Abstract: P112

Epithelial-to-mesenchymal transition is required for a therapeutic effect of epicardial-derived cells after myocardial infarction

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Introduction: The cells of the epicardium -the epithelial layer covering the outside of the heart-, are activated after ischemic injury. Upon damage these cells undergo epithelial-to-mesenchymal-transition (EMT). The epicardial-derived cells (EPDCs) contribute to repair either via migration and differentiation, or via a paracrine mechanism. Previous research revealed that direct transplantation of cultured human mesenchymal EPDCs into the infarcted mouse heart attenuated remodelling, increased vascularisation and improved cardiac function. We recently developed a cell culture protocol for human EPDCs in their cobblestone-like epithelial state (cEPDCs) allowing us to compare EPDCs prior to and post-EMT. cEPDCs are more plastic with the ability to differentiate into a range of mesenchymal cell types including smooth muscle cells, cardiac fibroblasts, and possibly to cardiomyocytes and endothelial cells. Therefore, we questioned whether cEPDCs have a better therapeutic potential compared to mesenchymal spindle-shaped EPDCs (sEPDCs) after myocardial infarction (MI).

Purpose: to investigate the importance of EMT in EPDCs prior to transplantation in preserving cardiac function after MI.

Methods: Epicardium was isolated from human atrial appendages and processed into a single cell suspension. After plating, cEPDCs were cultured with either ALK4/5/7 kinase inhibitor, or treated with TGF-β to induce EMT. Immediately after induction of MI in NOD-SCID mice we injected either sEPDCs, cEPDCs, or PBS into the border zone at 2 sites. Cardiac function was assessed for 6 weeks via ultrasound and hearts were isolated at 3 days and 6 weeks post-MI. Infarct size, human collagen deposition, number of engrafted cells and vascularization of the border zone were determined after 6 weeks. Short-term cell engraftment and immune response are determined at 3 days post-MI. The angiogenic secretome of EPDCs was determined with a human angiogenic antibody array, and confirmed by ELISA.

Results: Six weeks after transplantation only sEPDCs were able to partially preserve cardiac function compared to cEPDCs and PBS control. This coincided with a smaller infarct size in the sEPDC group. Immunostaining for human cell markers revealed that low numbers of EPDCs were present at six weeks in either group, suggesting a paracrine role rather than a cellular contribution. The secretome of the conditioned medium of cultured sEPDCs and cEPDCs showed angiogenic potential, however, the vascularization of the border zone at six weeks was similar in all groups. We observed a higher deposition of human collagen in the sEPDC group. We are currently investigating the cell survival and effect on immune response at 3 days post-MI.

Conclusion: sEPDCs ameliorated cardiac function, likely via a paracrine mechanism. Although more plastic, cEPDCs do not contribute to repair. These data will help in understanding the potential of EPDCs as a local source for endogenous cardiac repair.