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Commentary

Targeting matrix metalloproteinases in heart disease: Lessons from endogenous inhibitors

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ABSTRACT

Basic pharmacological/transgenic studies have clearly demonstrated a cause–effect relationship between the induction and activation of matrix metalloproteinases (MMPs) and adverse changes in the structure and function of the left ventricle (LV). Thus, regulation of MMP induction and/or activation would appear to be a potential therapeutic target in the context of cardiovascular disease, such as following myocardial infarction (MI). However, pharmacological approaches to inhibit MMPs have yet to be realized for clinical applications. The endogenous inhibitors of the MMPs (TIMPs) constitute a set of 4 small molecules with unique functionality and specificity. Thus, improved understanding on the function and roles of individual TIMPs may provide important insight into the design and targets for pharmacological applications in LV remodeling processes, such as MI. Therefore, the purpose of this review will be to briefly examine biological functions and relevance of the individual TIMPs in terms of adverse LV remodeling post-MI. Second is to examine the past outcomes and issues surrounding clinical trials targeting MMPs in the post MI context and how new insights into TIMP biology may provide new pharmacological targets. This review will put forward the case that initial pharmacological attempts at MMP inhibition were over-simplistic and that future strategies must recognize the diversity of this matrix proteolytic system and that lessons from TIMP biology may lead to future therapeutic strategies.

1. Introduction

Heart failure (HF) remains a major cause of morbidity, mortality, and constitutes a significant portion of medical care costs. In general clinical terms, HF is manifested by defects in cardiac pump function (ejection, filling, or a combination of both), which in turn will cause clinical signs and symptoms that are often progressive and result in emergent presentation and hospitalization. While the current standard of care for HF is appropriately focused upon the reduction in symptomatology, therapeutic strategies which specifically target the fundamental underpinnings of the HF process remain an unmet medical need and hence an important area for research and development. The term HF is not defined by a specific pathological stimulus but rather the downstream consequence of multifactorial events with the underlying causes being quite diverse, and as such, classification schemes can be problematic. Nevertheless, a generalized dual classification system has been developed that encompasses the HF presentation, and key underlying physiological manifestations have emerged [1]. Specifically, patients with a HF presentation and primarily left ventricular (LV) systolic dysfunction such as that which can occur following a myocardial infarction (MI), or that of primarily LV diastolic dysfunction, which can occur with a sustained pressure overload such as hypertension. The changes in LV geometry and myocardial structure, often referred to as LV remodeling, can also be different in these two classifications, and as such the therapeutic targets and pathways may also be distinctly different. For the purposes of this review and to maintain focus, the prototypical example of LV remodeling and progressive HF, as it applies to myocardial infarction (MI), will be utilized.

Despite significant improvements in the management of acute coronary syndromes and myocardial ischemic events, residual injury to the affected region of the myocardium (MI) can occur. This myocardial injury sets in motion a number of cellular and extracellular matrix (ECM) events. The death of cardiac myocytes in the context of ischemic injury and MI first occurs through the classical cell death pathway, necrosis. This region of necrotic

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myocytes then causes a cascade of biological events, which include the expression of inflammatory molecules and egress of inflammatory cells, proliferation and transdifferentiation of fibroblasts, and the induction of ECM degradation/synthetic pathways [2,3]. While this process is initially considered to be an appropriate and adaptive wound healing response, the persistence of these biological events, particularly that of continued ECM turnover, is considered to be maladaptive and contribute to the pathophysiology of LV remodeling and progression to HF [3–5]. Most specifically, the changes in ECM structure can contribute to a structural milestone in adverse post-MI remodeling–infarct expansion [5,6]. The affected region following the MI that contributes to infarct expansion, progressive LV remodeling, and systolic dysfunction not only is composed of the MI region itself but can also affect the viable myocardium surrounding the MI. Significant changes within the ECM occur during all time points post-MI and likely contribute to the overall adverse LV remodeling process. Firstly, the inflammatory response causes the release of matrix metalloproteinases (MMPs) as well as other proteases to degrade the ECM and allow for margination of inflammatory cells [8–10]. However, with a persistent inflammatory state, MMP induction will also destabilize the newly formed ECM and the nascent scar. Secondly, the transformed fibroblast population within the MI region as well as the surrounding viable myocardium causes a shift in the relative balance of MMPs and endogenous tissue inhibitors of MMPs (TIMPs) [6,8,9,11–14], favoring accelerated ECM turnover and a failure of mature scar formation. These observations led to significant initial exuberance by both industry and medical academia for the development of pharmacological reagents, which would inhibit MMP activity for the purposes of interrupting adverse LV remodeling post-MI [15–24]. However, this initial enthusiasm has been tempered by the recognition that MMPs constitute a diverse family of enzymes, all with unique functionality, and that only a subset of these MMPs may hold therapeutic relevance in terms of post-MI remodeling [6,21–23,25,26]. At the same time, there is growing awareness that the TIMPs may also be multifaceted in terms of biological roles relevant to the post-MI remodeling process well beyond that of inhibition of active MMPs [27–36]. Specifically, there are 4 known TIMPs, which appear to be differentially regulated in terms of temporal expression following tissue injury, may differentially affect MMP activity, and regulate fibroblast growth and viability [27–32,35–43]. Therefore, the purpose of this review is to place into context the functionality, expression profiles, and potential therapeutic application of these individual TIMPs in terms of post-MI remodeling.

2. TIMPs—Small molecules with diversity of function

The TIMPs constitute 4 unique, small molecular weight proteins (~20 kDa) that are distinctly different gene products with 50% or less homology [27–30]. The first TIMP, TIMP-1, was identified in the late 1970s and TIMP-4 was first described in the late 1990s [44,45], and while initially considered to simply bind to active MMPs in a 1:1 stoichiometric ratio, these molecules have unique and differential effects upon key aspects of ECM biology relevant to the post-MI remodeling process (Table 1). Using primary fibroblast cultures taken predominantly from either myocardial samples or from cancer related regions [27–37], divergent effects of specific TIMPs have been identified with respect to cell growth and viability. For example, TIMP-1 induces a robust effect on fibroblast growth and proliferation, whereas TIMP-2 and TIMP-4 appear to have a more modest or negative effect [29–37,41]. On the other hand, TIMP-1 has been shown to reduce relative apoptosis rates, whereas other TIMPs can accelerate cell death [31,32,37,41]. With respect to TIMP-2, a robust effect on fibroblast transdifferentiation, as defined as a transition to a more contractile phenotype, has been reported [37]. In contradistinction to other TIMPs, TIMP-3 modulates cytokine processing through an inhibition/interruption of a disintegrin–metalloproteases (ADAMs), including both ADAM-10 and ADAM-17 [27–30,39,40].

Other unique differences in TIMPs can be found in the relative affinity for MMP inhibition as well as activation. Specifically, TIMP-1 has been shown to have a very low affinity for the transmembrane MMPs, such as MT1-MMP [27,28,46]. Since MT1-MMP has been shown to play a significant role in ECM remodeling, including post-MI remodeling [47,48], then the weak inhibitory capacity of TIMP-1 on MT1-MMP likely holds relevance when considering TIMPs as a therapeutic. With respect to TIMP-2, it has now been well established that an activation complex is formed between proMMP-2, TIMP-2, and MT1-MMP, which will facilitate activation of MMP-2 [27,35,47,49]. Moreover, while other TIMPs, such as TIMP-4, can bind to pro-MMP-2, these pro-MMP-2/TIMP-4 complexes do not appear to facilitate MMP-2 activation [27,28,35,36]. In fact, in-vitro kinetic studies have identified TIMP-4 will inhibit the interaction and activation of pro-MMP-2 via the TIMP-2/MT1-MMP cascade and is also a potent inhibitor of MT1-MMP [27–29,35,36,42,50]. Thus, a duality of function exists for TIMP-2 whereby both MMP activation and inhibition can occur simultaneously and provide for a very precise localization of ECM turnover. With respect to TIMP-4, the direct and indirect effects on MMP activation and activity, along with the relatively restricted expression pattern to that of hollow muscular organs, such as the heart and uterus [42,51,52], underscore the unique functionality of each TIMP and potential relevance to the post-MI remodeling process.

While TIMP binding to specific MMP sequences results in both inhibition and activation, there is growing evidence that TIMPs can directly influence cell growth and function through a ligand–receptor mediated pathway [29–34]. In cancer associated fibroblasts, it has been demonstrated that TIMP-1 binds to the membrane receptor CD63 and can cause extracellular signal-regulated kinase activation [31]. In transformed fibroblasts, TIMP-1 induced activation of protein kinase B (Akt) pathway, whereby this cellular transduction event was demonstrated to be MMP

Table 1
Differential biological functionality of tissue inhibitors of MMPs (TIMPs) potentially relevant to post-MI remodeling.

	TIMP-1[a]	TIMP-2	TIMP-3	TIMP-4	References
Cell Growth/proliferation[b]	++	–	+	–	[31–34,36,37,41]
Cell apoptosis	–	+	+	+	[31,36,41]
Cytokine processing			++	+	[27,30]
Fibroblast transdifferentiation	+	+++		+	[36,37]
Pro-MMP complex formation	Pro-MMP-9	Pro-MMP-2	Pro-MMP-2	Pro-MMP-2[c]	[27,30,35,36]
Transgenic deletion and post-MI remodeling	↑ LV dilation	↑ LV dilation	Rupture, ↑ inflammation	LV dilation, accelerated HF	[17,38,40,43]

[a] Weak inhibitor of membrane bound MMPs.
[b] Derived from studies previously in fibroblasts/smooth muscle cell culture.
[c] Does not yield an activation complex.