Imaging of Matrix Metalloproteinase Activation and Left Ventricular Remodeling

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Introduction

Left ventricular (LV) remodeling is both a physiologic and, in its progression, a pathologic process that has direct implications on morbidity and mortality following cardiac injury, leading toward a downward spiral to heart failure. It is increasingly being recognized that LV remodeling encompasses a complex and dynamic interaction of extracellular matrix proteins, myocytes, and neurohormonal elements. Recent research has highlighted the role of matrix metalloproteinases (MMPs) in the modulation of the extracellular matrix and in the progression of LV remodeling in the immediate postinfarct period and in late stages of heart failure. Although much research has focused on plasma measurement of MMPs as well as tissue inhibitors of MMPs (TIMPs), in vivo imaging of MMPs provides a novel method to track biologically relevant activity in the myocardium and monitor LV remodeling as it is occurring. Noninvasive imaging techniques have the potential for estimating prognosis in addition to being a tool for treatment monitoring. The role of targeted noninvasive imaging of MMPs for better defining the underlying pathophysiology of the postinfarction remodeling process and for the identification of those patients potentially most at risk for LV remodeling are the primary focus of this review.

Pathophysiology of LV Remodeling

LV remodeling encompasses the changes in size, shape, and cardiac function that occur after myocardial injury. LV remodeling involves a sequence of events: infarct expansion, infarct zone dilation, progressive global LV dilation, hypertrophy of noninfarct zones, and overall ventricular remodeling, with the LV assuming a more spherical geometry. On the cellular level, remodeling involves myocyte hypertrophy, apoptosis, necrosis, fibrosis, collagen, and fibroblast proliferation. Ultimately, progressive remodeling is maladaptive, leading to increased end-systolic volume (ESV) index and depressed ejection fraction (EF) [1].

Recent research has focused on the diverse components of the myocardium, interstitium, fibroblasts, collagen, and coronary vasculature, as well as the diversity of cellular processes including ischemia, cell necrosis, and apoptosis. The myocardium is composed of a highly regulated extracellular matrix (ECM) that supports and orients myocytes to allow for coordinated contraction [2•]. The ECM is composed of matrix proteins, basement membrane proteins, proteoglycans, and glycosaminoglycans, which interact with cells via integrin receptors and signaling molecules. Together, the ECM provides support for myocytes as well as storage of growth factors, hormones, and cytokines. Although the myocyte encompasses the largest volume, the cardiac fibroblast is the most abundant cell in the myocardium and performs a regulatory role in the ECM. After injury, scarring and fibrosis occur in association with a net increase in the ECM.

Remodeling of the LV occurs with early ECM disruption leading to infarct expansion as well as infarct zone...
MMPs are a family of zinc-dependent proteolytic enzymes that degrade a wide spectrum of extracellular matrix proteins. MMPs are found in the ECM of several tissues and play a role in a number of normal physiologic processes such as embryonic development, organ morphogenesis, bone remodeling, wound healing, angiogenesis, and apoptosis. The same group of MMPs have been implicated in several pathologic processes including arthritis, cancer, cardiovascular disease, nephritis, skin ulceration, gastric ulceration, corneal ulceration, liver fibrosis, emphysema, and fibrotic lung disease.

There are approximately 25 different types of MMPs, which can be separated into subgroups based on their molecular structure, substrate specificity, and whether they are secreted or membrane bound. Members of the MMP family are identified by a numbering scheme as well as their subtype. The subgroups include gelatinases, collagensases, stromelysins, and membrane-type MMPs. Gelatinases, such as MMP-2 and MMP-9, can degrade type IV collagen and gelatins. Collagenases (MMP-1, MMP-8, MMP-13) cleave fibrillar collagens type I, II, and III. Stromelysins include MMP-3, MMP-10, and MMP-11, and can degrade several components of the ECM, such as laminins, fibronectin, proteoglycans and some collagens. Membrane-type MMPs are membrane-bound MMPs that also degrade several components of ECM, such as ECM glycoproteins and proteoglycans and activate other MMPs.

MMPs are regulated on at least three different levels: synthesis, activation, and inhibition. First, synthesis of MMPs is controlled at the transcriptional level through several signaling pathways via cytokines, growth factors, and neurohormones, such as interleukin (IL)-1, tumor necrosis factor-α, and IL-6. Activation of MMPs occurs via secreted MMPs through proteolytic cleavage of a propeptide. The proform of secreted MMPs requires cleavage of 10 kD propeptide in the amino terminus through a cysteine switch. With cleavage of the propeptide the active site is exposed. In vivo, these pro-MMP forms are activated by serine proteases and other MMPs, such as the membrane-bound MMPs. In the case of MMP-2 and MMP-9, the prototypical gelatinases, the proteolytic cleavage can occur by the plasminogen system by urokinase-type plasminogen activator.

In animal models of myocardial injury a causal relationship between MMP activity and adverse remodeling may be extracted. Transgenic MMP and TIMP knockout mice have demonstrated that removal of MMP inhibition by TIMP-1 deficiency exacerbated LV remodeling compared with wild-type mice, whereas deletion of MMP-9 attenuates LV remodeling. Pharmacologic treatment of experimental animals after MI with an MMP inhibitor also has demonstrated the cause and effect relationship of MMPs and remodeling as well as potential treatment venue. MMP expression was shown to precede LV dilation in a rat model of chronic volume overload, demonstrating the potential predictive value of MMP quantification.

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In this rat model of chronic volume overloading, treatment with a broad-spectrum MMP inhibitor led to improved LV geometry and function when compared with untreated volume overloaded rats. Other preclinical trials of MMP inhibition have also shown attenuated LV remodeling. Selective MMP inhibition, sparing MMP-1, MMP-3 and MMP-7, also proved effective in attenuating LV remodeling in similar infarct sizes of preclinical studies, when controlling for other factors.

MMP and spatial variability

MMP expression has also been shown to be region specific, with increases in MMP-9 greatest in the bordering and ECM deposition. MMPs contribute to this initial phase of infarct expansion through proteolytic actions on the ECM as well as the progressive global dilation that ensues. ECM disruption in noninfarct zones leads to overall dilation, myofibroblasts and infarct zone scar remodeling, ECM deposition, and noninfarct zone fibrosis. These changes translate into greater LV dysfunction leading toward heart failure and eventually end-stage heart disease. In myocardial remodeling, the extracellular remodeling is a critical step and the failure of the ECM to support the myocytes causes thinning and instability of the myocyte fascicles that leads to infarct expansion.

LV remodeling can be roughly divided into two stages, early and late [3]. Early remodeling after myocyte injury leads to infarct expansion causing ventricular dilation from degradation of collagen by serine proteases and MMP activation. Late remodeling occurs when the subsequent alteration of wall stress leads to signaling that stimulates myocyte hypertrophy to dissipate the increased wall stress [4]. As a result, progressive remodeling and the associated diminished cardiac function are associated with poor outcome and decreased 10-year survival following myocardial infarction (MI) [6]. The early identification of patients at risk for both early and late postinfarction LV remodeling would be extremely valuable for risk stratification of patients after MI.

MMPs Subtype and Activation

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