Mechanisms Responsible for the Greater Therapeutic Efficacy of Cardiac Mesenchymal Cells Cultured at Physiologic Oxygen Tension in Mice with Heart Failure Caused by Myocardial Infarction

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Cardiac mesenchymal cells (CMCs) are novel, promising stem cells that improve heart function in rodents after myocardial infarction (MI) and may soon be used in clinical trials. Stem cells are usually cultured at atmospheric oxygen tension (21%); however, physiologic O2 tension in the heart is ~5%, not 21%. Last year, I found that CMCs cultured at 5% O2 were more effective than 21% O2 CMCs in improving left ventricular (LV) ejection fraction (EF) in mice with heart failure. However, EF can be misleading because it is heavily dependent on loading conditions. The gold-standard measure of LV function is end-systolic elastance (load-independent). Further, the mechanism of action of 5% O2-CMCs is unknown. To investigate the effect of 5% O2-CMCs on elastance and their mechanism of action, 3 groups of mice with heart failure caused by MI received CMCs cultured at 21% O2 or 5% O2, or vehicle. Compared to 21% O2-CMCs, 5% O2-CMCs produced i) 3-fold greater increase in LV elastance; ii) lower myocardial collagen content and scar size (histology); iii) marked upregulation of numerous cardiac genes involved in myogenesis, contraction, and collagen turnover (transcriptome analysis with RNA-Seq). This is the first report that cell therapy activates a pro-myogenic and antifibrotic genetic program in the heart. In conclusion, CMCs cultured at physiologic (5%) O2 tension possess superior efficacy in improving both function and structure of failing hearts. Mechanistically, they induce cardiac genetic reprogramming that promotes formation of new contractile proteins and degradation of collagen. Since all clinical trials thus far have used cells grown at 21% O2, use of cells grown at 5% O2 could potentially benefit millions of patients with heart failure who are candidates for cell therapy.

Awards Won:

Second Award of $2,000