcitonin gene-related peptide. calcitonin gene-related peptide and its receptor involve the proliferation and the apoptosis in vivo and in vitro, exogenous receptor activity-modifying protein 1 enhances the antiproliferation effect of calcitonin gene-related peptide in vascular smooth muscle cells.

Bei Shi, Xianping Long, Ranzun Zhao, Zhijiang Liu, Dongmei Wang and Guanxue Xu, researchers at the First Affiliated Hospital of Zunyi Medical College within the Guizhou Province of China, have reported an approach for improving the use of stem cells for improvement of infarcted heart function and damage to the arteries in the March 2013 issue of *Experimental Biology and Medicine*. They have discovered that mesenchymal stem cells (MSCs) transfected with a recombinant adenovirus containing the human receptor activity-modifying protein 1 (hRAMP1) gene (EGFP-hRAMP1-MSCs) when transplanted into rabbit models for both Myocardial infarction (MI) and carotid artery injury inhibit vascular smooth muscle cell (VSMC) proliferation within the neointima, and greatly improved both infarcted heart function and endothelial recovery from artery injury more efficiently than the control EGFP-MSCs.

MSCs have good applicability for cell transplantation because they

possess self-renewal and multiple differentiation potential. With addition of either environmental or chemical substances, MSCs can differentiate into a variety of cell types. Numerous animal experiments and small clinical trials have shown that MSC transplantation can promote the formation of new blood vessels and reduce myocardial infarct size, and diminish the formation of scar tissue and ventricular remodeling, and improve cardiac functions. Nevertheless, MSCs have the potential to differentiate into VSMCs and may be the source of proliferating VSMCs during neointima formation after vascular injury. Recently, genetically modified MSCs, such as heme oxygenase-1(HO-1), granulocyte colony-stimulating factor (G-CSF) over-expressing MSCs, have proven to be more efficient at ameliorating infarcted myocardium than administering MSCs alone.

Calcitonin gene related protein (CGRP) is one of the most well-known potent vasodilators and can regulate vascular tone and other aspects of vascular function. The receptors for CGRP include the calcitonin receptor-like receptor (CRLR), RAMP1, and the receptor component protein. RAMP1 confers ligand specificity for CGRP. The relaxation of the artery in response to CGRP is dependent on RAMP1 expression. The response to CGRP is augmented after the increased expression of RAMP1 in VSMCs in culture.

RAMP1 over-expression increased CGRP-induced vasodilation and protected against angiotensin II-induced endothelial dysfunction as well as prevented VSMCs proliferation. In this study, we tested the effects of human RAMP1-over-expressing MSCs on infarcted heart function and intimal hyperplasia by means of cell transplantation in rabbit models for MI reperfusion and carotid artery injury. Bei Shi said "Our data has shown that hRAMP1 over-expression in MSCs through genetic modification significantly inhibits neointimal proliferation and improves infarcted heart function."

Dr. Steven R. Goodman, Editor-in-Chief of *Experimental Biology and Medicine* said "The effect of stem cell therapy with the RAMP1 expressing MSCs has been shown, by Bei Shi and colleagues, to reduce neointimal proliferation in the carotid angioplasty and myocardial infarction animal models. This approach could be important for the treatment of damaged vessels and the infracted heart".

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