EX VIVO AKT/HO-1 GENE THERAPY TO HUMAN ENDOTHELIAL PROGENITOR CELLS SYNERGISTICALLY ENHANCES FUNCTIONAL RECOVERY AFTER MYOCARDIAL INFARCTION

ACC Special Session
Ernest N. Morial Convention Center, Room 215
Sunday, April 03, 2011, 8:00 a.m.-8:15 a.m.

Session Title: Young Investigators Award Competition: ACCF/Herman K. Gold Young Investigator’s Award in Molecular and Cellular Cardiology
Abstract Category: Molecular and Cellular Cardiology
Presentation Number: 0406-05

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Background: Ischemic myocardial injury creates a hostile microenvironment, which is characterized by hypoxia, oxidative stress, and inflammation. To enhance recovery by endogenous cellular contributions and repair by exogenously delivered cells, as in cell-based therapy, we aimed to alter the hostile myocardium using gene therapy.

Methods: Human endothelial progenitor cells (EPCs) were isolated and transduced to express protein kinase B (Akt) and heme-oxygenase-1 (HO-1). Infarct conditions were simulated by adding hydrogen peroxide and tumor necrosis factor alpha in a hypoxic environment to human EPCs or cardiomyocytes; otherwise 5x10^5 cells were transplanted to post-myocardial infarct tissue of nude mice.

Results: Human EPCs transduced ex vivo with Akt and HO-1 alter their paracrine profile under stress, improving migration toward infarcted human cardiomyocytes and retention to extracellular matrix. Modified EPCs reduce the TNFα burden both in vitro and in vivo, attenuating the activity of the inflammatory transcription factor NF-κB and promoting cell survival. Akt and HO-1 act synergistically to enhance EPC neovascularization, resulting in improved cardiac performance and reduced negative remodeling after myocardial infarction.

Conclusions: Paracrine alteration of the hostile infarct microenvironment through gene modification of human EPCs enhances the function and retention of transplanted cells for restoration of cardiac function.