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Review

Characteristic adaptations of the extracellular matrix in dilated cardiomyopathy

Laura Louzao-Martinez [a,b], Aryan Vink [c], Magdalena Harakalova [b,c,d], Folkert W. Asselbergs [b,d,e], Marianne C. Verhaar [a], Caroline Cheng [a,f,*]

[a] Department of Nephrology and Hypertension, Division of Internal Medicine and Dermatology, University Medical Center Utrecht, The Netherlands
[b] Netherlands Heart Institute, University Medical Center Utrecht, The Netherlands
[c] Department of Pathology, University Medical Center Utrecht, The Netherlands
[d] Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, The Netherlands
[e] Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, United Kingdom
[f] Department of Cardiology, Thoraxcenter, Division of Experimental Cardiology, Erasmus University Medical Center Rotterdam, The Netherlands

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ABSTRACT

Dilated cardiomyopathy (DCM) is a relatively common heart muscle disease characterized by the dilation and thinning of the left ventricle accompanied with left ventricular systolic dysfunction. Myocardial fibrosis is a major feature in DCM and therefore it is inevitable that corresponding extracellular matrix (ECM) changes are involved in DCM onset and progression. Increasing our understanding of how ECM adaptations are involved in DCM could be important for the development of future interventions. This review article discusses the molecular adaptations in ECM composition and structure that have been reported in both animal and human studies of DCM. Furthermore, we provide a transcriptome-based catalogue of ECM genes that are associated with DCM, generated by using NCBI Gene Expression Omnibus database sets for DCM. Based on this in silico analysis, many novel ECM components involved in DCM are identified and discussed in this review. With the information gathered, we propose putative pathways of ECM adaptations in onset and progression of DCM.

1. Dilated cardiomyopathy

In the developed world 1–2% of the population suffers from heart failure, from which approximately half of the patients have systolic heart failure with a reduction in ejection fraction of at least 40%. The underlying cause for systolic heart failure is predominantly ischemic heart disease and dilated cardiomyopathy (DCM). DCM is a relatively common heart muscle disease with a prevalence that increases with age: it is rare in the pediatric population (1–2:100,000), however in adults it has an estimated prevalence of 1:2500 [1,2]. The disease is characterized by the dilation and thinning of the left ventricle accompanied with left ventricular systolic dysfunction [3,4]. The diagnosis is primarily based on evidence of dilation and impaired contraction of the left ventricle (left ventricular ejection fraction (LVEF) <45%) [3–5]. DCM has a poor prognosis with a five-year survival rate of approximately 50% after diagnosis [6].

The etiology of DCM can be divided into ischemic (50–70%) and non-ischemic (30–50%), with the latter phenotype including genetic and acquired causes [7]. In Western countries, 20–50% of DCM patients have evidence for familial disease. Autosomal dominant is the primary mode of inheritance, although X-linked, recessive and mitochondrial inheritance occur as well. It is important to consider that sporadic DCM cases can also be due to genetic mutations [4,8]. Genetic forms of DCM are caused by mutations in cytoskeletal, sacromeric protein, Z-band, nuclear membrane, intercalated disk protein genes etc. [3,8]. Recently, up to 110 nuclear genes and 24 mitochondrial DNA genes have been linked to DCM [9]. Regarding the acquired causes of DCM; chronic myocardial inflammation (myocarditis) can lead to DCM at a later stage and is most commonly evoked by infectious triggers. The majority of non-ischemic DCM cases (≥70%) are considered idiopathic: they remain unexplained after a thorough search for primary or secondary causes [7].

Myocardial fibrosis is a major feature in DCM [10–12]. In cardiac tissue, fibrosis has often been described to develop in the setting of an ischemic scar as a result of a myocardial infarction (MI). This reparative response is referred to as replacement fibrosis: dead cardiomyocytes are replaced mainly by collagen. Myocardial fibrosis has also been increasingly recognized in diffuse form in the absence of an ischemic trigger as reported in cardiomyopathies, including DCM [10,11]. Here, the

* Corresponding author at: Department of Nephrology and Hypertension, Division of Internal Medicine and Dermatology, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands.
E-mail address: K.L.Cheng-2@umcutrecht.nl (C. Cheng).

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cardiac interstitial space expands without cell loss, leaving a patchy fibrotic pattern in the myocardium or large collagen strands in between cardiomyocytes. This type of fibrosis is called reactive or interstitial fibrosis. Myocardial fibrosis is a pathogenic form of extracellular matrix (ECM) remodeling and therefore it is inevitable that corresponding ECM changes are involved in DCM development and progression.

Various animal and human studies have been performed in the last decades trying to elucidate the role of ECM components in DCM and the clinical manifestation of DCM, systolic heart failure (SHF). Studies based on non-ischemic and non-genetic DCM and SHF are summarized and briefly discussed in the following two paragraphs. The third paragraph will discuss the new information gathered from the online NCBI Gene Expression Omnibus (GEO) database sets for DCM. Based on this, we propose putative pathways of ECM adaptations in onset and progression of DCM.

2. Extracellular matrix adaptation in myocardial fibrosis associated with systolic heart failure and dilated cardiomyopathy

2.1. Animal studies

2.1.1. Collagen and type I/III collagen ratio

In relation to SHF and DCM, various animal models demonstrated that these diseases are causally associated with changes in ECM composition, structure and function. These changes are summarized in Table 1. Already in 1990, Weber and colleagues [13] performed a histopathological study with dilated LVs of dogs that underwent rapid ventricular pacing. In these tissue samples, disruption by degradation and disappearance of collagen fibers together with interstitial fibrosis in the midwall and epimyocardium was observed. The collagen network in the heart consist mostly of type I and III collagen, that self-organize into fibrils with a diameter ranging from 0.01 to 3 μm [14]. These fibrillar collagens aggregate into fibers that are connected through cross-links and form a strong tensile network that tethers cardiomyocytes in support of their alignment. Supported by this typical ECM configuration, the myocyte-generated force can be transduced in all directions. Procollagen molecules in their long and rigid triple helix forms are synthesized mostly by fibroblasts and secreted into the interstitial space. Here they will undergo cleavage of their end-terminal pro-peptide sequences to enable collagen fiber formation, since the resultant collagen molecule will be less soluble. This process is crucial in collagen network formation as it initiates self-assembly into collagen fibrils. Quantification of these cleaved terminal peptides can serve to measure the activity of the fibrotic process [15].

The ratio of type III to type I collagen can be considered as an index of myocardial distensibility, since type I is stiffer and provides more tensile strength when compared to type III, that is more elastic. The collagen type I/type III ratio is relatively stable in the healthy myocardium. However, in cardiomyopathies, studies imply that this ratio will shift. Subsequent studies performed by various research groups have analyzed in more detail the role of specific ECM components in DCM development and progression (Table 1). A study of ECM changes in a popular experimental model of DCM, hereditary dilated cardiomyopathy in hamsters (BIO 53.58 hamsters), demonstrated that type III collagen increases significantly at 10 weeks of age, whereas the total collagen content remains stable in control hamsters [16]. In addition, Masutomo and

Table 1
Summary of ECM response in myocardial fibrosis associated with DCM and SHF in animal studies.

Name		Expression	Study model	References
Core matrisome				
Glycoprotein				
ELN	Elastin	mRNA ↑	ACF-induced rat	Hutchinson et al. (2011)
Collagen				
COL1	Collagen, type I	mRNA ↑	SHF rat	Nishikawa et al. (2003)
			ACF-induced rat	Hutchinson et al. (2011)
		Protein ↑	SHF rat	Woodiwiss et al. (2001)
COL3	Collagen, type III	mRNA ↑	ACF-induced rat	Hutchinson et al. (2011)
		Protein ↑	BIO 53.58 hamster	Okada et al. (1996)
Matrisome-associated				
ECM-affiliated				
GSPG	Chondroitin sulfate proteoglycan	Protein ↑	Pacing-induced CM pig	Spinale et al. (1996)
ECM regulator				
PLAU	Plasminogen activator, urokinase	mRNA ↑	CVB3-infected mouse	Heymans et al. (2006)
		Activity ↑	CVB3-infected mouse	Heymans et al. (2006)
MMP-1	Matrix metallopeptidase 1	Protein ↑	Pacing-induced CM pig	Spinale et al. (1998); Coker et al. (1998)
MMP-2	Matrix metallopeptidase 2	mRNA ↑	CVB3-infected mouse	Cheung et al. (2006); Heymans et al. (2006)
		Protein ↑	Pacing-induced CM pig	Spinale et al. (1998); Coker et al. (1998)
		Activity ↑	SHF rat	Nishikawa et al. (2003)
			CVB3-infected mouse	Cheung et al. (2006)
MMP-3	Matrix metallopeptidase 3	mRNA ↑	CVB3-infected mouse	Li et al. (2002); Heymans et al. (2006)
		Protein ↑	Pacing-induced CM pig	Spinale et al. (1998); Coker et al. (1998)
			CVB3-infected mouse	Li et al. (2002)
MMP-7	Matrix metallopeptidase 7	mRNA ↑	ACF-induced rat	Hutchinson et al. (2011)
MMP-8	Matrix metallopeptidase 8	mRNA ↑	CVB3-infected mouse	Heymans et al. (2006)
MMP-9	Matrix metallopeptidase 9	mRNA ↑	CVB3-infected mouse	Li et al. (2002); Cheung et al. (2006); Heymans et al. (2006)
		Protein ↑	CVB3-infected mouse	Li et al. (2002); Heymans et al. (2006)
		Activity ↑	SHF rat	Nishikawa et al. (2003)
			CVB3-infected mouse	Cheung et al. (2006); Heymans et al. (2006)
MMP-12	Matrix metallopeptidase 12	mRNA ↑	CVB3-infected mouse	Cheung et al. (2006)
MMP-13	Matrix metallopeptidase 13	mRNA ↑	CVB3-infected mouse	Heymans et al. (2006)
MMP-14	Matrix metallopeptidase 14	mRNA ↓	CVB3-infected mouse	Li et al. (2002)
TIMP-1	Tissue inhibitor of metalloproteinases 1	mRNA ↑	SHF rat	Nishikawa et al. (2003)
		mRNA ↓	CVB3-infected mouse	Li et al. (2002)
TIMP-2	Tissue inhibitor of metalloproteinases 2	mRNA ↑	SHF rat	Nishikawa et al. (2003)
		mRNA ↑	ACF-induced rat	Hutchinson et al. (2011)
TIMP-3	Tissue inhibitor of metalloproteinases 3	Protein ↓	CVB3-infected mouse	Cheung et al. (2006)
TIMP-4	Tissue inhibitor of metalloproteinases 4	Protein ↓	CVB3-infected mouse	Li et al. (2002), Cheung et al. (2006)

Abbreviations: ACF, aortocaval fistula; ISO, isoproterenol; SHF, systolic heart failure; CM, cardiomyopathy; CVB3, coxsackievirus B3.