ACTIVATION OF VALVULAR INTERSTITIAL CELLS AND EXTRACELLULAR MATRIX REMODELING IN CALCIFIC AORTIC VALVE STENOSIS

Authors: Jurijs Sekretarjovs[1], Alīna Ļišņova[2]
Scientific research supervisor: Sandra Skuja[3], Valērija Groma[3]
[1] Faculty of Medicine 4th year, Riga Stradins University, Latvia
[2]Faculty of Medicine 6th year, University of Latvia, Latvia
[3]Institute of Anatomy and Anthropology, RSU, Latvia

Key words. Aortic stenosis, interstitial cells, immunohistochemistry.

Introduction. Calcific aortic stenosis is the most common cause of aortic valve replacement in developed countries, and this condition increases in prevalence with advancing age, afflicting 2-3% of the population by the age of 65 years. The primary cell types in the aortic valve are valvular endothelial and interstitial cells (VIC). Recently, five distinct phenotypes of the VIC have been described. These cells possess essential functions in normal valve physiology and in pathological processes. Abnormal aortic valve function likely results from extracellular matrix (ECM) remodeling associated with the disequilibrium between the synthesis of ECM components and their degradation.

Aim. The aim of this study was to analyze the evidence of extracellular matrix remodeling and phenotypical changes occurring in the VIC of the different histological layers of aortic valves, and to describe its contribution to the pathogenesis of aortic valve stenosis. Immunohistochemical performance on 17 stenotic aortic valves and 11 control valves was studied by semiquantitative counting of alpha smooth muscle actin (α-SMA), CD34 and MMP-9 expression and non-parametric tests.

Results. According to our results, expression of α-SMA by activated VIC was more prominent in stenotic valves compared with control valves ($p <$

0.001). Furthermore, increased expression of α-SMA was observed in *ventricularis* layer both in stenotic ($p = 0.015$) and control ($p < 0.001$) valves. We found CD34+ interstitial cells mainly in *fibrosa* and *spongiosa* layers. The expression of MMP-9 was more marked in stenotic valves compared with control valves ($p < 0.001$). In addition, MMP-9 expression was more prominent in *ventricularis* ($p = 0.030$) layer of calcific valves. We found that the source of the MMP-9 is activated VIC and mononuclear leukocytes. Weak positive correlations between α-SMA and MMP-9 expression (*rho* = 0.102; $p = 0.048$), and between MMP-9 and number of CD34-stained blood vessels (*rho* = 0.197; $p < 0.001$) were discovered.

Conclusions. For the first time we analyzed the expression of MMP-9 and phenotypical changes of the VIC of the different histological layers of aortic valve. Activated VIC express α-SMA and significantly increase in number as respond to valve injury. Furthermore, in the *ventricularis* layer the VIC possess the greatest capacity to differentiate into myofibroblasts. The expression of MMP-9 by activated VIC and mononuclear leukocytes was increased in stenotic valves, was more prominent in *ventricularis* layer, and weakly correlated with α-SMA expression and angiogenesis, suggesting the contribution of extracellular matrix remodeling in the pathogenesis of aortic valve stenosis.