

## **Stem Cell-derived Exosomes Induce Cardiac Repair via mRNA Modification**

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Exosomes are cell-derived nanovesicles that carry and shuttle microRNAs (miRNAs) to mediate cell-cell communication. Vast majority of cell types including cardiac myocytes and progenitors actively secrete exosomes, whose miRNA contents are altered after physiological or pathological changes such as myocardial ischemia (MI). In this new study, we have discovered that chemical modification to mRNAs is a novel regulator of ischemia-induced gene expression changes in the heart. We hypothesized that the benefits of human CD34<sup>+</sup> stem cell-derived exosomes (CD34exo) are mediated by mRNA modifications in the target cells via miRNA delivery. MiRNA profiling and bioinformatic analysis identified that CD34exo is selectively enriched with a number of miRNAs that directly target genes implicated in regulation of mRNA modifications. Interestingly, under myocardial ischemia, there was a significant increase in mRNA modifications in the mouse heart, which was decreased by about 70% with CD34exo-treatment. In line with the in vivo MI data, in vitro hypoxic stimulation in neonatal / adult rodent myocytes and non-myocytes increased mRNA modifications and controls known regulators of those mRNA modifications. Loss-of-function studies for regulators of mRNA modifications attenuated hypoxia-induced changes to epitranscriptome indicating important roles for these molecules under stress conditions. Finally, using gain-of-function and loss-of-function studies, we demonstrate that miR-126, one of the most enriched miRNAs in CD34exo, plays a critical role in regulating the mRNA modifications. We conclude that miRNAs enriched in CD34exo mediate their cardioprotective effect at least in part, by regulating the mRNA epitranscriptome of the target cell. Our new data suggests hypoxia as a novel regulator of the mRNA epitranscriptome and provides novel insights to post-transcriptional gene regulation in the heart.

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