

MULTISTEM<sup>®</sup> MODULATES ENDOTHELIAL CELL ADHESION MOLECULE CELL SURFACE EXPRESSION FOLLOWING ACTIVATION AND REDUCES INFLAMMATION FOLLOWING AMI IN RATS.

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Damage to the heart following AMI can be severe and extensive. Substantial cellular death can subsequently lead to fibrosis, left ventricular remodeling and ultimately, heart failure. The tissue damage induced by ischemia triggers an inflammatory response that consequently leads to cellular toxicity in the post AMI myocardium. This inflammatory response includes neutrophil homing and infiltration at the site of injury. Previous studies have shown that delivery of adult bone-marrow derived adherent pluripotent stem cells (MultiStem<sup>®</sup>) into peri-infarct sites following induction of myocardial infarction by direct left anterior descending (LAD) ligation resulted in improved cardiac function in animal models, including improved left ventricular contractile performance, increased vascular density and improved myocardial energetic characteristics. In this study, we examined whether MultiStem<sup>®</sup> improves cardiac function, in part, by reducing the inflammatory response induced by the ischemic event. To this end, we examined whether MultiStem<sup>®</sup> can modulate endothelial cell activation by examining the upregulation of cell adhesion molecules to the cell surface. We found that coculture of MultiStem<sup>®</sup> with aortic or pulmonary endothelial cells prevents upregulation of E-Selectin, V-CAM and to a lesser degree, I-CAM, to the cell surface of endothelial cells upon activation with TNF- $\alpha$  or interleukin-1 $\beta$ . Decreased upregulation of E-Selectin by coculture with MultiStem<sup>®</sup> does not appear to be a result of increased cleavage of E-Selectin from the cell surface. Instead, MultiStem<sup>®</sup> modulates cell surface upregulation, in part, through decreasing transcription of V-CAM, E-Selectin and ICAM. This reduction in adhesion molecule expression results in decreased neutrophil binding to endothelial cells as compared with untreated controls. This activity is not common to all bone marrow derived adherent stem cells since mesenchymal stem cells (MSC) are unable to modulate V-CAM, E-Selectin or I-CAM cell surface upregulation upon activation with TNF- $\alpha$ . These results suggest MSC and MultiStem<sup>®</sup> have distinct secretion profiles. In order to determine whether decreased endothelial cell activation could reduce inflammation and neutrophil infiltration following acute myocardial infarction, we examined whether MultiStem<sup>®</sup> improves cardiac function by reducing the inflammatory response induced by the ischemic event. We found decreased levels of neutrophil infiltration in MultiStem<sup>®</sup> treated hearts following permanent LAD ligation compared with vehicle treated controls. This study demonstrates that MultiStem<sup>®</sup> modulates the inflammatory response following AMI and implicates the downregulation of cellular adhesion molecules on activated endothelial cells as a possible mechanism for this immunomodulation.