Decellularized Zebrafish Heart Extracellular Matrix Promotes Myocardial Regeneration in Adult Mammals

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The adult human heart has very limited regenerative capacity after heart attack. However, evolutionarily primitive species generally have higher tissue regenerative capability than mammals. The tissue-specific extracellular matrix (ECM) in evolutionarily primitive species may induce regeneration post-injury and contribute to this difference. In marked contrast to the highly regenerative zebrafish heart, the injured adult mammalian heart typically elicits fibrotic, instead of regenerative, responses. Hence mammalian heart ECM may not be optimally inductive for myocardial regeneration. We hypothesize that administration of decellularized zebrafish heart ECM (zECM) made from normal or healing hearts promotes mammalian heart regeneration after myocardial infarction (MI). Using adult zebrafish and mouse as representative species of lower vertebrates and mammals, we show a single injection of zECM, particularly the healing one, enables mouse cardiac regeneration and functional recovery after acute MI. In particular, we observed proliferation of cardiomyocytes and multiple cardiac precursor cell (CPC) populations as well as reactivation of ErbB2 expression in cardiomyocytes in zECM-treated mouse hearts. Moreover, zECM exhibits pro-proliferative and chemotactic effects on human CPC populations *in vitro*. These regenerative responses correlate with the higher contractile function, less ventricular dilatation, and more elastic myocardium in zECM-treated hearts than control hearts treated with decellularized mouse heart ECM or saline. These benefits likely contribute to the structural preservation post-MI. We further demonstrated the critical role of ErbB2 in zECM-mediated benefits, likely via neuregulin-1 signaling, by chemical inhibition of ErbB2 activity. Overall this study pioneers the usage of decellularized ECM from evolutionarily primitive species in mammals and imposes a new approach for mammalian heart regeneration.