Matrix Reloaded
The Matrix Metalloproteinase Paradox
Anna N. Panek, Michael Bader

Chronic hypertension leads to adaptive processes in the heart, called remodeling, which are characterized by hypertrophic changes of cardiomyocytes and by structural alterations of the extracellular matrix. Although these processes are initially compensatory and preserve cardiac contractile performance, they finally lead to left ventricular (LV) dilatation and heart failure. Thus, factors playing a crucial role in remodeling are promising therapeutic targets.

Matrix metalloproteinases (MMPs) are proteolytic enzymes that are intimately involved in extracellular matrix remodeling. This family of >20 endopeptidases consists of collagenases (such as MMP-1 and MMP-13), stromelysins (MMP-3), and gelatinases (MMP-2 and MMP-9). The activity of MMPs is controlled by endogenous inhibitors called tissue inhibitors of metalloproteinases (TIMPs).

MMP-2 and MMP-9 are expressed by a multitude of cell types including cardiac myocytes and fibroblasts. It was reported that both enzymes are highly upregulated in hypertrophic and failing hearts, and they have been implicated in the progression of ventricular dilatation and the development and failure. However, MMP-2 and MMP-9 degrade type IV and V collagens, fibronectin, gelatins, laminin, and elastin, proteins that are accumulating in the damaged myocardium undergoing fibrosis. Thus, it is not clear whether MMPs are involved in the pathogenetic process of fibrosis or whether their upregulation represents a vain compensatory reaction.

In the current issue of *Hypertension*, Matsusaka et al evaluate effects of MMP-2 on structural and functional alterations of the left ventricle during cardiac hypertrophy because of pressure overload induced by transverse aortic constriction. They used an MMP-2 knockout (KO) mouse model, which allowed them to obtain direct evidence for the role of MMP-2 in myocardial remodeling and heart failure. The most striking observation of this study was the inhibition of myocardial hypertrophy and fibrosis in MMP-2 KO mice in comparison with wild-type (WT) animals under pressure overload conditions. LV wall thickness and LV mass increased in WT but much less in MMP-2 KO. Histological analysis showed increased deposition of collagen and myocyte enlargement in WT animals after transverse aortic constriction. Also, these effects were markedly ameliorated in MMP-2 KO mice. Taken together, the study demonstrates that MMP-2 ablation has protective effects on LV tissue under conditions of long-term pressure overload. Thus, MMP-2 seems to promote myocardial remodeling including hypertrophy of cardiomyocytes and, paradoxically, also fibrotic changes in the interstitium.

This study is in line with recent reports showing reduced hypertrophy and fibrosis after myocardial infarction in MMP-2 KO mice and after pressure overload in MMP-9 KO mice. Concordantly, pressure overload resulted in aggravated cardiac damage in TIMP-3 KO animals, in which MMP-2 and MMP-9 are activated, and myocardial infarction led to exaggerated LV hypertrophy in TIMP-1 KO mice.

Theoretically, a reduction of the proteolytic activity of gelatinases by genetic approaches or by inhibitors should lead to an accumulation of their substrates, in particular, collagens, and vice versa. The above-mentioned studies demonstrate unequivocally the opposite and justify the conclusion that MMP-2 and MMP-9 must have additional functions in the cardiac remodeling process other than the degradation of collagens. Accordingly, MMPs, including MMP-2 and MMP-9, have been shown to be involved in tissue invasion of inflammatory cells, such as macrophages, neutrophils, and lymphocytes, by several mechanisms. Some of the MMP degradation products of matrix proteins function as potent chemoattractants for these cells. In addition, cytokines, such as interleukin 1β, transforming growth factor β, and tumor necrosis factor (TNF) α, are activated by MMPs and mediate the infiltration and potentiate the actions of inflammatory cells. Moreover, leukocytes themselves use MMPs to pave their way through the different layers of the vascular wall when invading tissues. When these cells reach the myocardium, they release mediators, such as TNF-α and transforming growth factor β, which, in turn, are involved in the activation of cardiac fibroblasts and the hypertrophy of cardiomyocytes. Indeed, Matsumura et al showed that genetic ablation and pharmacological inhibition of MMP-2 reduced macrophage infiltration and thereby prevent cardiac rupture and delay remodeling after myocardial infarction. This indicates that a reduced inflammatory response results in the protection of failing myocardial tissue. Thus, it remains an intriguing speculation that the cardioprotective effects of MMP-2 ablation, as described by Matsusaka et al., are related to an attenuated inflammatory response in the pressure-overload model. This finding may render MMP-2 a potent target for a cardioprotective therapy in patients with hypertension.

However, inhibition of MMP-2 may also be detrimental in heart disease. In another recent report, the same group showed that ablation of MMP-2 under conditions of cardiac inflamma-
tion induced by transgenic TNF-α aggravates heart failure.\textsuperscript{10} In this case, the authors found an increase in inflammatory cell recruitment into the myocardium in MMP-2 KO/TNF-α transgenic mice.

In conclusion, MMPs play a crucial role in the complex interplay between inflammatory and vascular cells, fibroblasts, and cardiomyocytes, which can result in myocardial protection or destruction, depending on the etiology of the cardiac damage. Thus, any kind of therapeutic intervention targeting these enzymes has a great potential but should also be carefully evaluated.

References

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