Recovery of Myocardial Infarction via Unique Modulation of the Cardiac Microenvironment

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The cardiac microenvironment includes cardiomyocytes, fibroblasts and macrophages, which regulate remodeling after myocardial infarction (MI). Targeting this microenvironment is a novel therapeutic approach for MI. We investigated the therapeutic effect of natural compound derivative, BIO [(2'Z,3'E)-6-Bromoindirubin-3'-oxime], on cardiac microenvironment cells and remodeling post-MI. Using a series of co-culture studies, BIO was shown to induce proliferation in cardiomyocytes and inhibit proliferation in cardiac fibroblasts. BIO produced multiple anti-fibrotic effects in cardiac fibroblasts. In macrophages, BIO inhibited the expression of pro-inflammatory factors. Significantly, BIO modulated molecular crosstalk between cardiac fibroblasts and differentiating macrophages to induce polarization to the anti-inflammatory M2 phenotype. In the optically transparent zebrafish-based model of heart failure, BIO induced cardiomyocyte proliferation and completely recovered survival rate. BIO is a known glycogen synthase kinase-3β inhibitor, but these effects could not be recapitulated using the classical inhibitor, lithium chloride; indicating novel, potential therapeutic effects of BIO on remodeling. We identified the novel mechanism of BIO as differential modulation of p27 expression and potent induction of anti-inflammatory interleukin-10 in microenvironment cells. In a rat MI model, BIO reduced fibrosis and improved cardiac performance. Histological analysis revealed modulation of the cardiac microenvironment by BIO, with increased presence of anti-inflammatory M2 macrophages. Our results demonstrate that BIO produces unique effects in the cardiac microenvironment to promote recovery post-MI.