New insights into the pathophysiology of mitral valve disease: molecular characterisation and comparison of the different aetiologic subtypes

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Introduction: Mitral valve disease (MVD) is a frequent cause of heart failure and death. Data regarding its molecular basis are scarce, although current evidences show that primary MVD is an active process with the involvement of several molecular pathways. However, there are no studies that compare such mechanisms among the different subtypes of primary MVD. ST-2/interleukin (IL)-33 pathway is a potential pathophysiological mediator of cardiovascular diseases, although its role in heart valve diseases has not been explored.

Purpose: We aimed to analyse the molecular and cellular mechanisms involved in the main subtypes of primary chronic MVD: myxomatous degeneration, calcific or senile degeneration and rheumatic MVD.

Methods: 200 patients undergoing mitral valve replacement due to chronic primary MVD were enrolled. We classified them in the three main aetiologic subtypes according to echocardiographic features and surgeon's description: myxomatous degeneration (89 patients), senile or calcific degeneration (54 patients) and rheumatic disease (57 patients). In all patients the resected valve tissue and blood samples were collected. RT-PCR, Western Blot and ELISA were performed to analyse markers of inflammation (C-reactive protein, Rantes, IL-6, IL-1β/IL-1F2, tumor necrosis factor (TNF)-α), calcification (osteopontin, bone morphogenic protein (BMP)-2 and -4 and periostin), valvular endothelial cells (CD-31, E-cadherin), extracellular matrix remodeling (matrix metalloproteinase (MMP)-1, -2 and -9, tissue inhibitor of MMP-1 and -2), proteoglycans (aggrecan, hyaluronan, lumican, biglycan, syndecan-1, decorin) fibrosis (collagen-1, fibronectin, galectin-3, Transforming growth factor (TGF)-β) and ST-2/IL-33 system.

Results: Each aetiologic subtype showed a distinct marker profile. As compared with the other subtypes, myxomatous valves presented significantly higher levels of inflammatory markers (Rantes, IL-6), fibronectin, proteoglycans (hyaluronan, lumican and biglycan), ST-2 and IL-33. Senile degenerative valves presented significantly higher levels of calcification markers (osteopontin, BMP-2 and -4). Rheumatic valves were characterized by high levels of TNF-α and TGF-β compared to other subtypes and a significant increase in the expression and activity of matrix degradation enzymes (MMP-1 and -2).

Conclusions: Our study provides for the first time the molecular characterisation of the main aetiologic subtypes of chronic MVD. Proteoglycans accumulation, fibrosis and inflammation are the main features of myxomatous changes, whereas calcification define senile degeneration. Rheumatic valves exhibit elevated TNF-α and TGF-β and a dramatic increase in matrix turnover. Moreover, myxomatous valves overexpress the ST-2/IL-33 system, suggesting that this pathway could play a role in the development of myxomatous changes. Unravelling the underlying molecular mechanisms of each aetiology is essential to identify new therapeutic targets.

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