O f the many proteinases present in the myocardium, members of the matrix metalloproteinase (MMP) family have received most attention. However, the cysteine proteases and their inhibitors have now been implicated in the pathogenesis of cardiac remodeling in the hypertrophied and failing heart. Cathepsins, cysteine proteases of the papain family, are optimally active in the acidic pH of lysosomes and are responsible for the physiological digestive turnover of cellular molecules and organelles. We now know that the levels of cathepsins and their endogenous inhibitors, cystatins, can be regulated by a number of signaling molecules, and cathepsins can be released from lysosomes into the extracellular space. Cysteine proteinases may degrade extracellular matrix proteins, such as elastin and fibrillar collagens.\(^1\) Nonlysosomal cathepsin targets include degradation of matrix and bone via elastinolytic/collagenolytic activity, activation of pro-MMP, induction of anoikis-dependent apoptosis via matrix degradation, activation of caspases, and cleavage of focal adhesion kinases. A decade ago, measurement of cathepsin activity in heart tissue of different pathologies was used as a measure of lysosomal activity and integrity. Now, as in the article by Cheng et al\(^2\) in this issue of Hypertension, regulated cathepsin release and activity is believed to be an important mediator of cardiac remodeling.

In human dilated cardiomyopathy heart tissue, cathepsin B mRNA and expression is increased compared with control hearts.\(^3\) Cathepsin B can activate urokinase-plasminogen activator (serine proteinases) ultimately leading to activation of MMP activity. However, cathepsin B activity is very low at neutral pH. Work in macrophages\(^4\) has demonstrated that regulated lysosomal secretion translocates the lysosomal H\(^+\)-ATPase to the plasma membrane, creating a localized acidic environment. One may hypothesize that the local acidic environment permits cathepsin B activity and leads to activation of MMPs. However, MMP activity is optimal at neutral pH. Therefore, whereas the activation of MMPs by cathepsin occurs in the local acidic environment, the diffusion of MMPs away from this area would allow for their activity. This may also lead to an increase of cathepsin-dependent collagenolytic/elastinolytic activity in local areas and more diffuse MMP-dependent matrix degra-

dation in remote areas (Figure). The local matrix degradation may then lead to detachment of cells from the matrix and anoikis-dependent apoptosis.

The article by Cheng et al\(^2\) shows that pressure overload–dependent cardiac remodeling also leads to increased expression of cathepsins S and K in the remodelled human heart and failing rat heart. Although cathepsin S retains activity at neutral pH, cathepsin K activity is low at neutral pH and may also depend on a local acidic environment. The authors go on to show that in vitro neonatal cardiac myocytes increase cathepsin S, B, L, and K mRNA in response to the inflammatory cytokines interleukin 1\(\beta\) and tumor necrosis factor-\(\alpha\), identifying cardiac myocytes as a potential source of cathepsins. The role of inflammatory cytokine-dependent cathepsin expression in cardiovascular cells has also been demonstrated in vascular smooth muscle cells in culture that increase expression of cathepsin S and K in response to interleukin 1\(\beta\) and interferon-\(\gamma\).\(^5\) Lysosomal alterations and lysosomal enzyme activity after myocardial ischemia or infarction have also been extensively described in older literature. It will be interesting in light of the new information to revisit these paradigms and determine whether the release of cathepsins is because of cellular damage, regulated release concomitant with a localized acidification, or both.

The endogenous inhibitors of cathepsins, the cystatins, are also regulated in pressure overload–dependent cardiac remodeling. Cheng et al\(^2\) show that cystatin C mRNA and proteins are increased in failing human and rat hearts. In vascular endothelial cells and smooth muscle cells, inflammatory cytokines either do not increase or decrease expression of cystatin C.\(^6\) Because the sources of cystatin C in the remodeled heart are not known, the increases seen in cystatin C levels in pressure overload–dependent cardiac remodeling may reflect separate regulatory pathways and sources.

It is, thus, possible that, similar to constant myocardial MMP activation, activation of cathepsins and their inhibitors may contribute to the LV remodeling process by effective matrix destruction. Ultimately, the interest here is in the development of inhibitors of cysteine proteinases as therapeutic targets. However, lessons learned from pan-MMP inhibitors suggest that inhibiting one class of proteinases and significantly reducing total matrix destruction in the remodeled myocardium should be approached with caution.

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Inflammatory cytokines increase both the expression of cathepsins and the release of lysosomal cathepsins into the extracellular space. The release of lysosomal cathepsins is accompanied by a translocation of the lysosomal H+-ATPase to the plasma membrane. The mechanism of this process is not known. The plasma membrane H+-ATPase creates a local acidification milieu allowing for cathepsin activity. The local cathepsin activity may include elastinolytic/collagenolytic activity and activation of pro-MMPs. The MMPs are not active in the acidic environment but can diffuse to areas of neutral pH where they degrade matrix. Local cathepsin activity can also lead to anoikis-dependent apoptosis.

References


Digesting the Remodeled Heart: Role of Lysosomal Cysteine Proteases in Heart Failure
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