Abstract: P326

New signaling pathways potentially involved in human mitral valve prolapse

Authors:
P Songia, V Myasoedova, P Gripari, V Valerio, L Fusini, L Cavallotti, G Tamborini, M Pepi, P Poggio, 1
1Cardiology Center Monzino IRCCS - Milan - Italy,

Topic(s):
Basic Science - Cardiac Diseases: Valvular Heart Disease

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S83

Funding Acknowledgements:
Fondazione Gigi e Pupa Ferrari ONLUS

Introduction. Mitral valve prolapse (MVP) with severe regurgitation is one of the most common pathology of the mitral valve, afflicting more than 175 million people worldwide. No pharmacological treatments have been identified yet, leaving the surgical intervention the only effective treatment.

Hypothesis. Our aim was to evaluate circulating microRNA (miRNA) profile in human myxomatous MVP to identify the pathological processes and thus new potential therapeutic targets.

Methods. We analyzed plasma obtained from 30 patients that underwent mitral valve repair due to MVP and 30 controls. TaqMan Array Human MicroRNA Card A (v2.0) was used to assess the expression levels of 384 miRNA. Validation were performed using real-time PCR and expressed as log fold change (logFC). Functional analysis were carried out with Cytoscape (v3.4.0) and ClueGO (v2.3.3). In vitro studies were performed on valve endothelial cells isolated from MVP specimens.

Results. MiRNA profiling revealed that in MVP patients 6 miRNAs were up-regulated, while 22 were down-regulated when compared to controls. Validation analyses confirmed that miR-150-5p (logFC=+0.46±0.06; p<0.0001), miR-210-3p (logFC=+0.23±0.06; p=0.01), miR-451a (logFC=+0.50±0.09; p<0.0001), and miR-487a-3p (logFC=+0.54±0.16; p=0.003) were significantly up-regulated in MVP. MiR-27a-3p (logFC=-0.32±0.09; p=0.004), miR-323a-3p (logFC=-0.36±0.10; p=0.004), miR-361-5p (logFC=-0.35±0.09; p=0.0002), and miR-376c-3p (logFC=-1.37±0.36; p=0.003) were significantly down-regulated in MVP. Functional analysis identified several biological processes: 1) cellular response to oxidative stress and mechanical stimulus; 2) regulation of stress fiber assembly; 3) apoptosis; 4) transforming growth factor beta signaling pathway; 5) adherens junction and focal adhesion regulation; 6) response to hypoxia-inducible factor 1 signaling pathway; 7) endothelial and smooth muscle cell proliferation; 8) ErbB and apelin signaling pathways. Finally, endothelial cells, under oxidative stress stimuli, showed a positive regulation of myxomatous degeneration with a concomitant release of miR-150-5p (logFC=+3.73±0.2; p<0.0001).

Conclusions. To the best of our knowledge, this is the first study performed on human plasma and isolated valve endothelial cells from MVP patients, showing a strong association of miRNA and MVP pathology. The new identified pathways could represent new pharmacological targets to slow-down or even halt MVP progression.