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EDITED BY

Daniela Quaglini,
University of Modena and Reggio Emilia, Italy

REVIEWED BY

Laura Iop,
University of Padua, Italy
Dong Fan,
Zhuhai Campus of Zunyi Medical
University, China

*CORRESPONDENCE

Ayman M. Ibrahim,
✉ ayman.ibrahim@med.uni-goettingen.de,
✉ sci_ayman@cu.edu.eg
Cesare M. Terracciano,
✉ c.terracciano@imperial.ac.uk
Magdi Yacoub,
✉ m.yacoub@imperial.ac.uk

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Matrisome remodeling in the myocardium of hypertrophic cardiomyopathy; novel targets for molecular diagnostics

Ayman M. Ibrahim^{1,2*}, Hasnaa A. Elfawy³,
Cesare M. Terracciano^{4*} and Magdi Yacoub^{3,4*}

¹Department of Zoology, Faculty of Science, Cairo University, Giza, Egypt, ²Institute of Cardiovascular Physiology, University Medical Center Göttingen, Georg-August, University Göttingen, Göttingen, Germany, ³Aswan Heart Center, Magdi Yacoub Heart Foundation, Aswan, Egypt, ⁴National Heart and Lung Institute, Imperial College London, London, United Kingdom

Hypertrophic cardiomyopathy (HCM) is an inherited cardiac disorder characterized by left ventricular thickening and extracellular matrix (ECM) remodeling, often manifested as increased interstitial fibrosis that impair muscle function. The clinical and pathological presentations, as well as the genetic background, vary among patients, making HCM a heterogeneous disease with diverse clinical phenotyping and responses to treatment. In HCM, the myocardium exhibits an increased secretion of inflammatory mediators and ECM proteins, indicating a stress response to myocardial pathogenesis. The production of these ECM proteins is regulated by the interaction between cardiomyocytes and the surrounding stroma, including cardiac fibroblasts, immune cells, and microvasculature. This crosstalk defines the responsiveness to injury and the progression of the disease. In this review, we aim to dissect the composition of myocardial ECM in relation to HCM development, highlighting the key cellular contributions to ECM remodeling and identifying potential molecular targets for personalized diagnostics and therapeutics.

KEYWORDS

HCM, ECM, matrisome, inflammation, secretome

1 Introduction

A distinctive hallmark of Hypertrophic Cardiomyopathy (HCM) is the thickening of the left ventricle accompanied by ECM remodeling, typically characterized by increased interstitial fibrosis (Maron, 2002; Marian and Braunwald, 2017). The disease exhibits heterogeneity in clinical and pathological presentations, as well as in genetic backgrounds, resulting in diverse responses to treatment (Marian and Braunwald, 2017; Coats et al., 2018). This heterogeneity can be attributed to the highly variable genetic and epigenetic etiology that triggers pathological mechanisms extending beyond the sarcomere, and further beyond the myocardium (Chou and Chin, 2021; Repetti et al., 2021). The ECM constitutes an intricate network of proteins essential for preserving the structural integrity and functional homeostasis of cardiac tissue under various

stimuli in both physiological and pathological conditions (Hynes and Naba, 2012; Naba et al., 2012). This dynamic entity continuously undergoes remodeling to adapt to the changing demands of the heart in health and disease (Rienks et al., 2014). Maintaining a balance in collagen synthesis and degradation, protease activity, and the presence of fibulins, cytokines, and chemokines is critical for preserving cardiac function (Rienks et al., 2014; Fan et al., 2012). Therefore, comprehensive understanding of various interactions among these ECM components in physiological and pathological states is imperative for the development of targeted therapies aimed at mitigating adverse cardiac remodeling.

Currently, there are approximately 300 proteins recognized as ECM proteins (Matrisome) (Hynes and Naba, 2012), comprising collagens, proteoglycans, elastin, and glycoproteins (Figure 1). Each of these proteins possesses unique physical and biochemical characteristics, and their distribution is controlled via factors contributing to ECM remodeling, such as proteases, and molecules facilitating cell-ECM interaction, such as integrins, syndecans, and other receptors (Rienks et al., 2014; Fan et al., 2012). Maintaining the balance of these proteins within myocardial tissue is essential for responding to both physiological and pathological signals [Figure 2].

2 Myocardial ECM in physiological condition and HCM

2.1 Collagens

Collagens are the most abundant and well-studied ECM proteins in the heart (Eghbali and Weber, 1990; Ricard-Blum, 2011). They are deposited in the ECM and play structural roles contributing to mechanical properties, organization, and shape of tissues (Eghbali and Weber, 1990; Ricard-Blum, 2011; Villarreal and Dillmann, 1992). They interact with cells via several receptor families and regulate their proliferation, migration, and differentiation (Ricard-Blum, 2011).

2.1.1 Fibril-forming collagens

Collagen I, the most abundant type of collagen in the heart and provides tensile strength to the myocardium as a fundamental part of the fibrous tissue in the cardiac interstitium (Ricard-Blum, 2011; Lombardi et al., 2003). Collagen III: often found in association with collagen type I and contributes to the elasticity of the myocardium (Ricard-Blum, 2011; Nikolov and Popovski, 2022). Collagen V: plays a role in regulating the fibril diameter and assembly of collagen fibers (Yokota et al., 2020). Though other collagen components have not been primarily found in the myocardium, it's worth noting that collagen composition in various tissues can be complex, and in certain pathological conditions or specific developmental stages (Ricard-Blum, 2011; Lombardi et al., 2003), the presence of other collagens in the myocardium might be investigated.

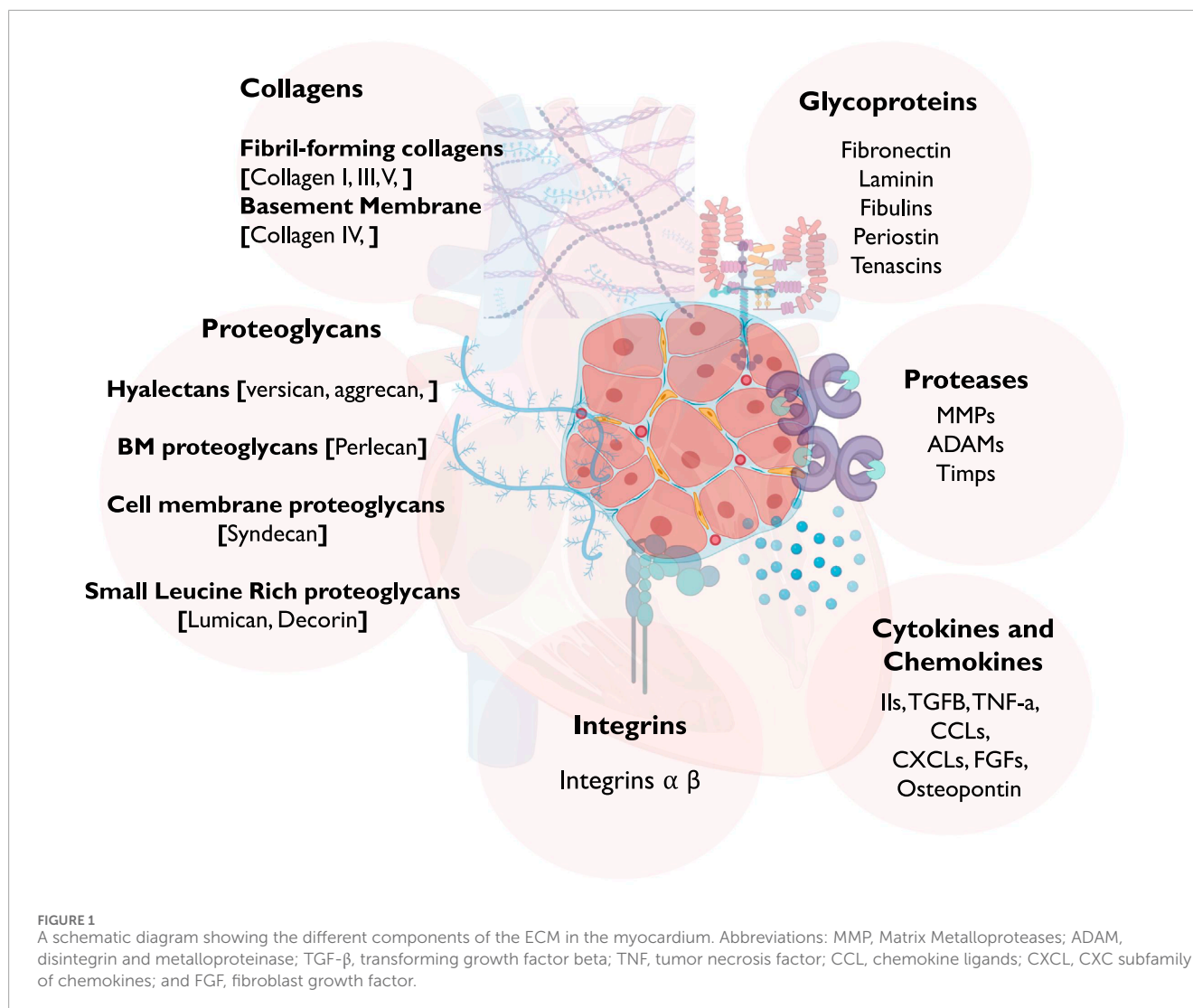
2.1.2 Basement membrane (BM)

Collagen IV is a major component of the BM and represents a type of network forming collagens (Bruggink et al., 2007). It provides support and separates different tissue layers within the

heart (Hynes and Naba, 2012; Ricard-Blum, 2011). Under normal physiological conditions, collagen serves to offer tensile strength, supporting the structural framework of myocytes, myofiber bundles, and sheets (Bruggink et al., 2007). This support is crucial for maintaining the normal functioning of the heart, and various cardiac disorders are linked to disturbances in the collagen matrix, such as its accumulation, depletion, or restructuring (Bruggink et al., 2007).

Several recent studies have highlighted the alteration of myocardial collagen upon myocardial hypertrophy, particularly with the hallmark of an increased interstitial fibrosis, which is considered an early manifestation of the diseases and mainly composed of fibrous collagen, influencing the stiffness of the myocardium, hindering the proper function of the heart (Ho et al., 2010; Díez et al., 2020). Alterations in myocardial collagen in HCM have been reported in several studies, with particular emphasis on collagen I and III, not only in the myocardium but further in the circulation as byproducts of collagen turnover, such as PIINP (collagen III synthesis), PICP, PINP (collagen I synthesis) and ICTP (collagen I degradation), which both showed relevance to HCM phenotype, however data is not yet conclusive (Nikolov and Popovski, 2022; Ellims et al., 2014). Other collagens were also examined in HCM patients; collagen IV has showed alterations in expression pattern in HCM with a discontinuous and destroyed basal lamina (Bruggink et al., 2007; Ibrahim et al., 2020a), and exhibited an increased serum level, in correlation to fractional shortening and end-diastolic volume (Bruggink et al., 2007). Collagen V was recently reported to be downregulated in cardiac fibroblasts (CFs) in HCM (Ibrahim et al., 2022a), suggested to regulate the size of heart scars in an integrin-dependent manner (Yokota et al., 2020). However, collagen V protein has been reported to increase in HCM tissue specimens, alongside collagen I and VI (Previs et al., 2022).

Further, imaging techniques including cardiac magnetic resonance imaging (CMR), Cardiac CT scan, and Echocardiography have been able to quantify collagen content and assess myocardial fibrosis in HCM patients (Ho et al., 2010; Piers et al., 2013; Marwick and Narula, 2010), of which studies aimed to link CMR data to histological data for a more accurate representation of interstitial fibrosis in HCM patients (Diao et al., 2016; Espeland et al., 2018; Haaf et al., 2016). Increased collagen turnover and myocardial fibrosis and Left Ventricular Stiffness are associated with diastolic dysfunction in HCM (Ho et al., 2010). Enhanced collagen turnover contributes to increased left ventricular stiffness, impacting the functional capacity of the heart in HCM (Lombardi et al., 2003). The extent of collagen turnover and fibrosis is associated with the severity of symptoms in HCM, including heart failure symptoms (Olivetto et al., 2008). Of note, myocardial fibrosis resulting from altered collagen turnover is linked to the occurrence of arrhythmias in HCM patients (O'Hanlon et al., 2010). Indeed, collagen turnover in the myocardium involves a dynamic balance between collagen synthesis and degradation processes (Lombardi et al., 2003). Several factors and signaling pathways contribute to the control of collagen turnover, directly or indirectly, in the myocardium, such as Transforming Growth Factor- β (TGF- β) Signaling, Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs), Angiotensin II Signaling, inflammation, other ECM proteins and other understudied factors such as miRNAs. Understanding the intricate regulation of collagen turnover in the myocardium is crucial for developing



targeted therapies to modulate fibrosis and prevent adverse cardiac remodeling (Maron, 2002).

2.2 Proteoglycans

Proteoglycans are complex molecules composed of a core protein and long chains of glycosaminoglycans (GAGs) (Hynes and Naba, 2012; Rienks et al., 2014). They play essential roles in the ECM, contributing to tissue structure, cell signaling, and various physiological processes. In the myocardium, proteoglycans are crucial for maintaining the structural integrity of the cardiac ECM and influencing cell behavior (Hynes and Naba, 2012; Wang et al., 2019). The expression of proteoglycans in the myocardium is tightly regulated and can be influenced by various physiological and pathological conditions (Wang et al., 2019; Barallobre-Barreiro et al., 2021). In cardiac diseases such as myocardial infarction or heart failure, alterations in proteoglycan expression and remodeling of the ECM occur, impacting cardiac function. While not specific to HCM, proteoglycans

expression has been reported to change in the aging heart, and some of the principles may apply to cardiac diseases (Christensen et al., 2019; Silva et al., 2020).

Hyalactans: Versican: a large chondroitin sulfate proteoglycan (CSPG) involved in tissue morphogenesis and inflammation (Sasi et al., 2023). It has been identified in the heart, where it influences cell adhesion and migration and has been known to be the major CSPG in the heart (Barallobre-Barreiro et al., 2021). It has recently been reported that versican is expressed after induction of pressure overload in mice, preceding collagen accumulation, particularly in collagen expressing CFs in transforming growth factor beta-dependent pathway (Sasi et al., 2023). Further, versican appeared to increase in the heart of HCM patients in conjunction with collagen increase, which suggests an involvement in the cardiac fibrosis (Previs et al., 2022; Sasi et al., 2023). Aggrecan: a large proteoglycan that forms giant hydrated aggregates with hyaluronan in the ECM is present in the heart and present in cardiac jelly, developing heart valves, and blood vessels during cardiovascular development, and contributes to the resilience and mechanical loading of the tissue (Krawetz et al., 2022).

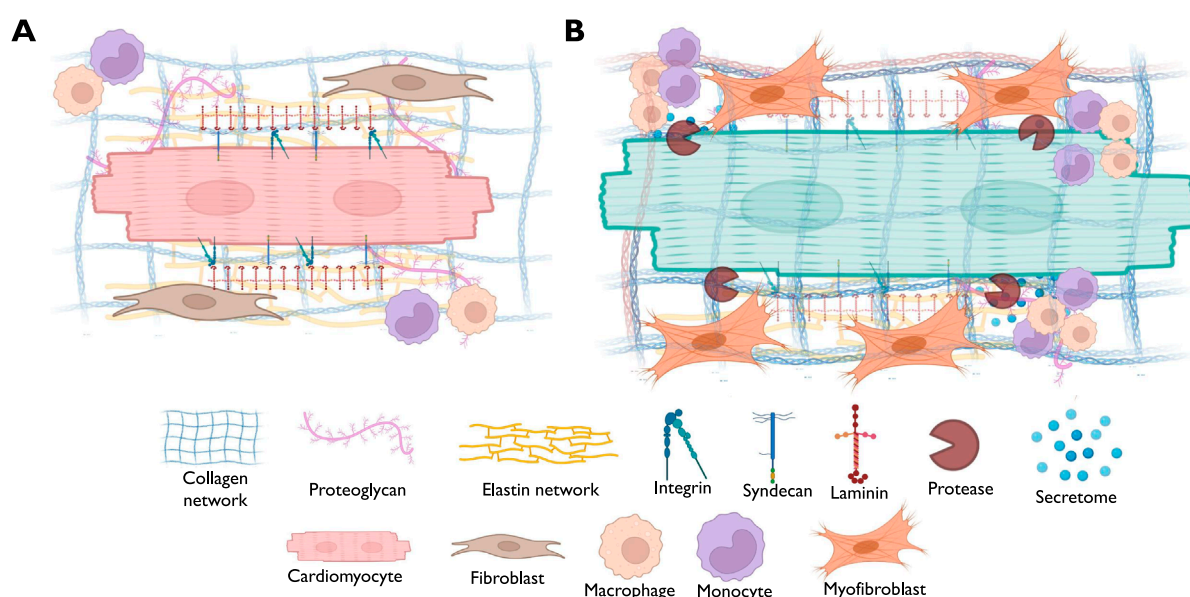


FIGURE 2

A schematic diagram demonstrating the possible alterations in different components of myocardial ECM in association with muscle hypertrophy. (A) The scheme points out to the normal status of the myocardium where cardiomyocytes are physiological interacting with the neighboring cells such as cardiac fibroblasts and immune cells, with intact basement membrane and receptors landscape. (B) The scheme highlights the pathological alterations associated with cardiomyocytes hypertrophy, such as the activation of cardiac fibroblasts that drive ECM deposition and turnover, along with the infiltration of immune cells, inducing inflammatory response.

Mice with mutant aggrecan have been reported to have HCM (Koch et al., 2020). Further, Wistar rats undergone aortic banding, exhibited an increase in aggrecan mRNA, along with versican and other proteases (Vistnes et al., 2014). Aggrecan has also been reported for its overexpression in the aneurysmal aortic walls, increasing interlamellar swelling pressure, and disorganizing the aortic wall's microstructure (Barallobre-Barreiro et al., 2020), which has recently been reported to be associated with HCM (Ibrahim et al., 2022b). BM proteoglycans: Perlecan: A heparan sulfate proteoglycan, found in the BM and participates in cell-matrix interactions and helps regulate growth factor activities (Sasse et al., 2008; Johnson et al., 2024). Altered expression of Perlecan has been observed in cardiac diseases, including HCM, where it may contribute to abnormal cell-matrix interactions and affect growth factor signaling (Johnson et al., 2024). Perlecan null mice, had a severe effect on laminin and collagen IV, components of BM, compared to controls, and further exhibited a more severe dysfunction upon myocardial infarction, due to impaired BM composition and cardiomyocytes crosstalk with surrounding stroma and ECM (Sasse et al., 2008). Of interest, human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) cultured on a Perlecan substrate have exhibited hypertrophy and show heightened nucleation, characteristic of hypertrophic growth (Johnson et al., 2024). Interestingly, Perlecan appears to exert an opposing influence compared to Agrin, fostering cellular maturation instead of hyperplasia and proliferation (Johnson et al., 2024).

Cell membrane proteoglycans: Syndecan: Syndecans are a family of transmembrane heparan sulfate proteoglycans that play important roles in the myocardium, contributing to various cellular

processes and tissue functions, such as Cell-ECM interaction, signal transduction, regulating CMs function, angiogenesis and tissue repair and remodeling (Lunde et al., 2016). Syndecans, particularly syndecan-4, are also involved in cardiac development, where they regulate signaling pathways involved in heart development, including Wnt, FGF, and BMP signaling (Mathiesen et al., 2019). A recent investigation into syndecan-4 underscored its significance in triggering the Ca^{2+} -dependent calcineurin-NFAT signaling pathway, leading to hypertrophic remodeling and dysfunction in CMs under pressure overload conditions (Mathiesen et al., 2019; Lunde et al., 2022). Additionally, syndecan-4 has been reported to mediate muscle LIM protein nuclear translocation in CMs, a mechanism associated to HCM and dilated cardiomyopathy (DCM) (Mathiesen et al., 2019). Further, mice lacking syndecan-4 exhibited less collagen cross linking and fibrosis (Herum et al., 2015; Finsen et al., 2011), and further exhibited diminished capillary density, reduced cardiomyocyte size, and deteriorated left ventricular cardiac function following transverse aortic constriction (Li et al., 2017). Further, Syndecan-4 was found to bind to osteopontin in LV and CFs protecting over deposition of collagen fibers (Herum et al., 2020). Interestingly, serum syndecan-4 has been shown potential as a new diagnostic and prognostic biomarker for LV remodeling in failing hearts (Takahashi et al., 2011).

Small Leucine Rich proteoglycans: Decorin is a small leucine-rich proteoglycan is expressed in the heart and is involved in collagen fibrillogenesis and interacts with various growth factors (Merline et al., 2009). Decorin has been suggested to induce cardiac hypertrophy by regulating the CaMKII/MEF-2 signaling pathway (Yang et al., 2021). However, other reports showed that

Decorin overexpression can inhibit hypertension-induced cardiac fibrosis and hypertrophy and improved cardiac function (Yan et al., 2009), and can further inhibit TGF- β pathway and its pro-fibrotic effects on the failing human heart (Yan et al., 2009; Jahanyar et al., 2007), which makes it a potential candidate in HCM pathogenesis. Lumican (LUM) is a keratan sulfate small leucine-rich proteoglycan (SLRP) localized to the ECM, and known to regulate collagen fibrillogenesis in connective tissues, e.g., cornea, tendon and skin (Nikitovic et al., 2008). LUM is abundant in fibrotic tissues including the thickened intima of human atherosclerotic coronary arteries and is present in the developing myocardium (Mohammadzadeh et al., 2019; Hultg rdh-Nilsson et al., 2015). It has previously shown that LUM levels are increased in hearts of mice and patients with heart failure, via mediation cardiac remodeling, fibrosis, and inflammation (Mohammadzadeh et al., 2019; Mohammadzadeh et al., 2020), and accumulates with collagen fibers during HCM (Rixon et al., 2023). Proteomic analysis of myocardial specimens of HCM patients has shown that LUM is upregulated, correlating with the left atrial area myocardial fibrosis and the presence of a pathogenic sarcomere mutation (Coats et al., 2018), however this expression is yet debatable whether it could have a cardio-protective function (Guo et al., 2023).

2.3 Glycoproteins

Fibronectin (Fn) is a glycoprotein found in the ECM of tissues and plays a crucial role in various cellular processes, such as cell adhesion, migration, and signaling (Fr h et al., 2015). In the myocardium, Fn contributes to the structural integrity of the ECM and participates in the regulation of cardiac development, remodeling, and repair (Talman and Ruskoaho, 2016). During embryonic development, Fn is expressed in the developing heart, where it contributes to the formation of the cardiac ECM (Jallerat and Feinberg, 2020). In adult myocardium, Fn is present in the ECM of the normal adult myocardium, where it forms a network that interacts with other ECM components, including collagen and proteoglycans (Chute et al., 2019). It further serves as a substrate for cell adhesion, allowing cells to attach and interact with the ECM via integrins and BM proteins (Farhadian et al., 1996). In response to cardiac injury, Fn expression can be upregulated in the myocardium in association with collagen deposition and TGF- β 1 signaling (Villarreal and Dillmann, 1992; Wi et al., 1991). During myocardial fibrosis, there may be an excessive deposition of Fn as part of the fibrotic response (Piek et al., 2016). It has been reported that Fn contributes to pathological cardiomyocyte hypertrophy *in vitro* and *in vivo* via Nuclear Factor of Activated T cells activation (Konstandin et al., 2013) or via integrin beta 1-dependent activation (Chen et al., 2005). Further, Fn signaling is thought to stimulate BNP secretion, a gold standard indicator of HCM and cardiac fibrosis (Hasegawa et al., 1993), accompanied by hypertrophic responses *in vitro* (Ogawa et al., 2002). Of interest, circulating levels of fibronectin have been reported to be reduced in patients with HCM (Fucikova et al., 2016; Moretti et al., 2007), which raises the question of whether Fn in the circulation correlates to the myocardial expression in HCM.

Laminin (LN) is an essential component of the BM providing the integrity and function of CMs and blood vessels within

the heart (Oliv  ro et al.). It also contributes to the structural framework of the myocardium, specifically in anchoring CMs to the ECM, facilitating cell-to-cell communication, and contributing to the overall mechanical stability for cardiac tissues homeostasis (Oliv  ro et al., 2000; Schwach and Passier, 2019). In hypertrophied CMs, LN was thought to contribute to alterations in sarcolemmal properties (Oliv  ro et al., 2000), and its deficiency can lead to malformation in the myocardial microvasculature and subsequent ischemia, represented in elevated levels of hypoxia-inducible factor 1 α (Hif1 α) and vascular endothelial growth factor A (VEGFA) transcripts (Wang et al., 2006). Of note, mutation in the laminin alpha4 chain results in an abnormal myocardial ECM and subsequent muscle hypertrophy (Wang et al., 2006).

Fibulins (FBLNs) are a family of glycoproteins involved in ECM assembly and stabilization in different biological systems (Timpl et al., 2003). The widespread distribution of FBLNs correlates with their broad binding repertoire for fibronectin, collagens, BM proteins, elastin and proteoglycans (Timpl et al., 2003; Argraves et al., 2003). FBLN 1 and 2 are highly expressed in migratory cardiac mesenchymal during cardiac valvular septal formation (Argraves et al., 2003; Cooley et al., 2008), which dragged attention to their role in cardiac development and further in pathological conditions such as HCM. While research on FBLNs in HCM is not extensive, recent reports indicated that FBLN2 plays an essential role in Ang II-induced TGF- β signaling and subsequent myocardial fibrosis (Khan et al., 2016). FBLN4 was reported to be crucial for elastic fiber formation (Halabi et al., 2017), and mutations in the *FBLN4* gene have been associated with aortic aneurysms and dissections (Loeys et al., 2005). FBLN5 is also involved in elastic fiber assembly and is expressed in various tissues, including the heart (Chapman et al., 2010; Wang et al., 2005). Knowledge on FBLN5 in the context of HCM specifically is limited, nonetheless, its role in ECM maintenance suggests potential implications for cardiac remodeling (McLaughlin et al., 2007). Of interest, we recently reported that CF-associated transcriptomics signature comprised upregulation of FBLN1 and FBLN5 genes, which was further confirmed in the tissues of HCM patients (Ibrahim et al., 2020a). We further reported that FBLN2, which has common binding partners with FBLN1 and FBLN5, is upregulated in the CMs and the circulation of HCM patients, however, protein expression in CFs did not significantly change; an observation that was further confirmed by our generated transcriptome signature of HCM-CFs (Ibrahim et al., 2020a). Further, it has been suggested that FBLN5 modulate TGF- β signaling, a pathway implicated in tissue fibrosis and remodeling (Nakasaki et al., 2015), hallmarks of HCM. It has also been reported that FBLNs 1, 2 and 5 are reduced in the aorta of HCM patients, in association with an increase in aortic stiffness, which introduce FBLNs as targets for cardiac and extra-cardiac tissues (Ibrahim et al., 2022b).

Periostin is a member of the glycoprotein family (Stansfield et al., 2009). Studies have indicated the significant involvement of periostin in fostering collagen fibrogenesis and promoting a fibroblastic lineage during the maturation of atrioventricular valves in cardiac development (Norris et al., 2008; Norris et al., 2009). While its expression remains low in adult hearts, periostin is crucial for maintaining the biomechanical characteristics of mature myocardium (K  hn et al., 2007). Periostin has been shown to correlate and contribute to cardiac remodeling and

fibrosis in overloaded hearts and heart failure (Zhao et al., 2014; Ioakeimidis et al., 2023). Interestingly, periostin has been shown to mediate the AngII via ERK1/2 and TGF- β 1/Smad signaling (Li et al., 2011). Nevertheless, some reports showed that periostin might be involved in the transdifferentiation of CMs leading to cardiac repair (Kühn et al., 2007). The distribution and expression patterns of periostin, which correlated with the degree of myocardial fibrosis, could serve as a potential biomarker for cardiac remodeling in patients with HCM heart failure (Zhao et al., 2014).

Tenascin-C (TNC) is a glycoprotein categorized as a matricellular protein and exhibits transient expression patterns at various crucial stages of embryonic heart development (Imanaka-Yoshida et al., 2020; Tucker and Chiquet-Ehrismann, 2009). In the normal adult heart, its presence is minimal, yet under pathological conditions linked to inflammation, such as myocardial infarction, hypertensive cardiac fibrosis, myocarditis, dilated cardiomyopathy, and Kawasaki disease, TNC is re-expressed in a spatially and temporally confined manner (Imanaka-Yoshida et al., 2020; Tucker and Chiquet-Ehrismann, 2009). It has recently been reported that upon myocardial infarction, interstitial cells located in the border zone begin producing TNC serving to weaken the adhesion between surviving CMs and ECM, potentially facilitating the reorganization of the tissue (Imanaka-Yoshida et al., 2001). TNC has also demonstrated the ability to induce inflammatory reactions by hastening the migration of macrophages and the production of proinflammatory and profibrotic cytokines through the integrin α V β 3/FAK-Src/NF- κ B pathway, leading to an increased fibrosis (Shimojo et al., 2015). TNC has been reported to prompt cardiac myocytes to enhance the activation of genes linked to hypertrophy and MMPs (Podesser et al., 2018). Conversely, removing TNC could lessen the inflammatory and fibrotic changes, as well as hypertrophy, and diminish contractile dysfunction in hearts undergoing TAC (Podesser et al., 2018). Of interest, serum TNC has shown a prognostic power in HCM patients (Kitaoka et al., 2012).

2.4 Proteases and their inhibitors: MMPs, ADAMs and TIMPs

MMPs are enzymes responsible for collagen degradation, while TIMPs inhibit MMP activity (Nagase et al., 2006). The balance between MMPs and TIMPs influences collagen turnover (Spinale, 2007; Cambronerio et al., 2009). Of the known MMPs in the myocardium are: MMP-1 and MMP-8, which are involved in the degradation of type I and type III collagens (which are classical major components of the myocardial fibrillar collagen and interstitial fibrosis) (Takahashi et al., 1999). MMP-2 (Gelatinase A), which is involved in the degradation of type IV collagen (Spinale, 2007), MMP-9 (Gelatinase B), which is involved in the degradation of type IV collagen and is associated with tissue remodeling and inflammatory processes (Yabluchanskiy et al., 2013), MMP-3 (Stromelysin-1), which participates in the breakdown of fibronectin and laminin (Rodríguez et al., 2010), MMP-13 (Collagenase-3), which targets type II collagen (Takahashi et al., 1999; Uesugi and Sakata, 2005), and MMP-14 (MT1-MMP), which plays a crucial role in ECM remodeling and activates other MMPs, contributing to tissue homeostasis (Nagase et al., 2006). In pathological cardiac

remodeling, a group of MMPs such as MMP-2 and MMP-9, are upregulated, leading to increased ECM degradation and subsequent fibrosis (Roldán et al., 2008; Takawale et al., 2017). and their levels in plasma were associated to NT-proBNP levels and further related to clinical parameters such as LV ejection fraction, LV end-diastolic dimension, exercise capacity and the maximum LV wall thickness (Roldán et al., 2008; Kitaoka et al., 2011; Bi et al., 2021). Although MMPs have been associated with myocardial fibrosis, MMP1 has been reported to attenuate the development of cardiac fibrosis in mouse models (Foronjy et al., 2008), however other studies reported the increase of circulating MMP1 levels in HCM patients (Fernlund et al., 2017). Therefore, understanding the pathophysiology mechanisms of MMPs, and cell-specific MMPs and (Ibrahim et al., 2022a; Toba et al., 2017), is crucial for identifying personalized targeting approaches.

TIMPs, on the other hand, act as inhibitors and regulators of MMPs (Nagase et al., 2006). TIMP-1, is a broad-spectrum inhibitor of MMPs and primarily inhibits MMP-1, MMP-2, MMP-3, and MMP-9 (Brew and Nagase, 2010), TIMP-2, inhibits a range of MMPs, including MMP-1, MMP-2, MMP-3, and MMP-9 and is also involved in regulating cell growth and apoptosis (Stetler-Stevens and on, 2008), TIMP-3, has a broader inhibitory profile, affecting MMP-1, MMP-2, MMP-3, MMP-9, and ADAMs (a disintegrin and metalloproteinases), and plays a crucial role in maintaining tissue integrity and inhibiting angiogenesis (Brew et al., 2000), and TIMP-4 inhibits MMP-2 and MMP-9 and plays a role in modulating tissue responses to injury and inflammation (Cabral-Pacheco et al., 2020). Circulating TIMP1 and TIMP2 were reported to be increased in HCM, in association with LV end-systolic dimension, Left atrium dimension, and LV ejection fraction (Kitaoka et al., 2010). Of interest, a recent study has shown that TIMP1 deficiency have significantly reduced myocardial fibrosis via meditating an association between CD63 (cell surface receptor for TIMP1) and integrin β 1 on CFs, leading to *de novo* collagen synthesis, reducing myocardial fibrosis, independent from MMPs (Takawale et al., 2017).

Besides, ADAMs are membrane-anchored proteins that mediate ectodomain shedding of substrate proteins, and play diverse roles in the normal myocardium, including cell adhesion, proteolysis, and signaling, however, their exact role requires further investigation (Weber and Saftig, 2012). ADAM12 for instance, mitigates the excess hypertrophic response by attenuating integrin-mediated downstream signaling (Nakamura et al., 2020).

Further, activation of protease-activated receptors (PARs) by proteases, such as thrombin, has been implicated in cardiac hypertrophy (Antoniak et al., 2011). PARs may contribute to signaling pathways that influence hypertrophic responses (Antoniak et al., 2011).

2.5 Cytokines and chemokines

Cytokines are small signaling proteins that play crucial roles in the regulation of immune responses, inflammation, tissue repair, remodeling, and adaptation to various physiological stimuli (Hanna and Frangogiannis, 2020). While the heart is traditionally viewed as an organ with limited immune activity, it does produce and respond to certain cytokines under healthy conditions

(Hanna and Frangogiannis, 2020; Mann, 2015). In physiological conditions, the myocardium maintains a balanced and regulated environment, and the expression of cytokines is generally at low levels (Fang et al., 2017). In HCM however, pro-inflammatory cytokines are elevated, contributing to fibrosis and ECM alterations, which has been suggested to compose a chronic “low grade” inflammatory microenvironment (Hanna and Frangogiannis, 2020; Lillo et al., 2023). Interleukin-10 (IL-10) and IL-1 β are pro-inflammatory cytokines that are involved in immune responses and inflammation (Xu et al., 2021). In physiological conditions, their expression in the heart is generally low, only sufficient to help regulate immune responses and reduce inflammation (Xu et al., 2021). In HCM, IL-10 may play a protective role by modulating inflammatory responses and attenuating myocardial remodeling (Sziksz et al., 2015). IL-1 β is involved in inflammatory responses and may contribute to the progression of cardiac hypertrophy in HCM (Schwinger et al., 1994).

TGF- β is a multifunctional cytokine involved in maintaining tissue integrity and preventing excessive inflammation in the myocardium (Hanna and Frangogiannis, 2019). In HCM, TGF- β signaling has been long known for its upregulation in experimental models of myocardial infarction and cardiac hypertrophy (Frangogiannis, 2020; Teekakirikul et al., 2010). Endogenous TGF- β plays a crucial role in the development of cardiac fibrotic and hypertrophic remodeling, as well as in regulating ECM metabolism in the pressure-overloaded heart (Frangogiannis, 2020). TGF- β deactivates inflammatory macrophages while facilitating myofibroblast transdifferentiation and ECM synthesis through Smad3-dependent pathways (Saadat et al., 2020). Consequently, TGF- β may function as the pivotal “master switch” orchestrating the transition from the inflammatory phase to scar formation in the infarcted heart (Rienks et al., 2014), and activate Angiotensin II signaling (via FBLN2 mediation) (Zhang et al., 2014) (Figure 3), all of which are hallmarks of HCM. Efforts aimed at translating these concepts into therapeutic approaches to mitigate cardiac hypertrophy and fibrosis face challenges due to the intricate, multifaceted nature of TGF- β signaling (Hanna and Frangogiannis, 2019). Concerns arise regarding the potential harmful effects of inhibiting TGF- β and the possibility of limited benefits for patients already receiving optimal treatment with ACE inhibitors and β -adrenergic blockers (Lim et al., 2001; D et al., 2011).

IL-6 has both pro-inflammatory and anti-inflammatory properties, and may contribute to normal physiological processes, such as the response to exercise and stress (Scheller et al., 2011). IL-6 has been associated with inflammation and cardiac hypertrophy in HCM and increased IL-6 levels may contribute to disease progression (Teekakirikul et al., 2010). IL-6 has been found to be essential in increasing collagen content regulated by isolated CFs and played a role in mediating a phenotypic conversion to myofibroblasts, via Angiotensin II induction (Meléndez et al., 2010). It has also been reported for its mediation to the Angiotensin II signaling during cardiac hypertrophy (Gro et al., 2019; Högye et al., 2004). Higher IL-6 levels in the both the myocardium and the circulation have been associated with larger infarct size and decreased cardiac function in HCM (Gro et al., 2019; Högye et al., 2004).

Tumor Necrosis Factor-Alpha (TNF- α) is a pro-inflammatory cytokine that is typically associated with immune responses and

plays a role in adaptation to exercise (Jang et al., 2021). (Xu et al., 2021) TNF- α has been reported to contribute to myocardial dysfunction (Tian et al., 2015), with an association of higher expression along with IL6, with HCM (Sano et al., 2000). CMs-specific expression of TNF- α has shown to lead to LV hypertrophy (Schumacher and Naga Prasad, 2018), however, studies have shown contradiction of TNF- α effect based on its source (Miao et al., 2020; Yokoyama et al., 1997; Feldman et al., 2000). Of interest, inhibition of TNF- α reduces adverse myocardial remodeling in a rat model of volume overload (Jobe et al., 2009). Another recently studied interleukin in HCM is IL11, which is a member of the IL6 family, and its receptors are mainly expressed in CFs (Alter et al., 2023). In IL11-stimulated CFs, collagen, ECM remodeling components such as periostin and MMP2 are strongly upregulated at the protein level (Sweeney et al., 2020). Blocking of IL11 signaling with Lutein has recently been suggested to attenuate angiotensin II- induced cardiac remodeling and fibrosis (Chen et al., 2021) (Figure 3). As a biomarker, elevated plasma IL-11 levels have been associated with a notable rise in cardiac events and indicate a poor prognosis in HCM and heart failure patients (Ye et al., 2019). On the other hand, chemokines, such as monocyte chemoattractant protein-1 (MCP-1), play a role in recruiting immune cells to the heart during inflammation, which can subsequently impact ECM homeostasis (Sun et al., 2021). MCP-1/CCL2 is associated with the recruitment of monocytes and macrophages to the site of inflammation (Shen et al., 2014). Myocardial and circulating MCP1 levels have been reported to increase in HCM patients particularly in patients with systolic dysfunction (Iwasaki et al., 2009). MCP1-driven pro-inflammatory signaling may accentuate cardiomyocyte death and can mediate fibrosis upon recruiting monocytes and macrophages that secrete mediators, such as TGF- β (Hanna and Frangogiannis, 2020), a key driver in myocardial fibrosis in HCM (Ibrahim et al., 2020a). Of interest, *in vitro* experiments have revealed that a combination of IL-6 with MCP1 sustained STAT3 activation in CMs, promoting the differentiation of CFs into myofibroblasts under hypoxic conditions (Morimoto et al., 2006). In agreement, we have recently reported that CCL2 is overexpressed in HCM CFs and myocardium in association with IL6 and other pro-inflammatory drivers, such as CCL11 and CCL4 (Ibrahim et al., 2022a).

Osteopontin (OPN) is a matricellular protein that mediates diverse biological functions and functions as a proinflammatory cytokine promoting cell-mediated immune responses (Shirakawa and Sano, 2021). OPN has been implicated in the progression of fibrosis induced by Ang II (Mohamed et al., 2019; Matsui et al., 2004), a key driver of interstitial fibrosis in HCM (Zhang et al., 2014). It has exhibited interactions with diverse ECM proteins such as fibronectin and collagen, indicating its potential involvement in organizing and stabilizing the matrix structure (Matsui et al., 2004). Lack of OPN could potentially decrease the rise in blood pressure induced by Ang II and improve the progression of cardiac fibrosis (Matsui et al., 2004). It has therefore been suggested as a therapeutic target for HCM and heart failure for its role in cardiac fibrosis (Mohamed et al., 2019).

Fibroblast growth factors 2 and 16 (FGF2 and FGF16): FGFs are proteins that serve a variety of functions in the tissue development, repair, and metabolism (Itoh and Ornitz, 2008). FGF16 stands out among paracrine FGFs as it is predominantly expressed in cardiac tissue (Itoh and Ohta, 2013; Hotta et al.,

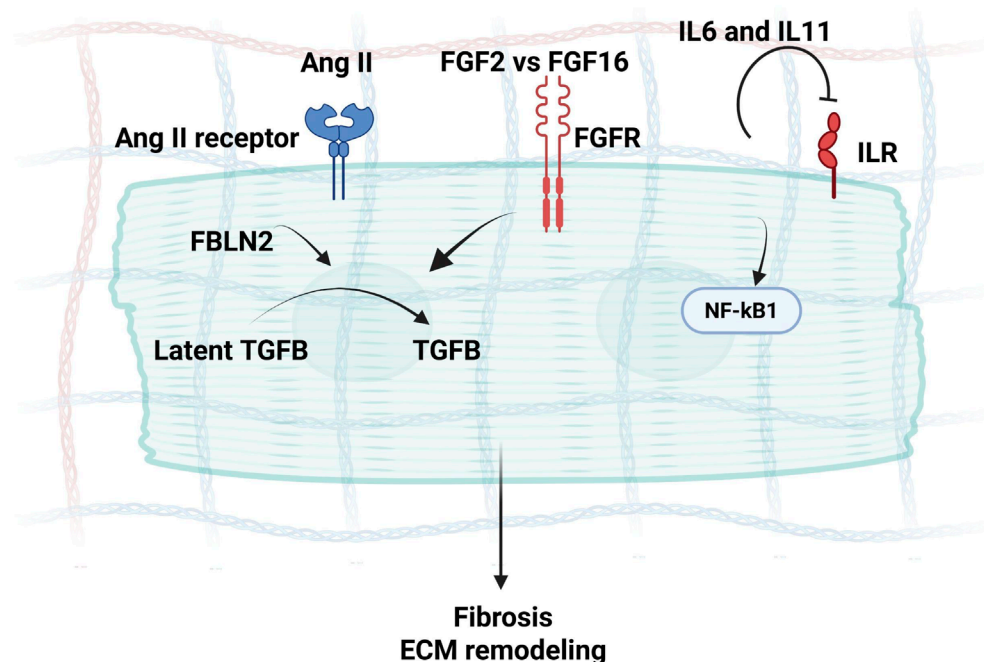


FIGURE 3

A schematic diagram demonstrating secretome mediators of Ang II signaling in CMs during interstitial fibrosis and Hypertrophy, where Fibulin-2 can mediate Angiotensin signaling via the activation of TGF- β , along with the concurrent FGF and IL6 signaling, inducing myocardial fibrosis.

2008). While FGF16 expression is relatively low in the embryonic heart, it becomes more abundant during adulthood compared to embryonic stages, which suggest potential roles for FGF16 in cardiac function (Tacer et al., 2010). A recent study on a mouse model, has shown that FGF16 prevents angiotensin II-induced cardiac hypertrophy and fibrosis by antagonizing FGF2 (Matsumoto et al., 2013). Further, deleting FGF2 attenuates muscle hypertrophy in adult mice (Schultz et al., 1999). We have recently reported CF-specific upregulation of FGF16 and downregulation of FGF2 in HCM patients. Nonetheless, the interplay between FGF16 and FGF2 in the cardiac tissue microenvironment is yet debatable and arise from their competition on FGFR to activate MAPK signaling and induce tissue remodeling (Itoh and Ohta, 2013).

2.6 Integrins

Integrins: Integrins play several crucial roles in the myocardium, serving as key mediators of cell-cell and cell-ECM interactions (Ross and Borg, 2001). They can be expressed on either CFs or CMs, mainly for mediating the interaction between them and the ECM, particularly collagen (such as integrins $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 11\beta 1$) (Ross and Borg, 2001; Mezu-Ndubuisi and Maheshwari, 2020; Harston and Kuppuswamy, 2011). Integrins are also involved in Mechanical Signaling bidirectionally between the ECM and the intracellular cytoskeleton, which is essential for regulating cellular processes such as cell contraction, proliferation, and gene expression in response to

changes in mechanical forces (Ross and Borg, 2001; Israeli-Rosenberg et al., 2014). Signal Transduction via activating intracellular signaling pathways in response to ECM ligands, for cell survival, proliferation, differentiation, and gene expression (Harston and Kuppuswamy, 2011; Ross, 2002). Angiogenesis via mediating the adhesion and migration of endothelial cells (ECs), which are essential for the formation of new blood vessels during myocardial development, tissue repair, and ischemic injury (Mezu-Ndubuisi and Maheshwari, 2020). Electrical Coupling between CMs and the ECM, contributing to the transmission of electrical signals between cells and modulating cardiac conduction properties (Valencik et al., 2006; Dabiri et al., 2012).

Several *In vitro* and *in vivo* models have studied the association of integrins with cardiac hypertrophy (Harston and Kuppuswamy, 2011). In the pathological myocardium, expression of the integrins isoforms is altered leading to alterations in CFs, the ECM and CMs, and in response to the mechanical stretch resulting from hypertrophy (Brancaccio et al., 2006). Integrin pathological signaling may result in the activation of myofibroblasts or the development of CM hypertrophy (Maitra et al., 2000). Deletion of $\beta 1$ integrin in mice has been reported to reduce myocardial proliferation and impaired ventricular compaction. (Maitra et al., 2000). Interestingly, it has been recently reported that Integrin beta-like 1 is an important functional mediator between fibroblast-cardiomyocyte crosstalk and could be an effective target for cardiac remodeling in myocardial hypertrophy and HCM (Chen et al., 2023), particularly with its reported interaction with multiple ECM proteins during myocardial remodeling (Laser et al., 2000).

3 Interactions between matrisome components in the myocardium

As previously highlighted, the matrisome comprises a network of core ECM proteins (e.g., collagens, proteoglycans, glycoproteins) and matrisome-associated proteins (e.g., ECM regulators, affiliated proteins, and secreted factors), which interact to determine the structural and signaling microenvironment of the myocardium. In HCM, dysregulation of these interactions contributes to pathological fibrosis, impaired mechano-transduction, and chronic inflammation (Dabiri et al., 2012; Martino et al., 2018). For example, fibronectin interacts with collagen I and III via specific domains to promote fibrillogenesis and scaffold assembly (Singh et al., 2010), while decorin and lumican regulate collagen fiber diameter and cross-linking, modulating tissue stiffness (Chen et al., 2020). Perlecan binds laminin and collagen IV in the basement membrane, supporting endothelial cell adhesion and barrier function (Yousif et al., 2013). Proteoglycans like versican form large aggregates with hyaluronan, facilitating hydration and influencing leukocyte infiltration during inflammation. Furthermore, fibulins serve as bridging molecules, linking elastin, collagen, and glycoproteins like fibronectin, and modulating growth factor availability such as TGF- β sequestration (Sasi et al., 2023). Further, Fibulins were repeatedly reported to interact with each other's and with BM proteins such as laminin and Col IV (Ibrahim et al., 2018; Olijnyk et al., 2014; WalyEldeen et al., 2024).

These protein–protein interactions are dynamic and context-dependent, influenced by post-translational modifications, mechanical cues, and localized cellular and molecular activity in the myocardium. Their disruption or overactivation in HCM alters ECM organization, leading to increased myocardial stiffness, altered electrical conductivity, and myocyte-ECM uncoupling. Therefore, dissecting the physical and biochemical interplay between matrisome components may offer new insights into the progression of HCM and the identification of matrix-based therapeutic targets.

4 Sources of ECM components

The human heart consists of five primary cell types: CMs, CFs, ECs and immune cells such as macrophages, and adipocytes (Hall et al., 2021). The dynamic interplay between various cell types and their secreted products regulates the structural and functional properties of the myocardial ECM (Rienks et al., 2014). Understanding the sources and regulation of ECM components is crucial for deciphering the complex biology of the heart. Several sources contribute to the composition of the ECM in myocardial tissue (Figure 4).

4.1 Cardiac fibroblasts

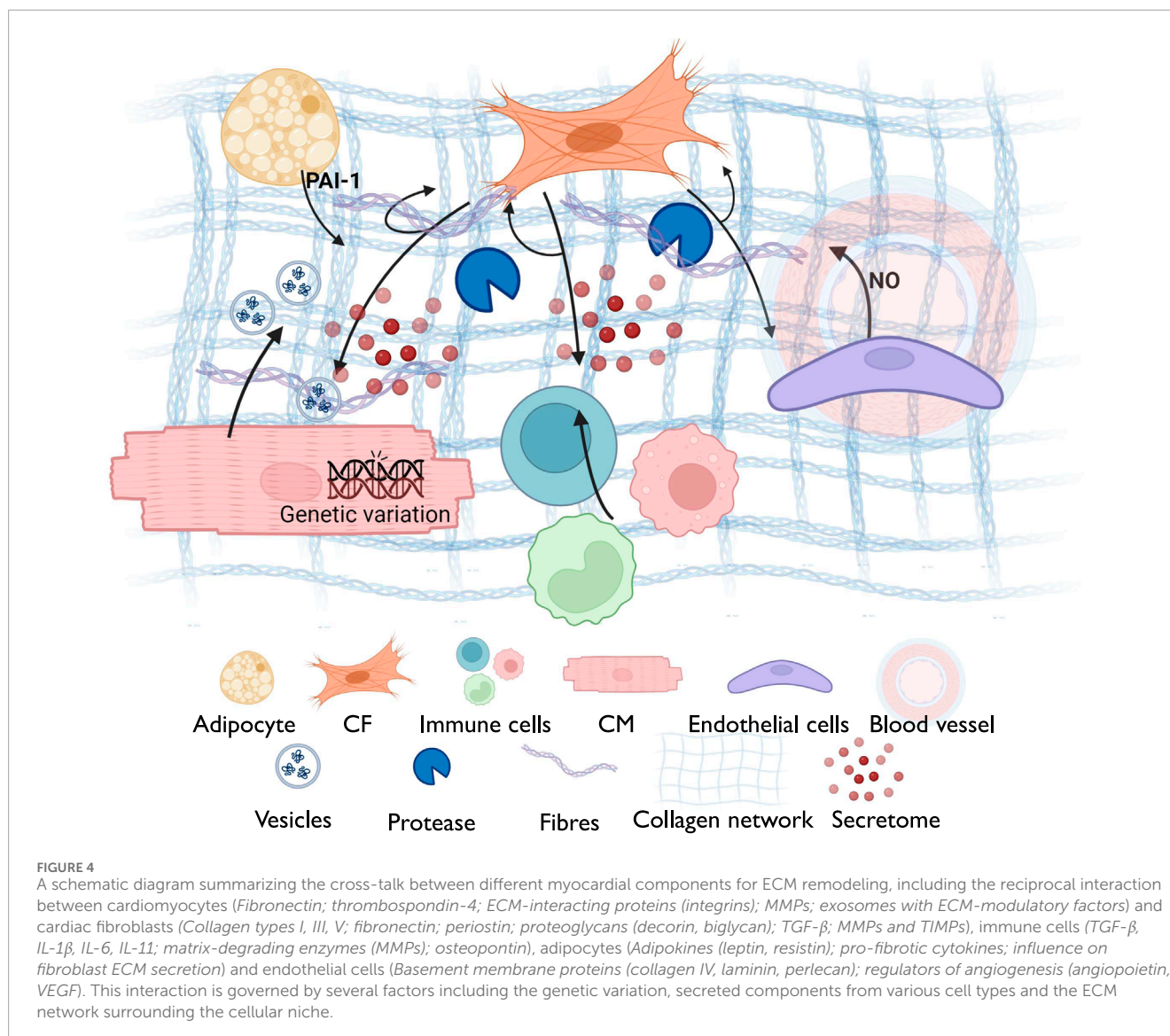
CFs represent the major non-cardiomyocyte cell lineage that maintain the myocardial homeostasis and ECM turnover (Travers et al., 2017). They are the primary cell type responsible for producing and regulating the majority of the known ECM components (Fan et al., 2012; Travers et al., 2017). CFs are the

main source of collagen, particularly collagen types I and III (Verdecchia et al., 2012; Kanisicak et al., 2016). They also contribute to the synthesis of Fn, MMPs and TIMPs (Fan et al., 2012; Travers et al., 2017). During myocardial injury and HCM, CFs become activated, via mechanical and/or molecular signaling, and may differentiate to myofibroblasts, with an expression of smooth muscle actin (SMA), increased secretion of inflammatory mediators, and increased deposition of ECM proteins (Marian and Braunwald, 2017; Fan et al., 2012), which represent stress responses that aggravate heart diseases (Fan et al., 2012). CFs-associated FGF2 and FGF16 contribute to cardiac hypertrophy via stimulating CMs in a paracrine fashion (Fujiu and Nagai, 2014). Further, interleukins such as IL6 and IL11 were reported to be secreted by CFs during cardiac injury and hypertrophy (Hall et al., 2021). CFs alternatively respond to inflammatory mediators and adipokines either via autocrine or paracrine loops, contributing to an inflammatory environment that influences ECM remodeling in HCM (Camelliti et al., 2005; Tallquist and Molkentin, 2017). Activated CFs exhibit dysregulated MMPs and TIMPs expression, influencing ECM turnover (Fan et al., 2012). They are involved in the activation of the TGF- β signaling pathway, which is associated with fibrosis and ECM remodeling in HCM (Fujiu and Nagai, 2014; Lasala et al., 2012).

The crosstalk between CFs and CMs, as well as with the surrounding stroma/ECM, is bidirectional and crucial for tissue homeostasis (Hall et al., 2021; Bursac, 2014). In pathological conditions, all these elements are influenced by altered signaling cascades, leading to a microenvironment that chronically affects CFs phenotype and relevant response (Hall et al., 2021). CM-associated signals such as TGF- β , angiotensin II, and microRNAs promoting CFs activation, myofibroblast transition, and increased collagen, fibronectin, and periostin synthesis. CFs have recently become targets for novel cardiac therapeutics due to their primary contribution to ECM remodeling, their direct interaction with CMs, and their ability to differentiate and regenerate (Hall et al., 2021). While CFs are the primary ECM-producing cells in the myocardium, the intricate crosstalk between CMs and other cell types in the heart contributes to the dynamic and finely tuned process of ECM remodeling (Camelliti et al., 2005; Bursac, 2014). Understanding these interactions is crucial for unraveling the complexities of cardiac physiology and pathology, particularly in conditions like myocardial infarction, hypertrophy, and heart failure.

4.2 Cardiomyocytes

While CMs are traditionally recognized for their contractile function in the heart, CMs also play a significant role in ECM remodeling (Rienks et al., 2014; Mouw et al., 2014). CMs can secrete fibronectin and MMPs, regulated, in part, by factors like mechanical stretch, cytokines, and neurohormones (Aoyagi and Matsui, 2011). CMs-Integrins mediate the interaction between CMs and the ECM which activates intracellular signaling pathways that can influence cell behavior, including gene expression related to ECM remodeling (Aoyagi and Matsui, 2011). Mechanical forces, such as those generated during contraction, can affect CMs behavior and gene expression, and can activate pathways that influence ECM synthesis and remodeling for maintaining tissue integrity and preventing



adverse remodeling (Martino et al., 2018). CMs release extracellular vesicles, including exosomes, which can transport bioactive molecules including microRNAs, that influence neighboring cells, including CFs involved in ECM regulation (Aoyagi and Matsui, 2011). Adaptive Responses to Stress: Under conditions of stress, such as hypertrophy or ischemia, CMs can undergo adaptive changes that influence ECM remodeling. This may involve alterations in gene expression profiles that impact the synthesis and degradation of ECM components. Indeed, the genetic variations encompass HCM etiology, particularly those associated with sarcomere proteins (Marian and Braunwald, 2017; Allouba et al., 2023), accounts for the cellular and molecular alterations in CMs that can cause downstream alterations in the ECM (Dour et al., 2017).

4.3 Endothelial cells

Endothelial Cells are lining the blood vessels within the myocardium secrete various ECM components, including BM

proteins such as laminin and collagen IV (Widyantoro et al., 2010). ECs can also secrete various ECM components, including fibronectin and laminins, which are important for maintaining the structural integrity of blood vessels and the surrounding tissue (Yousif et al., 2013). ECs are crucial for angiogenesis, which requires balanced ECM remodeling for vessel sprouting, branching, and stabilization (Gogiraju et al., 2019). ECs release various growth factors and cytokines that influence the behavior of neighboring cells, including CFs (Mai et al., 2013). These factors can modulate ECM turnover and remodeling (Davis and Senger, 2005; Bischoff et al., 2005). Of interest, ECs produce nitric oxide (NO), which has vasodilatory effects and plays a role in maintaining vascular tone (Bischoff et al., 2005). Dysregulation of NO production may influence ECM remodeling and contribute to vascular changes (Heiss et al., 2015). Of note, changes in the microvasculature, influenced by ECs, may impact nutrient and oxygen supply to the myocardium. These changes can have downstream effects on ECM homeostasis.

4.4 Immune cells

Various immune cells, including macrophages, play a role in tissue repair (Davies et al., 2013; Wang et al., 2020). While immune cells are primarily associated with the immune response and inflammation, their interactions with other cell types, including CFs and CMs, can influence ECM remodeling (Toba et al., 2017; Lavine et al., 2018). Immune cells can infiltrate the myocardium in response to various stimuli and contribute to ECM remodeling and has recently been suggested to halt myocardial fibrosis and promote angiogenesis (Revelo et al., 2021; O'Rourke et al., 2019). Immune cells release cytokines, which are signaling molecules that can influence the behavior of CFs and other cells involved in ECM maintenance (Frieler and Mortensen, 2015). An Altered cytokine expression, including pro-inflammatory cytokines, has been reported in HCM and may contribute to cardiac remodeling (Piek et al., 2016). As mentioned earlier, immune cells can produce MMPs and TIMPs, in response to pathological stimuli and in coordination with CFs and CMs (Lavine et al., 2018; Frieler and Mortensen, 2015). CFs may respond to signals from immune cells, influencing collagen synthesis and deposition (Hitscherich and Lee, 2021). This stimulation cascade varies based on tissue status. During acute myocardial infarction, pro-inflammatory cytokines are released to initiate inflammation and clear necrotic tissue. Once the necrotic tissue is removed, macrophages transition to an anti-inflammatory phenotype, stimulating CFs to deposit collagen and promote fibrotic tissue formation (Chen et al., 2024), a mechanism similarly observed in cancer models (Ibrahim et al., 2020b; Wang et al., 2020). This interplay is activated in various cardiac pathologies, including ischemia and pressure-overloaded myocardium, and is linked to the regulation of ECM proteins, such as MMPs (Chen et al., 2024; Waleczek et al., 2022), and can be orchestrated via myocardium-resident macrophages (Waleczek et al., 2022), or previously activated monocytes (Chen et al., 2024).

4.5 Adipocytes

Adipocytes are fat cells found in the myocardial tissue and can contribute to the ECM by secreting various adipokines and other signaling molecules (Chait and den Hartigh, 2020). The specific role of adipocytes in ECM maintenance in the myocardium, particularly in HCM, has not been extensively studied. Increased epicardial fat thickness has been associated with disease severity and adverse clinical outcomes (Hajsadeghi et al., 2014; Talman et al., 2014), such as atrial fibrillation and coronary heart conditions, which are complications of HCM (Macintyre and Lakdawala, 2016). Associations between epicardial adipose tissue volume and arrhythmias may have relevance to HCM patients with arrhythmic complications (Conte et al., 2022). Adipokines secreted by the adipose tissue, such as adiponectin and leptin, have the potential to influence the restructuring of the ECM in the myocardium, via regulating the expression of proteases (TIMPs and MMPs), plasminogen activator inhibitor type 1, primarily synthesized by adipose tissue, controls the function of plasmin, a serine protease crucial for regulating the ECM (Zibadi et al., 2011; Schram and Sweeney, 2008). Adipocytes can

engage in paracrine signaling with neighboring cells, including CFs and CMs (Krishnan et al., 2021). The interplay between adipocytes and the cardiac microenvironment is an active area of research, and there are several considerations regarding their potential contributions.

5 Candidate myocardial ECM proteins with clinical relevance

A plethora of biomarkers have been defined in myocardial pathologies, in particular HF and HCM, and are associated with pathophysiological pathways in disease progression, such as markers of neurohormonal activation (ET-1) (Widyantoro et al., 2010), oxidative stress (Myeloperoxidase (MPO)), and myocyte injury and stress (cardiac troponins, Brain Natriuretic Peptide (BNP) and NT-ProBNP) (Ho et al., 2017; Captur et al., 2020). ECM remodeling biomarkers have recently been introduced to clinical research as an attempt to expand the phenotype screening of HCM, especially with the disease clinical heterogeneity. Inflammation and ECM-associated markers such as sST-2, TGF- β , TIMPs and MMPs, have been a focus of recent studies for that purpose (Matthia et al., 2022). Elevated levels of collagen turnover biomarkers—such as PIIINP, PICP, PINP, and ICTP correlate with fibrosis severity and phenotype differentiation, making them valuable non-invasive markers of ECM remodeling (Lombardi et al., 2003; Matthia et al., 2022). TGF- β is a central regulator of myocardial fibrosis and inflammation, linking molecular pathways to phenotypes and serving as an experimental therapeutic target despite the challenges posed by its pleiotropic nature (Hanna and Frangogiannis, 2020; Hanna and Frangogiannis, 2019; Matthia et al., 2022). The circulating levels of MMPs and TIMPs correlate with fibrosis severity and outcomes, offering diagnostic and therapeutic insights (Spinale, 2007; Matthia et al., 2022). Similarly, reduced fibronectin levels are associated with myocardial hypertrophy progression, and it has been explored for diagnostic correlation with BNP secretion and fibrosis, as well as a target for anti-fibrotic therapies (Konstandin et al., 2013; Matthia et al., 2022).

Other ECM proteins also contribute to fibrosis and hypertrophy in HCM; Lumican, identified through proteomic analyses, correlates with fibrosis severity and left atrial enlargement, and has been proposed as a marker of advanced fibrosis (Rixon et al., 2023). TNC is associated with inflammation-driven HCM and adverse outcomes, with serum levels offering prognostic value in heart failure (Kitaoka et al., 2012; Kitaoka et al., 2010; Matthia et al., 2022). Syndecan-4, involved in fibrosis progression and myocardial stiffness, is under investigation as both a biomarker and therapeutic target (Takahashi et al., 2011). OPN levels increase significantly with fibrosis and adverse remodeling, making it a biomarker and therapeutic target (Mohamed et al., 2019; Matthia et al., 2022). Having been intensively studied, interleukins, such as IL-6 and IL-11, stratify patients based on fibrosis and inflammation burden. IL-11 in particular predicts poor prognosis and has therapeutic potential (Gro et al., 2019; Högye et al., 2004; Sano et al., 2000; Ye et al., 2019; Cook, 2023). Lastly, fibulins—especially circulating Fibulin-2—are suggested to correlate with myocardial fibrosis in HCM, adding further value to the pool of ECM-related biomarkers in cardiac disease management (Ibrahim et al., 2020a).

6 *In Vitro* modeling and future directions

HCM is increasingly recognized not only as a disease of the sarcomere but also as a complex condition involving extensive remodeling of the myocardial ECM. The evidence presented in this review highlights that ECM components—including collagens, proteoglycans, glycoproteins, proteases, cytokines, and integrins—undergo substantial quantitative and qualitative changes that contribute to hallmark features of HCM such as interstitial fibrosis, diastolic dysfunction, and arrhythmogenesis. Recent advances in disease modeling have expanded our ability to explore these ECM changes with greater specificity and translational relevance. In particular, *in vitro* systems such as human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) and engineered heart tissues (EHTs) provide platforms to study the molecular and cellular interactions between ECM components and cardiac cells under genetic and biomechanical stress (Yildirim et al., 2025; Jebran et al., 2025). iPSC-CMs derived from HCM patients exhibit aberrant fibronectin deposition, BNP secretion, and ECM-associated signaling responses (e.g., TGF- β activation), allowing mechanistic dissection and therapeutic screening. Co-culture systems with CFs or immune cells further enable modeling of the cellular crosstalk driving ECM remodeling. These models, combined with high-content imaging and single-cell omics, offer insights into disease heterogeneity and therapeutic responsiveness.

Despite significant progress, several key questions remain unanswered. Notably, the spatial and temporal regulation of ECM components across HCM stages is poorly defined, and it is unclear how ECM remodeling varies between genotypes or clinical phenotypes. Moreover, the mechanistic links between specific ECM alterations and clinical outcomes—such as arrhythmia burden, progression to heart failure, or sudden cardiac death—are not yet fully elucidated.

To address these gaps, future research should focus on:

- Cell-type-specific and single-cell transcriptomic and proteomic profiling to dissect the heterogeneity of ECM-producing cells and their contributions to fibrosis and hypertrophy.
- Longitudinal and multi-omics studies in HCM patients, integrating advanced imaging, circulating ECM biomarkers, and genetic data to enable more precise phenotyping and outcome prediction.
- Functional validation of ECM-related targets *in vitro* and *in vivo*, using iPSC-based platforms and preclinical animal models to establish causality and therapeutic efficacy.
- Comparative analyses of primary (genetic) versus secondary (acquired) hypertrophy, to delineate shared and divergent ECM remodeling pathways.

- Translational pipelines that link ECM biology to clinical applications—including the development of circulating ECM biomarkers, risk stratification tools, and anti-fibrotic or immunomodulatory therapies.

In conclusion, incorporating ECM biology into the diagnostic, prognostic, and therapeutic frameworks of HCM has the potential to transform patient care. By leveraging innovative *in vitro* disease models and clinically anchored translational research, the field is poised to develop precision-based strategies that address not only the genetic substrate but also the fibrotic and inflammatory landscape that underpins disease progression.

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