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Deregulation of Extracellular Matrix Components in Hypertrophic and Dilated Cardiomyopathy

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Abstract

Cardiomyopathies are an important category of cardiovascular diseases associated with cardiac dysfunction. The extracellular matrix (ECM) plays a vital role in maintaining cardiac homeostasis by offering structural support, assisting mechanical transmission and by providing vital signals to different cells of the cardiac system. Alterations in the ECM profile are associated with the pathogenesis of heart failure. This review discusses on the alterations in gene expression signatures of cardiomyopathy with special emphasis of hypertrophic and dilated cardiomyopathy. Understanding the mechanism of ECM remodeling and regulation in cardiomyopathy is helpful in the identification of therapeutic targets to diminish remodeling, reduce cardiac dysfunction and stimulate myocardial regeneration.

Introduction

The heart is a highly organized tissue and consists of ventricular or atrial cardiomyocytes, pacemaker cells, Purkinje cells, vasculature, and connective tissue. It exerts striking responses to a series of genetic and environmental factors inorder to maintain its contractile function. Disruption in such responses, mediated by signalling pathways, promotes cardiac dysfunction leading to cardiomyopathy. Cardiomyocytes are the contracting cell in the heart, that exist in a three-dimensional network of endothelial cells, vascular smooth muscle, and plenty of fibroblast as well as a transcient population of immune cells. The contraction of individual cardiomyocytes is coordinated electrochemically by gap junctions, and the connection of these cardiomyocytes with the ECM transduces force and directs the overall contraction of the heart [1].

Sarcomere, the basic functional unit of the cardiomyocyte contains ~ 20 proteins. These 20 proteins in addition to 20 other proteins connects the myocytes and the ECM, there by regulates muscle contract, disrupt of these interactions leads dysfunction. Among the remarkable number of intrinsic and extrinsic stimuli induce cardiomyopathy, mutations in genes expressed in cardiomyocytes are found to be important [2], mutations in most of these genes leads to different cardiomyopathies, many with overlapping clinical phenotype. Moreover, several studies reported the involvement of a same gene in different disease phenotypes, suggesting that the position of mutation with in the genes influences cardiac phenotype. Therefore, characterization and mechanistic study of cardiomyocytes remain challenging due to the complexity in protein structures, multitudes of disease causing mutations and modulators of pathology. Number of inherited and acquired cardiomyopathies has been described by the WHO: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM) and a wide group of unclassified cardiomyopathies and among which HCM and DCM are the most predominant [3].

Genetic causes of cardiomyopathy

Several genetic mutations have been reported in gene expression signatures associated with cardiomyopathy in particular HCM and DCM. HCM is a disease that results due to the abnormal thickening of heart muscle. Mutations in sarcomere genes remain the major cause of HCM. The molecular mechanisms related to such mutations are not well understood [3]. Mutations in other genes, for example changes in the dystroglycan complex (DGC), which mechanically connects the extracellular matrix to the intracellular cytoskeleton and the integrin complexes [5], caused by mutations in genes encoding DGC components like α-dystrobrebin and caveolin have been reported to have association with HCM [6,7]. A genome-wide linkage study by Song and their group identified a novel locus on chromosome 7 in a large family with HCM. However, subsequent studies aiming in identification of causal genes located in this region have not yet been successful [8]. Mutations in multiple genes have found to cause DCM [9,10]. Mutations in sarcomeric proteins including Z-disc proteins [11], intermediate filament and cytoskeletal proteins can cause DCM, by interferring force transmission in the myocytes [4]. Mutations in members of DGC, namely (DMD) dystrophin [12], δ-sarcoglycan (SAGD) gene [13], laminin α4 (LAMA4) and integrin linked kinase (ILK) gene were also observed in DCM. Moreover, mutations in sarcomeric genes including ACTC1, TNNT2 [11], MYH6 [14], MYBPC3 [15], TNNI3 [16], TPM1 [17] and TTN [18] were observed in both DCM and HCM. This overlap occur contradictory, but the variations in functional alterations could explain the different pathological patterns. For example, some DCM associated mutations in TNNT2 causes decreased Ca2+ sensitivity, whereas increased Ca2+ sensitivity of myofilaments was observed in DCM [19].

Key players in ECM degradation and remodeling

ECM constitutes various biochemically and structurally diverse components which can be categorised biochemically into proteins, proteoglycans and glycoproteins, each with diverse sub-categories and varied physic-chemical properties. Few of the ECM proteins namely fibrillar collagens, elastins provide tensile strength and viscoelasticity of the tissue. Some of the proteins such as fibronectin, laminin and nidogen contribute to matrix network building as linker proteins [20,21]. Protein components inside and outside a cell undergo modification and degradation and matrix metalloproteinases (MMPs) are the most essential enzymes responsible for ECM remodelling [22]. The unusual variations in the ECM under different disease conditions like tissue fibrosis reveal the essential role of ECM in regulating cell behaviours and their deregulation which often initiate disease progression [23].

ECM remodelling in Cardiomyopathy

ECM is a vastly dynamic three dimensional network seen in all tissues and plays vital regulatory roles in biological processes such as cell attachment,

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migration, differentiation, tissue regeneration and development [24]. The accumulation of ECM and myocardial fibrosis results in increased myocardial wall stiffness cause disturbances in diastole leading to HF. Several extracellular matrix proteins such as collagens) are altered in HF, whereas aldosterone is found to be a major stimulator in deposition of collagen in the heart [25,26]. The Remodeling of ECM in cardiomyocytes alter the structure and function of tissues, causing increased cardiac stiffness, a predictor of death with [2] and his group reported the changes in expression of genes related to extracellular matrix (ECM) remodelling in left ventricular myocardium in patients with end stage DCM vs non failing heart, suggesting their role in heart failure. Their study further helped the identification of their potential roles in HF [2]. Keeping in view the role of ECM components in the proper functioning of the heart, this review focuses on the deregulation of the ECM components based on our study on gene expression changes in cardiomyopathy [27].

ECM associated changes in HCM

The extracellular matrix protein (ECM2), members of small leucine rich proteoglycan family (LUM, ASPN), protein kinase (NRK) and collagen genes (COL1A2, COL5A2, COL3A1, COL5A1, COL8A1, COL12A1 and COL14A1) were found to be up regulated in our study. Over expression of these ECM proteins will lead to excessive accumulation of ECM proteins, a distinguished characteristic of HCM. Lumican (LUM), a small leucine rich proteoglycan (SLPR) can interact with collagens, especially of type VI, XII, XIV, fibronectin, elastin and growth factors. Hence its up regulation might leads to over expression of type XIV collagen (COL14A1) leading to disruption in ECM framework. Their interactions with growth factor TGF-β give attention to the importance of TGF-β signalling pathway in HCM. ASPN, the third class I SLPR differs from other proteoglycans by their contiguous polyaspartate sequence (14 aspartate residue). The difference in number of these aspartate residues will alter the TGF-β driven chondrogenesis[28]. The commonly up regulated genes POSTN, OGN, OMD and LRRC17 shares a functional similarity, involving cell adhesion and localized in proteinaceous extracellular matrix. Activation of POSTN (periostin, osteoblast specific factor) will enhance the incorporation of BMP-1 in the fibronectin matrix of connective tissues, which increase fibrosis, a prominent feature in both types of cardiomyopathy. SSPN (Sarcospan), encodes a member of dystrophin-glycoprotein complex (DGC), provides a structural linkage connecting the sub-sarcolemmal cytoskeleton and the extracellular matrix of the muscle cells. This might interact with ECM proteins, allowing cardiomyocytes to sense and respond to contraction. The over expression of SSPN, disrupts cell adhesion and signaling pathways, which affects the level of reactive oxygen species [29], resulting in extracellular matrix accumulation, cardiac dyshomeostasis and apoptosis (loss of cardiomyocyte in case of DCM) which further leads to cardiomyopathy [27]l

ECM associated changes in DCM

The most significant characteristic of DCM is the accumulation of ECM proteins, mainly collagen and they vary from other type of cardiomyopathy by lack of inflammatory response [29-32]. Up regulation of collagen genes COL1A1, COL1A2, COL5A1 and other ECM proteins COMP, ELN implies their importance in ECM accumulation. Some of the genes, including Natriuretic peptide A (NPPA) (Gopal and Sam., 2013), Connective tissue Growth factor (CTGF), Nephroblastoma over expressed (NOV) which were already reported to be associated with heart failure were identified as differentially expressed by the study. TGF-β plays a major role in hypertrophic and dilated cardiomyopathy by stimulating the growth in cardiomyocyte and by inducing interstitial fibrosis [24]. Increased expression of genes encoding TGF-β binding proteins LTBP1 (Latent transforming growth factor beta binding protein 1) and LTBP2 (Latent transforming growth factor beta binding protein 2), which plays structural role in ECM. TGF-β can also stimulate CTGF and the irregular expression of CTGF will lead to cardiac fibrosis [30].

Moreover, both HCM and DCM gene signatures showed the over expression of POSTN, OGN, OMD and LRRC17 which shares a functional similarity, involving cell adhesion and ECM localizaton. Activation of POSTN (periostin, osteoblast specific factor) increases the incorporation of BMP-1 in the fibronectin matrix of connective tissues, which induce fibrosis, a prominent feature in both types of cardiomyopathy. SSPN (Sarcospan), which encodes a member of dystrophin-glycoprotein complex (DGC), provides structural linkage connecting the sub-sarcolemmal cytoskeleton and the ECM of muscle cells thereby interacting with ECM proteins, allowing cardiomyocytes to sense and respond to contraction. The over expression of SSPN, disrupts cell adhesion and signaling pathways, which affects the level of reactive oxygen species [33-37], resulting in ECM accumulation, cardiac dyshomeostasis and apoptosis (loss of cardiomyocyte in case of DCM) which further leads to cardiomyopathy [30].

Conclusion

The cardiac ECM plays a vital role in maintaining cardiac homeostasis by offering structural and mechanical support by providing vital signals to different cells of the cardiac system and is a major regulator of cardiac remodeling. The altered genes expression signatures in cardiomyopathy provide insights into the pathogenetic basis of ECM in cardiac dysfunction. Although these genetic alterations revealed the genetic factors associated with degradation and remodelling of ECM, future research focussing on finding diverse and novel roles of ECM components with respect to the physical, biochemical and biomechanical properties in the cardiac system would be needed.

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