The effect of cardiosphere-derived cell extracellular vesicles embedded in cardiac matrix hydrogel on cardiac remodeling in a porcine model of ischemic cardiomyopathy

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Background: Numerous preclinical studies have confirmed that stem cell-derived extracellular vesicles (EVs) can prevent from negative cardiac remodeling after an ischemic injury, reduce the scar and preserve heart function. It is believed that by increasing the engraftment of the therapeutic product at the target site may bust its efficacy. The use of bioengineering materials such as hydrogels as delivery scaffolds for intramyocardial EVs administration may constitute a minimally invasive therapeutic strategy that improves the efficacy of EVs by increasing their permanence in the tissue.

Objective: To evaluate the therapeutic efficacy of a new regenerative product constituted by the combination of EVs secreted by cardiosphere-derived cell (CDC-EVs) embedded in a hydrogel-based scaffold made from decellularized cardiac matrix (HDM).

Methods: Twelve pigs (50% females) with induced ischemic cardiomyopathy were randomly assigned to receive: phosphate-buffer saline (PBS) as control group (n=4), CDC-EVs alone (n=4) and combination of CDC-EVs and HDM (EV-HDM, n=4). Treatment was administered via percutaneous intramyocardial injection in the scar border zone 1-month after myocardial infarction with NOGA system. Animals were followed-up another month and sacrificed. Hearts were excised for histological analysis performed according to the cardiac area: scar (anterior wall), scar border zone and remote zone (inferior wall). Functional evaluation was performed with cardiac magnetic resonance imaging immediately before- and 1-month after treatment.

Results: Cardiomyocytes size was significantly lower in EV-HDM group compared to control PBS both at scar border (4660 ± 2088 vs. 5254 ± 2294 pixels; p=0.02) and remote areas (3381 ± 1259 vs. 4237 ± 1256 pixels; p<0.001), while no changes were observed in CDC-EV alone group compared to controls. Interstitial fibrosis was significantly lower in EV-HDM group compared to PBS controls both at scar epicardial side (34% vs. 44%; p=0.01) and remote areas (16% vs. 20%; p<0.01), similarly to CDC-EV vs. PBS (34% at the scar; p<0.01 and 17% at the remote zone; p=0.01). While left ventricular ejection fraction (LVEF) tended to decrease in PBS group from 36% to 32%, it showed an opposite trend in CDC-EV (from 35% to 38%) and EV-HDM (from 31% to 37%).

Conclusion: The combined product of EV-HDM reduce cardiac fibrosis and hypertrophy, favorably affecting the remodeling process and may thus increase LVEF in ischemic heart disease. The results of our study fail to clearly demonstrate the superiority of EV-HDM over CDC-EVs alone, although it may exist.