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Short Communication

Ossification of Heart Valves – An Immune Mediated Rheumatic Inflammation

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Received date: August 18, 2025; Accepted date: August 29, 2025; Published date: September 05, 2025

Citation: Ramachandran Muthiah, (2025), Ossification of Heart Valves – An Immune Mediated Rheumatic Inflammation, *Cardiology Research and Reports*, 7(5); **DOI:10.31579/2692-9759/180**

Abstract

Ossification is the hardening of the valve due to the deposition of calcium salts. Any valve can become calcified. However, calcification is more likely to affect the valves on the left side of the heart (mitral and aortic valves) since they experience greater pressure, and more wear-and-tear damage. Calcification earlier in life was seen in severely damaged valves by the rheumatic process and therapeutic strategies are targeted to reverse this process by understanding its biological mediators.

Keywords: rheumatic inflammation; mineralization of heart valves; cellular process; therapeutic interventions

1.Introduction

Calcification in the region of mitral-aortic continuity is significant at its origin and etiopathogenesis. The etiology of valvular calcification may be divided into 3 groups, namely, inflammation, degeneration and metabolic disturbances. The heterotopic ossification of left-sided heart valves is due to rheumatic inflammation and biomineralization. Calcification of valves is a complex process and involves different cell types and matrix architecture of heart valves. The senile valve calcification also known as 'dystrophic calcification', occurs on the heart valves usually in adults over 50 years of age. The mitral-aortic intervalvular fibrosa is the junctional tissue between the elements of mitral and aortic valves, called as mitral-aortic membrane or curtain which is relatively avascular and offers little resistance to infection.

2. Pathogenesis

Calcification of heart valves is an immune-inflammatory disease process. The rheumatic involvement produces an inflammatory tissue environment that disrupts the endothelial layer of valve leaflets. The VECs (valvular endothelial cells), lose the endothelial cell properties and these 'transformed' VECs migrate into the surrounding tissues. Once the endothelial-to-mesenchymal transition(EnMT) occurs, the BMP 2 and 4 (bone morphogenic proteins) secreted by the activated endothelial cells stimulate the calcification by activating Smad and Wnt/B-catenin signaling and upregulate the expression of osteochondrogenic transcription factor Msx2 and the faster osteoblast transcription factor Runx2 [1]. Once Runx2 is expressed, the cells are committed to an osteoblast lineage, upregulated the expression of calcification-related proteins (osteopontin, bone sialoprotein II, osteocalcin) and undergo calcification. A subpopulation of VICs (valve interstitial cells) [2] become activated in the inflammatory zone of the valve and differentiated into myofibroblasts. These myofibroblasts secrete matrix metalloproteinases which play a role in the restructuring of valve leaflet matrix and responsible for accelerated fibrosis in this process. Under the influence of signaling pathways, Wnt-3-Lrp5-β catenin, OPG/RANK/RANKL pathway (osteoproteogen/receptor activation of nuclear factor kappa B/RANK ligand, Runx-2/NOTCH1, activated by BMPs, the myofibroblasts undergo differentiation into osteoblasts, which subsequently coordinate calcification as a part of a highly regulated process akin to new bone formation and mineralize to form calcific nodules on the valves as shown in the Figure

3. Gene transfer

Gene transfer or cell-based therapies are investigated to modulate the cellular mechanism of calcification. The expressing Runx2 in VICs (valvular interstitial cells) commits these cells to an osteoblast-like phenotype. Gene transfer of small interfering RNA (siRNA) that targets Runx2 using adenovirus or recombinant nonviral vectors have been shown to prevent calcification both in vitro and in vivo [3]

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DOI:10.31579/2692-9759/180