Heterogeneity of fibrosis and fibroblast differentiation in the left ventricle after myocardial infarction

Authors:
C Kadur Nagaraju1, P Claus2, E Dries1, A Angelo Singh1, K Vermeulen1, HL Roderick1, KR Sipido1, RB Driesen1, 1KU Leuven, Division of Experimental Cardiology, Department of Cardiovascular Sciences, KU Leuven - Leuven - Belgium, 2KU Leuven, Division of Imaging and Cardiovascular Dynamics, Department of Cardiovascular Sciences, - Leuven - Belgium,

Topic(s):
Extracellular matrix and fibrosis - Heart

Citation:
Cardiovascular Research Supplements (2016) 111 (S1), S25

Background: After myocardial infarction (MI) remodeling of the non-infarcted tissue contributes to reduced cardiac function; fibroblast (Fb) differentiation and interstitial fibrosis are part of this remodeling process.

Purpose: We investigated the Fb differentiation and properties in different regions of the heart after MI.

Methods: A copper coated stent was implanted in the left anterior descending coronary artery (LAD, young adult pigs) leading to high grade stenosis and MI (10% of left ventricular mass). After 6 weeks after MI, biopsies were collected from the MI scar, the myocardium adjacent (MIadjacent) and remote to MI (MIremote) and from corresponding regions in SHAM (N=6 SHAM, N=10 MI). Fb were isolated and cultured in DME medium with 10% fetal bovine serum for 4 days to determine Fb phenotypes and proliferation capacity. Immuno-staining and 3-D collagen contraction was used to evaluate Fb differentiation. Fibrosis and collagen subtypes were studied in sirius red stained paraffin sections and imaged using polarized light. Tissue lysates were used to measure TGF-β1 and lysyl oxidase (Lox) concentration and lox enzyme activity, markers for collagen cross-linking.

Results: Fb from all regions of MI demonstrated differentiation towards myofibroblasts (MyoFb) as shown by the high number of cells with F-actin stress fibers and increase in cell size. The MyoFb induced contraction of 3-D collagen matrices: this was highest for scar > MIadjacent > MIremote. Despite differentiation, proliferation capacity was maintained for MyoFb from all the regions. Interstitial fibrosis was increased by 3-fold in MIadjacent but not in MIremote. A 7-fold increase of collagen type I was noted within the interstitial area of the MIadjacent. Arteriole perivascular fibrosis was increased solely in the MIadjacent (5-fold increase of collagen type I). Protein levels of TGF-β1 were elevated in MIadjacent and MIremote whereas Lox protein expression and enzyme activity were only upregulated in MIadjacent by 1.4-fold and 1.5-fold respectively.

Conclusion: Differentiation to MyoFb occurs in all regions of the heart after MI with little cellular phenotype difference in vitro. In vivo, MyoFb in MIadjacent contributes to interstitial fibrosis via collagen cross-linking and this is less so for MIremote. This in vivo difference may be due to increase in lysyl oxidase activity present only in MIadjacent.