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BONE MARROW-DERIVED MESENCHYMAL STEM CELLS CONTRIBUTE TO INTIMAL HYPERPLASIA AFTER VASCULAR INJURY: CONCERNS AND ALTERNATIVE STRATEGY OF STEM CELL THERAPY

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BACKGROUND: Mesenchymal stem cells (MSCs) have the capacity to differentiate into cardiomyocytes, endothelial (ECs) and smooth muscle cells (SMCs), and have been used for cardiac regeneration. However, it has not been determined whether MSC therapy also causes a detrimental effect on diseased vessels, such as those with intimal hyperplasia.

METHODS: A variety of stem/progenitor cells were cultured. In vitro and in vivo adhesion assays were performed with each cell type. To demonstrate the contribution of MSC to neointimal formation, two models of bone marrow transplantation (BMTx) were used: (1) Wild-type mice after femoral artery wire-injury were injected via tail vein with MSCs from eGFP transgenic mice; (2) Direct BMTx with eGFP-MSCs to tibias of the irradiated wild type mice.

RESULTS: Wire injury caused a 10-fold increase in blood G-CSF levels and a four-fold increase in circulating MSC compared with controls. Compared with SMC, MSC had 2.5- to 2.8-fold increases in adhesion to the matrix in vitro, and a 12-fold increase in adhesion capacity in vivo. In vivo, eGFP-MSCs significantly contributed to the intimal hyperplasia after vascular injury (32 ± 15%) in both of the animal models. Furthermore, MSCs differentiated into either endothelial or smooth muscle lineage while proliferating in the injured vessel wall. EC therapy significantly attenuated the neointimal thickness contributed by MSCs. Co-culture experiments demonstrated that ECs help MSCs transcribe the mRNA of a variety of endothelial markers and help MSCs differentiate into cells expressing endothelial phenotypes.

CONCLUSION: This study demonstrated the detrimental effect of stem cell therapy on atherosclerosis. MSC therapy requires a strategy to attenuate its high potential of developing intimal hyperplasia on diseased vessels.

Key words: Mesenchymal stem cell, intimal hyperplasia, restenosis