Myocardial proteases and matrix remodeling in inflammatory heart disease

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Abstract

Recently, it has been demonstrated that myocardial inflammation plays a pivotal role in the development and progression of congestive heart failure. The myocardial inflammatory reaction not only affects myocardial hypertrophy and apoptosis, but it has a major influence on the regulation of extracellular matrix turnover. The balance between collagen synthesis and degradation is of crucial relevance in maintaining the structural integrity of the heart. Therefore, the overwhelming inflammatory response, as seen in acute myocarditis or inflammatory cardiomyopathy, could lead to a breakdown of this tightly regulated system. This is an additional key factor in the development and progression of heart failure.

This review summarizes the importance of myocardial inflammation in respect to extracellular matrix remodeling and its possible pathophysiological role in the development and progression of left ventricular dysfunction in inflammatory heart disease.

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1. Introduction

Myocarditis, an inflammatory disorder, which is most commonly caused by viral infection (especially enterovirus and parvovirus), is associated with acute left ventricular dysfunction accompanied by myocardial inflammatory cell infiltration and increased release of proinflammatory cytokines [1]. The presence of viral genome in endomyocardial biopsies of patients with dilated cardiomyopathy (DCM) demonstrates an interrelationship between acute myocarditis and DCM [2–4]. A similar frequency of intramyocardial inflammation was found in patients with DCM, which reflects the relevance of chronic inflammation in the development of left ventricular dysfunction [5]. However, not only viral persistence and chronic inflammatory response seem to play an important role in the pathogenesis of inflammatory cardiomyopathy. The latest investigations adver to a momentous role of matrix metalloproteinases in the disruption of the extracellular matrix (ECM) architecture involving a pathological elevated myocardial collagen turnover which leads to the loss of structural integrity of the heart resulting in left ventricular dysfunction [1,6–8]. In the latest investigations these factors have been shown to play a crucial role in the disruption of the ECM architecture. A pathologically elevated myocardial collagen turnover leads to the loss of structural integrity of the heart and ensuing left ventricular dysfunction.

Acute left ventricular dysfunction in experimental induced acute myocarditis is associated with induction of proinflammatory cytokines and an imbalance of the matrix metalloproteinases (MMPs) and the tissue inhibitors of MMPs (TIMPs) system [1]. Proinflammatory cytokines like TNF-α and IL-1β contribute not only to depression of LV function and cardiomyocyte loss by apoptosis, they also play a critical role in maintaining the balance in ECM remodelling [9–11], showing the importance of chronic inflammation in myocardial remodeling process as well as in the development of DCM [12]. They regulate cardiac fibroblast function with the expression of collagen types I and III and fibronectin, and moreover also regulate the
matrix degradation system by influencing the expression of matrix metalloproteinases (MMPs), the tissue inhibitors of MMPs (TIMPs) and their activators like urokinase type plasminogen activator and tissue type plasminogen activator (uPA, tPA) [12–15]. This seems to indicate that the maintenance of the physiological myocardial matrix turnover involves a highly regulated interaction between cardiac and noncardiac cells, in response to the release of inflammatory mediators and components of the matrix degradation system.

2. Heart failure and cytokines

Chronic heart failure is a disease with multiple causes of which an inflammatory reaction is the most important. Over the past years inflammatory cytokines and neurohormones have been shown to contribute to the development and progression of left ventricular dysfunction. Congestive heart failure is now commonly seen as a state of chronic inflammation. Proinflammatory cytokines like TNF-α and IL-6 are elevated in different entities of heart failure like acute myocardial infarction, stable angina pectoris or acute myocarditis with perpetuation of congestive heart failure and relevance for prognosis of the disease [16–19]. For instance, TNF-α has been shown to induce myocardial hypertrophy and fibrosis [20], increase cardiac myocyte apoptosis and induce activation of the inducible form of nitric oxide synthase (iNOS) [21]. IL-1 has been demonstrated to depress myocardial contractility in a dose-dependent manner and to contribute to myocardial apoptosis and hypertrophy. In collaboration with IL-1β, TNF-α also promotes Coxsackie virus B3 myocarditis in resistant Balb/c-mice [22]. In our previous investigations we could show a close correlation between the development of left ventricular dysfunction and the increase of myocardial mRNA abundance of IL-1β and TNF-α in a murine model of CVB-3 induced acute myocarditis (Fig. 1). Furthermore, Liu and Zhao have demonstrated that heart function is improved by declining circulating TNF-α concentration [23]. The neurohumoral activation and the elevated oxidative stress during the development of left ventricular dysfunction in congestive heart failure can be triggered by proinflammatory cytokines. Increased free oxidative radicals are able to lead to an activation of p38-MAP-kinase and nuclear factor kappa B (NFkB). These directly affect left ventricular dysfunction by inducing cardiomyocyte apoptosis and by the negative inotropic effects of reduced calcium uptake by the sarcoplasmatic reticulum [24,25]. Another important pathophysiologic process in the development of congestive heart failure concerns the sympathetic nervous system with increased levels of catecholamines, which may result in an overwhelming inflammatory reaction. Murray et al. have demonstrated that chronic β-adrenergic stimulation leads to an increase of myocardial gene expression and protein production of TNF-α, IL-1β and IL-6 [26]. This result confirms previous studies showing that isoproterenol advances myocardial hypertrophy [27], myocyte degeneration and inflammatory cell infiltration [28]. This is also in line with our investigation, as described below, which shows that the treatment of acute myocarditis with a β-adrenergic receptor blocker leads to a reduced inflammatory response, modulated immune reaction and decreased ECM remodeling as well as an improved left ventricular function [29].
3. Myocarditis and dilated cardiomyopathy

Myocarditis, an inflammatory disease of the myocardium, diagnosed by standardized histological and immunohistological methods [30], is caused by both infectious and noninfectious agents [31]. However, the main cause is the viral infection of the myocardium with cardiotropic viruses, like enterovirus or parvovirus [32]. Previous investigations on endomyocardial biopsies showed that several other viral agents like adenovirus or parvovirus B19 are also involved in the etiology of myocarditis [3,4]. For the pathogenesis of myocarditis, Kawai described a triphasic model with an acute, subacute and chronic phase [33]. During the acute phase the myocardium mainly expresses proinflammatory cytokines, such as IL-1β, TNF-α and Interferon-γ [34,35]. These elevated proinflammatory cytokine levels are linked to histological changes such as myocyte necrosis and apoptosis [36,37]. In this early stage of disease there is very little infiltration of natural killer cells and macrophages in the myocardium [38,39]. This phase is characterized by a dominance of direct pathogenicity of viral action and myocyte apoptosis with direct alteration of myocardial architecture by destroying dystrophin [40–43]. In the subacute phase an increase in myocardial cell infiltration, especially T-lymphocytes, natural killer cells and fibroblasts follows [33]. The protective effect of natural killer cells is based on their suppression of viral replication by the perforin-induced disturbance of infected cardiomyocytes [44,45]. The importance of early suppression of viral replication is shown by the more severe myocarditis seen in a murine myocarditis model with a defect of NK-cells [46]. Seko et al. could detect a time-dependent release of cytokines, with an initial increase of proinflammatory cytokines (IL-1β, IL-6, TNF-α, Interferon-γ) to the 7th day after infection, followed by regulatory cytokines like IL-2, IL-4 and IL-10 [47]. The outcome of the virus-induced immune response is not straightforward and may vary greatly. An efficient viral elimination through a radical immune response is required for a better outcome of the disease. For example, patients with myocarditis who have higher cardiac specific IgG have better survival prospects [48] and furthermore, acute fulminant myocarditis with an initial massive inflammation and more pronounced cellular injury has a better long-term outcome as compared with acute nonfulminant myocarditis [49]. On the other hand an uncontrolled immune response is associated with an inefficient viral elimination, pathological myocardial inflammation, and initiating of cross-reacting antibodies, which result in progressive cellular injury and matrix remodeling. The increase of cardiac cell-infiltration and release of inflammatory cytokines directly correlate to the development of left ventricular dysfunction [50]. Viral persistence and chronic inflammation may finally lead to the third and chronic phase of myocarditis with the development of dilated cardiomyopathy. Entroviral genome could be detected in the myocardium up to 90 days after viral infection in a murine model of myocarditis, which indicates one causal step of chronic myocardial cell infiltration [51,52]. The importance of latent or persistent virus with induced chronic myocardial inflammation has been demonstrated in persistent Cytomegalovirus-myocarditis [53] and in the development of left ventricular dilatation in mice with persistence of Coxsackievirus B3 [54]. The presence of viral genome in endomyocardial biopsies of patients with dilated cardiomyopathy underlines the relationship between myocarditis and the development of left ventricular dysfunction [2]. Another important step in the development and progression of acute left ventricular dysfunction and dilatation is the initiation of an adverse remodeling of the ECM by immune mediators. Chronic myocardial inflammation induces the pathological collagen turnover resulting in loss of structural integrity of the myocardium and in the development of left ventricular dysfunction.

4. The extracellular matrix—collagen and cytokines

Myocardial ECM (mainly collagen type I and III and fibronectin, elastin, etc.) forms a three dimensional cross-linked collagen-network which supports the cellular and structural integrity of the heart. After secretion into the ECM, the fibril-forming collagens aggregate spontaneously after following the processing of procollagens into ordered fibrillar network, stabilized by covalent cross-links. The structural elements are dynamic and there is a complex network of receptors and enzymes within the ECM which controls the turnover of this tightly regulated system. Collagen production and degradation is an important process in the development of left ventricular dysfunction in acute and chronic myocarditis and determines the maintenance of cardiac architecture.

Collagen synthesis by cardiac fibroblasts is regulated by multiple factors, including inflammatory cytokines like TNF-α, IL-1β or TGF-β, TNF-α and IL-1β have been shown to decrease the expression of procollagen type I and III and increase the expression of fibronectin and non-fibrillar procollagen type IV. Furthermore, several other factors like aldosterone, TGF-β or mechanical stretch have been shown to induce the mRNA synthesis of collagen [12]. The renin-angiotensine-system also partakes in the regulation of collagen synthesis; angiotensin II induces ECM protein synthesis and accumulation via AT1-receptor stimulation, effects that are mediated by TGF-β; and endothelin-1 [55]. A rat model of myocardial infarction showed the importance of this myocardial remodeling: ACE inhibition prevented collagen accumulation and DNA synthesis and furthermore completely inhibited collagen deposition with AT1-receptor antagonism [56].

Fibrillar collagen turnover results from the equilibrium between the synthesis and the degradation of collagen, mainly types I and III. In the healthy left ventricle ECM
replacement is about 5% to 9%, in pathological conditions, e.g. after myocardial infarction, this figure can rise to 50% [57]. Furthermore the rate of collagen synthesis per day is much slower than of noncollagen proteins with a longer half-life period of collagen, implying a fairly slow ECM replacement after degradation and potential vulnerability for adverse remodeling [58]. This additionally reduces the ability to form the three dimensional network with collagen cross-links, which leads to alteration in the composition and structure of myocardial collagen.

5. The MMP system

Collagen degradation is an important step in ECM remodeling, mainly due to matrix metalloproteinases (MMPs) and serine-proteinases. The matrix metalloproteinases are a family of 20 different species of zinc-dependent enzymes [59], which could be expressed under basal conditions by fibroblasts and myocytes and also in response to inflammatory reactions by infiltrating macrophages and lymphocytes. One group of MMPs is secreted into the extracellular space in a latent or proenzyme form and the other group is membrane-bound. Regarding the catalytic domain of MMPs, a large extracellular binding domain at the C-terminus is responsible for the substrate specificity and the specific binding to ECM proteins [59,60]. In addition, these substrate specificities and functions classify the secreted MMPs in three different groups. First the collagenases (MMP-1, MMP-8, MMP-13) decompose the insoluble collagen fibrils into soluble fragments [61]. The cleaving of these soluble fragments is continued by gelatinases (MMP-2, MMP-9), which are highly expressed in the left ventricular myocardium [7,62]. Coker et al. showed an isolated expression of these gelatinases in LV-myocytes, which supports the possibility of a direct processing of matrix remodeling by the synthesis and release of MMPs [63]. MMP-2 is thereby constitutively expressed in the myocardium, whereas MMP-9 is an inducible form of the MMPs and becomes more relevant under inflammation with inducible expression in neutrophils and macrophages [64,65]. The third group, the stromelysine-like MMP-3, degrades not only a wide range of components of the ECM, it can also initiate the activation of the inactive pro-MMPs.

The group of membrane-bound MMPs (Membrane Type-MMP, MT-MMP) plays also a critical role in matrix remodeling, which on the one hand cleaves intact fibrillar collagen and basement membrane components and on the other hand directly activates different pro-MMPs [66]. However MMPs do not only play a role in the degradation of the ECM-components, the final fragmented matrix peptides also have biological activities and have been shown to stimulate new collagen synthesis by cardiac fibroblasts [67].

Beside the ECM components, the target substrates of the MMPs also include nonmatrix proteins such as cytokines, receptors and adhesions molecules [68–70]. This explains additional functions of MMPs as for example regulating growth, cell pathways, and angiogenesis [71]. The capability of activated MMPs to degrade the complete ECM is conditioned by a tightly controlled system. First, the control at the transcriptional level by several cytokines or growth factors; second the control of pro-MMP activation by serine proteinases (Plasmin-system), MT-MMPs or stromelysines; and last the inhibition of activated MMPs by the tissue inhibitors of MMPs (TIMP1–4) (Fig. 2).

Fig. 2. Simplified mechanism of regulation in the Matrix-Degradation-System. Importance of inflammatory mediators.
5.1. Synthesis of MMPs

The synthesis of MMPs at the transcriptional level is influenced by multiple cytokines, neurohormones and growth factors [72]. Different signaling pathways have been shown to be involved in regulation of the expression of MMPs [73-80].

It could be demonstrated that proinflammatory cytokines like IL-1β, TNF-α or IL-6 induce MMP-synthesis [12,13]. Furthermore, in mice with over expressing TNF-α, a progressive development of left ventricular dilatation is associated with increased MMP-activity [20]. In collaboration with TNF-α, interferon-γ enhances the MMP-1 synthesis in human monocytes and neutralizing antibodies against TNF-α block the induction of MMP-1 by interferon-γ [81]. By contrast, TGF-β1 on the one hand decreases the proteolytic activity of MMP-1 and MMP-3 by suppressing MMP gene expression through the TGF-β inhibitory element (TIE) and on the other hand increases the expression of MMP-2 and MMP-9 [14,82]. Beside inflammatory cytokines, several other bioactive molecules also influence the synthesis of MMPs. Angiotensin II plays a pivotal role here: It has been demonstrated that angiotensin II induces the expression of MMP-2, -9 and -14 in neonatal rat fibroblast [83]. Its importance in this regulating process is further shown by an improvement in left ventricular function and myocardial geometry through reduced MMP-synthesis after ACE-inhibition or AT-1 blockade [84,85]. Endothelin-1 enhances the production of MMP-2 and MMP-9 and endothelin receptor blockade results in reduced levels of MMP-2 and -9 [86]. Furthermore, natriuretic peptides like BNP (brain natriuretic peptide) are able to induce the MMP-synthesis in chronic heart failure and myocardial remodeling [87].

5.2. Activation of MMPs

MT-MMPs and MMP-3 activate different members of the MMP family by proteolytic cleavage of the MMP-propeptide [15,66,88]. Even more important is the plasminogen system (plasminogen activators (PA), tissue-type PA (t-PA), urokinase-type PA (uPA) and the PA-inhibitor (PAI)), which activates the inactive proMMPs as described above [88]. The importance of this system in disrupting the cardiac collagen network has been previously demonstrated in mice lacking uPA or mice with acute pressure overload with PAI gene transfer showing improved left ventricular function with reduced myocardial fibrosis and preserved interstitial matrix [89]. Beside MMP-activation the PA are also able to cleave matrix proteins like fibrin and fibronectin. The expression of uPA [90], which has the same transcription factor binding elements (AP-1, PEA3) in the promotor region like MMP-1 and MMP-3 is induced by IL-1β and TNF-α [91]. In fibroblasts, IL-1β increases not only the protein and mRNA expression of uPA but also its receptor uPAR [92]. Furthermore, there is a feedback regulation between the MMPs and the plasmin-system; MMP-3 has been demonstrated to cleave their physiological inhibitor (PAI, α2-antiplasmin) resulting in neutralization [93,94].

5.3. Inhibition of MMPs

Active MMPs are specifically inhibited by their endogenous inhibitors, the TIMPs that are composed of four subtypes (TIMP-1-4) [81,95-97]. TIMPs bind to the active site of MMP in a 1:1 stoichiometrical, blocking their access to collagen substrate [15,98]. Furthermore they can bind latent MMPs at the aminoterminus thereby preventing their activation [99]. Some differences in the inhibitory properties of the different TIMPs have been reported. TIMP-2 and TIMP-3 have been proven to be effective inhibitors of membrane-bound-MMPs, and TIMP-3 is the only TIMP which can inhibit TNF-α converting enzyme [100,101]. Mice deficient of TIMP-1 gene develop increased left ventricular mass and increased end diastolic volume suggesting its important role in the prevented activation of the protease cascade and in the maintenance of a dynamic matrix balance. Inflammatory mediators also influence this third step in the control of MMP-activity; IL-1 and TNF-α can down regulate the expression of TIMP-1 [15]. Beside this specific inhibition α2 macroglubulin and heparin nonspecifically inhibit MMP-activity [102,103].

This widespread influence of inflammatory reaction on the regulation of the matrix degradation system reflects a deregulation in disease with pathologically elevated inflammatory mediators.

6. Extracellular matrix remodeling

6.1. ECM in acute myocarditis

Our previous investigations focused on the inflammatory reaction in virus-induced acute myocarditis caused by disruption of the collagen turnover and the resulting changes in the ECM and its influence on left ventricular dysfunction [1]. We could show that in the early phase of myocarditis the main disruption of ECM is caused by qualitative changes in the collagen network. Expression of myocardial mRNA and protein abundance of collagen type I was unchanged as was total collagen content measured by picrosirius red staining. However Western blot analysis demonstrated an increased fraction of soluble collagen, suggesting an initial dominance of posttranslational collagen variation contingent on an imbalance in the matrix degradation system. Corroborating these findings, Woodiwiss et al. have demonstrated that a reduction in collagen cross-links is responsible for the decreased native insoluble or increased soluble collagen and is associated with left ventricular dysfunction, remodeling and chamber dilatation [104]. MMP-9, which depolimerizes the cross-linked
polymers of collagen type I \[105\], seems to play an important role. Furthermore, LV enlargement after myocardial infarction could be prevented by deletion of the MMP-9 gene \[106\]. CVB-3 infection of the myocardium caused a significant release of proinflammatory cytokines such as IL-1\(\beta\), TNF-\(\alpha\) and TGF-\(\beta\) on the 10th day post infection. This was accompanied by an up regulated expression of MMP-3 and MMP-9 and reduced levels of their endogenous specific inhibitors TIMP-1 and TIMP-4. Furthermore, our unpublished data show evidence of an imbalance in the plasmin regulation system in this acute early phase of myocarditis by significant induced mRNA abundance of uPA with simultaneously reduced levels of PAI mRNA abundance (Fig. 3). As described above, a restored interstitial matrix with an undilated chamber could be demonstrated in a uPA knock-out model of chronic volume overload \[89\], suggesting that the above demonstrated imbalance in the matrix degradation system was mainly responsible for the development of left ventricular dysfunction. Increased levels of MMPs, decreased levels of TIMPs and the activated plasmin system in the acute phase of myocarditis may lead to an imbalance in the matrix degradation system in favour of matrix protein degradation. This ultimately reduces the matrix integrity and disrupts the three dimensional collagen network by cleaving the cross-links between the collagen molecules, which then leads to left ventricular dysfunction and dilatation.

6.2. ECM in dilated cardiomyopathy

As described above, previous investigations suggested an association between myocarditis and inflammatory cardiomyopathy caused by viral persistence. Signs are dystrophin degradation, myocardial inflammation with cytotoxic T-lymphocyte-mediated myocytolysis, B-lymphocyte-mediated generation of autoantibodies and induction of the MMP-system with pathologic collagen degradation and left ventricular dilatation. The results of our recent analysis of endomyocardial biopsies emphasize the importance of persistent inflammation in dilated cardiomyopathy regarding ECM alterations and the development of left ventricular dysfunction. The myocardial mRNA abundance of MMP-3 and TIMP-1 was analyzed in endomyocardial biopsies of patients with dilated cardiomyopathy with or without inflammation and in biopsies of patients with normal left ventricular function without histological signs of inflammation. We could demonstrate a significantly induced expression of myocardial MMP-3 in inflammatory cardiomyopathy accompanied by a reduced expression of TIMP-4 \[107\] in dilated cardiomyopathy without inflammation. This is in line with the results of Schwartzkopff et al. who have shown elevated serum markers of collagen degradation accompanied by increased levels of MMP-1 in patients with DCM \[108\]. Furthermore there was a negative correlation between the MMP/TIMP ratio and the degree of LV-dilatation.

Fig. 3. Differential mRNA abundances of myocardial MMP-3, TIMP-1, PAI and uPA and gelatinase activity in acute myocarditis on 10th day post infection. Dominance of matrix degrading components with loss of their controlling agents. \(*p<0.05\) were considered as significant.
underlining the importance of collagen degradation in the development of left ventricular dysfunction. Moreover, we could detect a co-localization of CD-3 and MMP-3, measured by immune histochemistry, which further emphasizes the importance of inflammation in this pathogenesis.

The increased production of collagen in the later stage of myocarditis seems to be a response to collagen degradation caused by increased MMP-activity. Since matrixes enhance the synthesis of procollagen it might be possible that after the initial importance of degradation, fibrosis takes over in the later phase of myocarditis [58]. This was also verified by Pauschinger et al. in patients with DCM, who had an increase in the myocardial collagen content measured by picrosirius red staining [8]. McCormick et al. speculated that there was a defect in collagen cross-linking pathways, leading to an increase in collagen concentration and collagenase activity with ventricular dilatation since in patients with idiopathic dilated cardiomyopathy, collagen deposition was doubled but hydroxyproline concentration increased [8]. McCormick et al. had an increase in the myocardial collagen content verified by Pauschinger et al. in patients with DCM, who over in the later phase of myocarditis [58]. This was also shown in hearts of Coxsackievirus B3 infected Balb/c mice on the 10th day after infection. Carvedilol could improve left ventricular dysfunction with a significant enhancement of LVESP, \( \frac{dP}{dt_{\max}} \) and \( \frac{dP}{dt_{\min}} \) [113]. This improvement was accompanied by a reduced inflammatory reaction as shown by the reduced release of proinflammatory cytokines such as IL-1\( \beta \), TNF-\( \alpha \) and TGF-\( \beta \).

The importance of proinflammatory cytokines in the development of left ventricular function was demonstrated by a significant correlation between the myocardial enlargement caused by proinflammatory cytokines and cardiac hemodynamic parameters. We could furthermore show an improved balance of the MMP/TIMP-system with reduced levels of myocardial mRNA abundance of MMPs, especially MMP-8, reflecting a reduced myocardial cell infiltration by the cell specific expression of neutrophils underlined by its significant correlation to the regulation of IL-1\( \beta \), TNF-\( \alpha \). This emphasizes the complex interaction of ECM remodeling, neurohumoral activation, reactive oxygen species, myocardial cell infiltration and release of proinflammatory cytokines. A comparison between carvedilol and metoprolol showed that carvedilol exerts a better effect in the improvement of left ventricular function. This might be due to the absent effect of the selective \( \beta \)-adrenergic blocker metoprolol on the release of myocardial proinflammatory cytokines and MMPs. Nishio et al. demonstrated that the actions of epinephrine could be blocked by carvedilol and propanolol, but not by metoprolol, suggesting maintenance of epinephrine effects over \( \beta_2 \)-adrenergic receptor stimulation [114]. Besides antioxidative properties [115], carvedilol has also been proven to inhibit the generation of free oxygen radicals by neutrophils [116] and to reduce the production of oxidized low density lipoproteins [117]. This might partially explain its expanded effects on the MMP/TIMP-system which could explain the improved cardiac function.

7. Conclusion

The myocardial ECM is a complex network which balance determines the structural integrity of the heart. Alteration in the matrix degradation system caused by inflammatory mediators, oxygen species and neurohumoral reaction leads to an impairment of left ventricular function as seen in myocarditis and inflammatory cardiomyopathy. The imbalance of the matrix degrading system with induced expression of MMPs and plasminogen activators as well as the reduced expression of TIMPs, leads to a pathologic collagen turnover, with the loss of structural integrity of the heart and an impairment of LV function. Therefore, the regulation of the MMP/TIMP system is an important therapeutic target in the prevention of the progression of inflammatory heart failure. Further investigations are needed to determine the best target for intervention in order...
to influence this complex system leading to a dynamic balance between collagen accumulation and degradation.

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