Protein Complexes as Novel Therapeutics for Myocardial Infarction.

Myocardial infarction (MI), an interruption of blood supply to the heart, leads to oxygen and nutrient deprivation and cell death. Despite numerous clinical trials for potential adult stem/progenitor cell-based therapeutics for MI, only modest success has been achieved in terms of preservation of cardiac structure and function. Importantly, while the role of stem/progenitor cell therapies has focused on cell injections and direct cell replacement, most of the beneficial effects of cell transplants appear attributable to paracrine effects of factors secreted or released from administered cells. Our laboratory isolated adult stem/progenitor cells from the epicardium (cover) of the human heart that respond to injury by undergoing epithelial to mesenchymal transformation and secreting a wide variety of cardioprotective ligands. After concentrating the secreted factors by 30-fold, we observe protein-protein interactions of growth factors and carrier proteins. We found that arterial administration of concentrated conditioned medium, at the time of reperfusion, dramatically preserved cardiac structure and function, reducing infarct size by 50%. We hypothesize that the formation of protein complexes during concentration increases the half-life and retention of cardioprotective factors in the infarct zone, leading to prolonged rescue effects. The association of growth factors with carrier proteins decreases the effective dose needed for cardioprotection from micrograms of individual factors down to nano- or picogram amounts. Our results suggest that combinatorial therapeutics based on reduced concentrations of individual factors will lead to improved tissue protection and reduced negative side-effects.