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Anti-fibrotic effects of cardiac progenitor cells in a 3D-model of human cardiac fibrosis.

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Purpose: Excessive matrix deposition upon cardiac injury results in perpetuation of pro-fibrotic signaling, which contributes to progressive adverse cardiac remodeling during heart failure. It has been recognized that cardiac stem cell therapy for chronic ischemic heart failure might target fibroblast behavior. However, no reliable tissue model exists to evaluate the effect of cardiac stem cell therapy. Therefore, we developed a three dimensional (3D), tunable model of human cardiac fibrosis to allow for physiologically relevant in vitro testing of fibroblast behavior upon stem cell therapy.

Methods: A photocrosslinkable hydrogel, composed of gelatin methacryloyl (GelMA) combined with human fetal cardiac fibroblast (hfCF), was used to study fibroblast characteristics. hfCF-laden gels were cultured for 7 days in normal or pro-fibrotic medium (2 ng/ml TGF-ß1). To determine possible paracrine effects of cardiac progenitor cells (CPC), hfCF were co-cultured with 1) CPC, 2) conditioned medium derived from the co-culture of hfCF-laden GelMA and CPC (co-CM), 3) conditioned medium derived from CPC monoculture (CM), or 4) CPC derived extracellular vesicles (EV). As a measure of hfCF activation, a-SMA and Col1a1 levels were analyzed by qPCR and immunohistochemistry.

Results: 3D culture of hfCF resulted in quiescent cell behavior as demonstrated by a 3.0-fold lower a-SMA expression when compared to 2D culture (p = 0.05). In addition, reproducible cell activation was observed in a pro-fibrotic environment, as shown by a 2.1-fold increase in a-SMA expression (p < 0.001) and a 10.3-fold increase in collagen type 1 alpha chain 1 (COL1a1) expression (p < 0.01). Immunohistochemistry confirmed this finding: the number of COL1a1-positive cells was higher in the TGF-ß1-treated group (21 ± 7% vs. 35 ± 9%, p = 0.01). This was accompanied by accumulation of extracellular matrix as shown in a picrosirius red staining (mean grey value 0.02 ± 0.003 vs. 0.04 ± 0.016, p = 0.1). The observed fibrogenic response was strongly decreased upon co-culture with CPC, as the a-SMA expression was 2.7-fold lower (p = 0.02). We further demonstrated that the anti-fibrotic effect was transferable via co-CM (1.8-fold decrease in a-SMA expression, p = ns), but not via CPC-CM or isolated CPC-EV.

Conclusions: We showed the suitability of hfCF-laden GelMA as a 3D culture model to study cardiac fibrosis and the possibility to modulate cellular fibrotic responses. Moreover, our approach demonstrated paracrine inhibitory effects of CPC on matrix remodeling in vitro and revealed crosstalk between hfCF and CPC to be indispensable for the observed anti-fibrotic effect.