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REVIEW ARTICLE

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Myocardial proteases and cardiac remodeling

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Cardiac hypertrophy (CH), characterized by the enlargement of cardiomyocytes, fibrosis and apoptosis, is one of the leading causes of death worldwide. Despite the advances in cardiovascular research, there remains a need to further investigate the signaling pathways that mediate CH in order to identify novel therapeutic targets. One of the hallmarks of CH is the remodeling of the extracellular matrix (ECM). Multiple studies have shown an important role of cysteine proteases and matrix metalloproteinases (MMPs) in the remodeled heart. This review focuses on the role of cysteine cathepsins and MMPs in cardiac remodeling.

KEYWORDS

cardiac remodeling, cathepsins, extracellular matrix, heart failure, matrix metalloproteinases

1 | CARDIAC REMODELING

The World Health Organization predicts that by 2030, 23.3 million people will die of cardiovascular pathologies with heart failure being the leading cause of death (Mathers & Loncar, 2006). Clearly, heart failure imposes a substantial health-care burden, despite recent treatment advances. Cardiac remodeling is a key pathophysiological process that ultimately leads to heart failure, which occurs in response to cardiac hypertrophy (CH), hypertension, and myocardial infarction (MI) (de Couto, Ouzounian, & Liu, 2010; Dupree, 2010). Cardiac remodeling is characterized by intrinsic changes of the cardiomyocyte and the interstitium such as the reorganization of myocytes, increased collagen deposition, increased fibrosis, changes in intercellular matrix components as well as enlargement of the cardiomyocytes. The remodeling of the extracellular matrix (ECM) is an important contributor of cardiac remodeling. Disruption of the ECM network structure interrupts the connection between cardiomyocytes and blood vessels, thereby compromising the structural integrity and function of the heart. An excess production and the accumulation of ECM structural proteins results in enhanced stiffness of the myocardium and impedes ventricular contraction and relaxation, leading to distorted architecture and function of the heart (Lu, Takai, Weaver, & Werb, 2011). Components of the ECM including cathepsin cysteine proteases and matrix metalloproteinases (MMPs) have a central role in ECM remodeling and are the focus of this review.

2 | EXTRACELLULAR MATRIX (ECM) AND CARDIAC REMODELING

The ECM is composed of proteins such as collagens, elastin, proteoglycans, and non-collagenous glycoproteins and forms a complex, three-dimensional network among the cells of different tissues in an organ-specific manner. Maintenance of a healthy cardiac system relies on controlled biosynthesis, maturation, function, and breakdown of ECM proteins. The remodeling of the ECM occurs through a variety of post-translational modifications, which can be enzymatic or non-enzymatic. Among the enzymatic modifications, proteolytic processing and degradation are among the most important. Through proteolysis, proteases such as cathepsins and MMPs release bioactive factors, which influence growth, morphogenesis, and pathological processes, modifying the ECM structure (Visse & Nagase, 2003). Although, the proteolytic activity allows the degradation of misfolded or malfunctioning proteins, dysregulation in these proteolytic enzymes may cause an imbalance between the synthesis and degradation of ECM proteins resulting in uncontrolled ECM remodeling.

2.1 | Cathepsins

Cysteine proteases, discovered in the second half of the 20th century, are the largest sub family of cathepsins. There is about an 80% homology between the mouse and the human genetic sequence encoding the enzyme (Chan, San Segundo, McCormick, & Steiner, 1986). They are ubiquitously expressed in all cell types and can be primarily found within the lysosomes, where they function to remove damaged and unwanted proteins. Cathepsins have been shown to be expressed by cardiomyocytes (Cheng et al., 2006), macrophages (Kaakinen, Lindstedt, Sneck, Kovanen, & Oorni, 2007), and immune cells (Staun-Ram & Miller, 2011).

2.1.1 | Cathepsin isoforms

Cathepsins comprise of eleven different isoforms (Cat B, C, L, F, H, K, O, S, V, W, and X) (V. Turk, Turk, & Turk, 2001). Cathepsins are further divided into endopeptidases (Cat F, K, L, S, and V) (Staun-Ram & Miller, 2011) or exopeptidases (Cat B, C, H, and X) based upon their cleavages sites (Brix, Dunkhorst, Mayer, & Jordans, 2008; Brömme & Wilson, 2011; B. Turk, Turk, & Turk, 2000). Cat B is unique in this respect as it has the ability to have both activities along with having peptidyl dipeptidase (Aronson & Barrett, 1978) and carboxypeptidase (Brömme & Wilson, 2011; Hook, Jacobsen, Grabstein, Kindy, & Hook, 2015). This unique property of Cat B has been attributed to a particular element in its structure called the occluding loop (Musil et al., 1991).

2.1.2 | Structure and synthesis of cathepsins

Cathepsins have been shown to be composed of three general domains, a single peptide, pro region, and a catalytic domain (consisting of a heavy chain, and a light chain) (Mohamed & Sloane, 2006; Qin & Shi, 2011; Sol-Church et al., 2002; V. Turk et al., 2001). The single peptide, located at the N-terminal of the enzyme, is about 10–20 amino acids in length and is responsible for the translocation of the enzymes into the endoplasmic reticulum (ER) during messenger ribonucleic acid (mRNA) translation (Reiser, Adair, & Reinheckel, 2010). The cathepsins are then moved to the acidic compartments of lysosomes or endosomes through either the mannose-6-phosphate (M6P) receptor dependent or independent pathways. Within the compartments of the lysosomes or endosomes, the pro region is cleaved off. This results in the liberation of the fully active form of the cathepsin (Kuliawat, Klumperman, Ludwig, & Arvan, 1997; Nishimura, Kawabata, Yano, & Kato, 1990). The catalytic domain contains the active site of the enzyme. The pro and the active forms of cathepsins can also be secreted into the extracellular compartment by exocytosis (Cheng et al., 2012) (Figure 1).

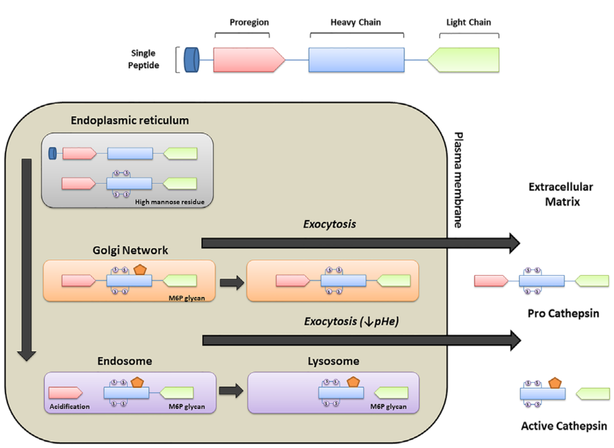

FIGURE 1 Model of the cathepsin primary structure and cathepsin maturation processes. Cathepsins contains a signaling peptide, pro region, heavy chain, and light chain. The cathepsins maturation process is as follows: The single peptide is removed in the ER and disulfide-bound formation, followed by glycosylation of the M6P residue and translocation into the Golgi network. The cathepsins are then translocated into the endosomes or lysosomes where the pro region is cleaved off. The Ca^{2+}-mediated organelle fusion and secretion into extracellular spaces can also take place from the endosomes or lysosomes. ER, endoplasmic reticulum; M6P, mannose-6 residue phosphorylation

2.1.3 | pH regulation of cathepsins

Cathepsins are primarily regulated by pH when they are localized within the lysosomes. Once they are released from the lysosomes into the cytosol or into the extracellular compartment, their activity is regulated by the cystatins, cathepsin endogenous inhibitors (Brömme & Wilson, 2011). Generally lysosomal cathepsins are optimally active at slightly acidic pH (Rozhin, Sameni, Ziegler, & Sloane, 1994). The low pH also creates a reducing environment within the lysosomes which prevents the oxidation of the thiol group on the active site of the cathepsins and hence, prevents their inactivation (Brömme & Wilson, 2011). Cat B shows dominant endopeptidase activity at lower pH values whereas it shows more dominant exopeptidase activity at higher pH values. At low pH, an occluding loop covers the active site hence, limiting access of its active site to polypeptides. This limits the enzyme's endopeptidase activity but retains its dipeptidase and carboxypeptidase activities (Illy et al., 1997). At physiological pH, the loop uncovers the active site thereby granting more access to the enzyme's active site (Illy et al., 1997). Nonetheless, it has been found that Cat B still retains significant proteolytic activity at neutral pH as well (Pratt, Sekedat, Chiang, & Muir, 2009).

2.1.4 | Physiological role of cathepsins

Cathepsins have various physiological functions which are important for many biological processes. Cat S and Cat L are involved in the processing of the major histocompatibility complex (MHC) class II associated invariant chain (Nakagawa et al., 1999). Cat K, found primarily within the osteoclasts, has been shown in multiple studies to be an important player in normal bone remodeling processes (Chapman, Riese, & Shi, 1997). Cat F, found in the macrophages, has recently been suggested to be an important player in the atherosclerotic process and remodeling of the intimal ECM (Kaakinen et al., 2007). Lysosomal Cat, B, H and L are primarily involved in the bulk protein degradation of proteins within the lysosomes (Barrett & Kirschke, 1981; Mason, 2008; Pham & Ley, 1999; V. Turk et al., 2001). Lysosomal cathepsins are also involved in the conversion of pro hormones into their active forms by cleavage of their pro peptides (Tepel, Bromme, Herzog, & Brix, 2000).

2.1.5 | Cathepsins in cardiovascular pathologies

Cathepsins have been shown to be important mediators in many cardiac pathologies. Evidence suggests that cathepsins play diverse role in the CVS where some act as cardioprotective while others play a more cardiotoxic role.

Cardiotoxic role of cathepsins in the cardiovascular system

In numerous studies, cathepsins have demonstrated to contribute to the progression and development of varsiou cardiac pathologies in vitro, in vivo and in humans. Cat S and/or K gene and protein levels were shown to be increased in the failing rat myocardium in association with hypertension and in the failing myocardium of patients with hypertensive heart failure (Cheng et al., 2006). In a model of Dahl salt sensitive rats, Cat S, B, and K genes have also been shown to be increased whereas those of the endogenous cathepsin inhibitor, cystatin C, showed no significant changes (Cheng et al., 2006). Furthermore, the elastase assays demonstrated that elastase activity of Cat S and K was increased significantly in the tissue extracts from the failing rat myocardium. This response was blunted by the broad spectrum cysteine protease inhibitor E64 or a specific inhibitor of Cat S (Cheng et al., 2006, 2008). Levels of Cat S, B, L, and/or K were also shown to be increased in subjects with dilated and hypertrophic cardiomyopathies compared with control subjects (Cheng et al., 2012). Another recent study reported an increase in Cat B levels post-MI in vivo. Cat B inhibition, using specific pharmacologic inhibitor CA-074Me, significantly attenuated cardiac dysfunction, and reduced cardiomyocyte size and cardiac fibrosis in the experimental MI model, by inhibiting NLRP3 activation (Liu, Gao, Zhang, & Cui, 2013). Taken together, it seems that various cathepsins are intimately involved in the pathological processes contributing to cardiovascular diseases.

Cardioprotective role of cathepsins in the cardiovascular system

In addition to the cardiotoxic role of cathepsins, numerous studies have demonstrated that cathepsins contribute to the progression and development of various cardiac pathologies in vitro, in vivo and in humans. It was demonstrated in two hypertensive heart failure models (aortic banding and Ang II infusion) that the human Cat L transgenic heart shows a decrease in overload- induced CH and fibrosis through blocking of the AKT/GSK3 signaling pathway (Tang et al., 2009). A study reported that MI induced by left coronary artery ligation in wild-type rats caused rapid Cat L activation in myocardium and bone marrow and its deficiency contributed to diminished function and adverse remodeling late post-MI (Sun et al., 2011). This study showed that cardiac repair and remodeling benefits from activation of Cat L to improve cardiac function after MI injury (Sun et al., 2011). Another study reported that forced expression of Cat L in mature endothelial cells considerably enhanced their invasiveness and increased their angiogenic capacity in vivo (Urbich et al., 2005). Moreover, Cat S seems to play a role in cardiac maintenance as well since its deletion exacerbated angiotensin (Ang) II induced cardiac inflammation (Pan et al., 2012). Taken together, it seems that expression of various cathepsins including Cat S and L are protective against pathological processes that contribute to cardiovascular diseases.

Cathepsin B

Wu et al. (2015) hypothesized that Cat B could also play a prominent role in the pathology of pressure overload-induced cardiac remodeling. Wu et al. showed that Cat B levels were upregulated in cardiomyocytes in response to hypertrophic stimuli both in vivo and in vitro. Moreover, knockout of Cat B attenuated pressure overload-induced CH, fibrosis, dysfunction, and apoptosis. These results were further confirmed in in vitro studies utilizing H9c2 cardiomyocytes in which cardiomyocyte hypertrophy was induced by Ang II. Pharmacological Cat B inhibition using CA-074Me suppressed the cardiomyocytes hypertrophy by inhibiting the ASK1/JNK pathway (Wu et al., 2015). Although, the exact mechanism by which Cat B acts in cardiac diseases is still unclear, these data indicate an important role of Cat B in the modulation of cardiomyocyte hypertrophic response by regulating the signaling pathways involved in cardiac remodeling. Taken together, it seem that there is an interplay between the various forms of cathepsins in CH and heart failure.

Decreased extracellular pH values, which can be caused by an overactive NHE1 (Bourguignon, Singleton, Diedrich, Stern, & Gilad, 2004; Greco et al., 2014), can cause increased redistribution of lysosomes to the cell surface (Glunde et al., 2003; Heuser, 1989; Rozhin et al., 1994) which may be accompanied by fusion with an autophagosome (Sun et al., 2013). Subsequently, the lysosomal contents can be secreted into the ECM as it has been shown for Cat B (Rozhin et al., 1994). A study demonstrated that extracellular acidic pH values caused the redistribution of the lysosome to the cell periphery which paralleled Cat B secretion. Interestingly, this effect was blocked with several broad and specific NHE inhibitors (Steffan, Snider, Skalli, Welbourne, & Cardelli, 2009). However, the role of the autophagy-lysosomal pathway in mediating the hypertrophic cascade in relation to Cat B and NHE1 has not been investigated and remains unknown.

2.1.6 | Cathepsins in clinical trials

A few cathepsin inhibitors are now being investigated in human trials for several diseases such as osteoporosis and rheumatoid arthritis. At least four different Cat K inhibitors have entered clinical trials for the treatment of osteoporosis and skeletal disorders with excessive bone remodeling (Illy et al., 1997). Cat S inhibitors are in preclinical trials for the treatment of rheumatoid arthritis (Yasuda, Kaleta, & Bromme, 2005). One Cat B inhibitor has completed Phase 1 for fatty liver disease (Alkhouri, Carter-Kent, & Feldstein, 2011) and another is in late preclinical stage for treating Chagas disease (Doyle, Zhou, Engel, & McKerrow, 2007). However, no cathepsin inhibitors have been examined for their effect in the setting of cardiovascular diseases.

3 | MATRIX METALLOPROTEINASES

MMPs are a group of proteolytic enzymes that are primarily responsible for the maintenance of the ECM. Apart from maintenance of the ECM they also take part in various biological processes such as degradation of connective tissue, morphogenesis, angiogenesis, growth, and wound healing (Birkedal-Hansen, 1995; Shapiro, 1998).

3.1 | Isoforms and classification of MMPs

MMPs are classified into six distinct categories based upon their target substrates. They are collagenases, stromelysins, matrilysins, gelatinases, membrane-type metalloproteinases (MT- MMPs), and other MMPs, namely zinc- and calcium-dependent endopeptidases (Lee & Murphy, 2004) (Figure 2). MMP-1, −8, −13 constitute the collagenases family and are responsible for breaking down collagen type I, II, and III at neutral pH (Netzel-Arnett, Fields, Birkedal-Hansen,& Van Wart,

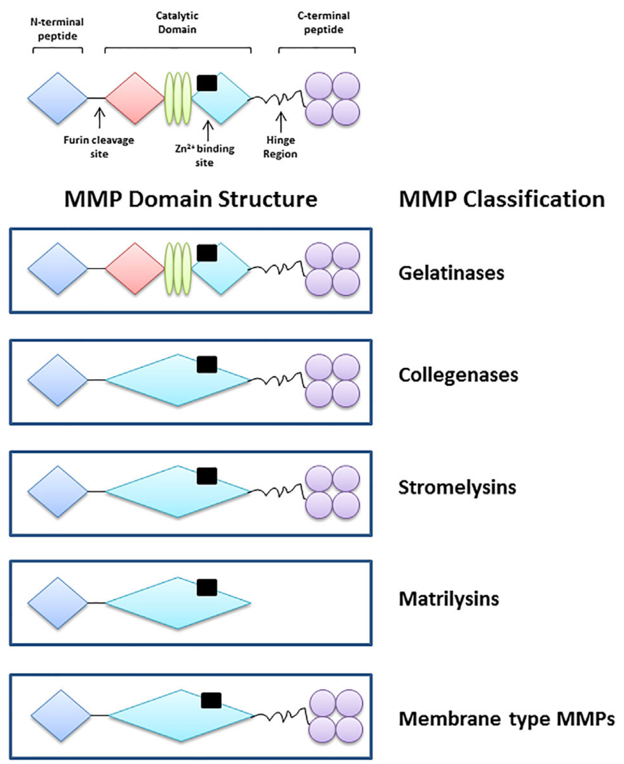

FIGURE 2 MMP domain structure and classification. A proenzyme molecule is organized into the three basic structural domains: N-terminal propeptide, catalytic domain, and the C-terminal part of the molecule. MMPs are classified into gelatinases, collagenases, stromelysins, matrilysins, and membrane type MMPs. MMP, matrix metalloproteinases

1991; Prockop & Kivirikko, 1995). The gelatinases family include MMP-2 and MMP-9. In particular gelatinases break down gelatin, denatured collagen, type IV, intact collagen of basal membranes and also non- denatured collagens type V, VII, X, XIV, fibronectin, agrecan, and elastin (Aimes & Quigley, 1995). Stromelysins include MMP-3, MMP-10, MMP-11 and have a wide substrate specificity. They are responsible for the degradation of all non-collagen ECM proteins such as proteoglycans, glycoproteins, fibronectin, and laminin (Matziari, Dive, & Yiotakis, 2007). Macrophagous elastase, MMP-12, have the ability to break down elastin. Gelatinases and matrilysins are also able to degrade elastin along with fibronectin, laminin, basal membrane collagen, entactin, chondrotin sulfate (Gronski et al., 1997).

3.2 | Structure of MMPs

All MMP proenzyme consists of three common domains: N-terminal propeptide, catalytic domain, and the C-terminal domain (Figure 2). N-terminal propeptide consists of about 80–90 amino acids containing cysteine residue. The cysteine residues interacts with the catalytic zinc through its side chain thiol group, and this ensures the inactivity of the proenzyme. Cleavage of a highly conserved sequence present in the propeptide region causes activation of the zymogene (Becker et al., 1995; Van Wart & Birkedal-Hansen, 1990). The catalytic domain contains the active site along with the Zn^{2+} ion which is bound by three histidine residues. The C-terminal domain determines the substrate specificity and is also the site of interaction with TIMPs (tissue inhibitor of metalloproteinases). MMPs are synthesized as pre-proenzymes. The pre region is cleaved off to allow for the secretion of the inactive proenzymes from the cell into the ECM whereby they are activated by other proteases or matrix components. The regulation of MMPs activity includes various levels of activation of latent MMPs, inhibition by tissue inhibitors of metalloproteinases (TIMPs), secretion of the enzyme molecule and the regulation of gene transcription.

3.3 | pH regulation of MMPs

While the activation of MMP-9 is complex and not well defined, a potential role for NHE1 in MMP-9 activation has been identified. Increase extracellular protease activity has been associated with NHE1 and cell migration in several cell lines (Bourguignon et al., 2004; Greco et al., 2014). NHE1 and MMP-9 activities are co-localized in invadopodia in breast cancer cells (Greco et al., 2014). Here, they directly interact with each other to promote ECM degradation at an extracellular pH optimum that is acidic (Greco et al., 2014). Another study reported that CCL39 cells that were pre-treated with PE resulted in an increase inMMP-9 activity (Wess, 1997). The involvement of NHE1 was confirmed by using EIPA, an inhibitor of NHE1. Cells pre-treated with EIPA prior to PE addition resulted in a decrease in MMP-9 activation and cell invasion as compared to control. Moreover, the knockout of NHE1 in CCL39 cell demonstrated no increase in MMP-9 activity or cell invasion in response to PE treatment. Moreover, MMP-9 activity was also shown to be induced by over active NHE1 in NCI-H358 non-small cell lung cancer (NSCL) cells (Taves et al., 2008). Another study reported that the inhibition of NHE1 using EIPA suppressed invasion and migration of HepG2 cells, which was partly mediated by the down regulation of MMP-9 (Yang, Wang, Dong, Song, & Dou, 2010). Taken together, it is clear that MMP-9 takes part in ECM degradation in cooperation with NHE1. However, the underlying mechanisms are still undefined.

3.4 | MMPs in cardiovascular pathologies

Multiple lines of evidence suggest that enhanced levels of vasoactive molecules in the circulation can lead to abnormal or enhanced activation of MMPs, which contributes to uncontrolled ECM remodeling (Dhalla et al., 2009).

3.4.1 | MMPs in hypertension and CH

Among the various isoforms of MMPs, MMP-9, and MMP2 have been shown to be the most commonly upregulated MMPs in hypertension and CH. Studies have demonstrated an increase in MMP-9 protein expression and activity whereas, those of TIMP-4 were reduced in Dahl salt- sensitive rats, a model of hypertension (Rodriguez et al., 2008). In Dahl salt-sensitive rats, the gene expression and MMP-2 and MMP-9 activity were shown to be upregulated prior to the occurrence of left ventricular dilatation, systolic dysfunction, and pulmonary edema. Taken together, the findings from both hypertensive animal models and hypertensive patients suggest that various MMPs may be involved in the development of hypertensive cardiomyopathies.

Increased MMP-9 and MMP-2 expression have also been associated with increased heart weight and cardiomyocyte area (Xu et al., 2010). Serum levels of both MMP-2 and MMP-9 have been shown to be increased in patients with hypertrophic cardiomyopathy. However, only MMP- 9 levels were associated with fibrosis (Roldan et al., 2008). It has also been reported that increased MMP-2 and MMP-9 levels in CH are associated with a significant imbalance between MMPs and their endogenous inhibitors, TIMPs.

3.4.2 | MMPs in dilated cardiomyopathy

n general, MMPs activities appear to contribute to the development of both MI-induced and idiopathic DCM as a result of their extensive ECM remodeling capability. MMP-1 and MMP-13 are able to degrade both intact collagen and proteoglycans which are further altered by MMP-2 and MMP-9 (Spinale, 2007). In a DCM rat model, increased levels of MMP-2, MMP-9, and TIMP- 1 mRNA were reported at 2 weeks post DCM induction (Matsumoto, Park, & Kohyama, 2009). However, as the DCM progressed into its 6th week, only the level of MMP-2 mRNA were seen to be elevated. The results from this study imply that in DCM, MMP-9 plays a role in disease progression during the early stages, whereas MMP-2 remains involved for the entire developmental stages of DCM (Matsumoto et al., 2009). Another study reported that MMP-9 protein levels were increased, whereas the increase in MMP-2 activity was normalized at the end of an 8-week period post-aortic banding (Givvimani et al., 2010). Although, there are discrepancies in MMPs activities between these two experimental models, it is clear that differential activation of specific MMPs results in the progression of cardiac remodeling. In addition, increased levels of MMP-2, MMP- 3, and MMP-9 have been observed in patients with DCM (Li, Feldman, Sun, & McTiernan, 1998; Spinale et al., 2000; Thomas et al., 1998). It is clear from the results that various form of MMPs are involve in the processes of cardiac remodeling.

4 | CONCLUSION

In this review, we highlighted Cat B and MMP-9 as important players and potential targets in CH. A deeper understanding of the cellular interplay between Cat B and MMP-9 in the cardiovascular system is necessary for understanding the underlying mechanisms. Nevertheless, Cat B appears to serve as a potential therapeutic target to reverse cardiac remodeling and to mitigate cardiac dysfunction. Inhibition of Cat B may prove to be a beneficial therapeutic solution.

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