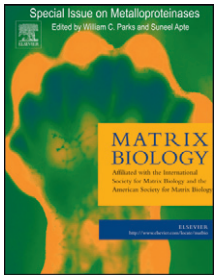
Review



Metalloproteinases promote plaque rupture and myocardial infarction: A persuasive concept waiting for clinical translation

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Abstract

Atherosclerotic plaque rupture provokes most myocardial infarctions. Matrix metalloproteinases (MMPs) have counteracting roles in intimal thickening, which stabilizes plaques, on the one hand and extracellular matrix destruction that leads to plaque rupture on the other. This review briefly summarizes the key points supporting the involvement of individual MMPs in provoking plaque rupture and discusses the barriers that stand in the way of clinical translation, which can be itemised as follows: structural and functional complexity of the MMP family; lack of adequate preclinical models partly owing to different expression patterns of MMPs and TIMPs in mouse and human macrophages; the need to target individual MMPs selectively; the difficulties in establishing causality in human studies; and the requirement for surrogate markers of efficacy. Overcoming these barriers would open the way to new treatments that could have a major impact on cardiovascular mortality worldwide.

Introduction

As previously reviewed in depth [1,2], matrix metalloproteinases (MMPs) are implicated in the intimal thickening that is responsible for restenosis after angioplasty and the occlusion of venous artery bypass grafts. On the other hand, MMPs and other proteinases can provoke net destruction of the vascular extracellular matrix (ECM) in late-stage atherosclerosis [3,4]. Importantly, loss of collagen in the shoulder regions of thin-capped fibro-atheromas could reduce tensile strength and precipitate plaque rupture, leading to myocardial infarctions (MIs) or strokes [5]. Given that MIs and strokes together account for as much as a third of deaths worldwide, preventing plaque rupture is the most pressing task currently facing vascular biologists. MMPs also have a clear role in destroying the ECM in abdominal aortic aneurysms (AAAs) [6] and this has led to pivotal trials with tetracyclines, which are pleiotropic inhibitors of MMP secretion and activity [7].

How can the same proteinase systems mediate intimal thickening and fibrosis on the one hand but ECM destruction and thinning of the fibrous cap or aneurysm rupture on the other? Counteracting adverse and beneficial roles of different proteinases could be responsible and, if so, identifying harmful proteinases that can be safely inhibited without causing unwanted side-effects becomes an attractive treatment strategy. Alternatively, a wider complement or higher levels of proteinases accompanied by reduced proteinase inhibitors could tip the balance towards ECM destruction rather than fibrosis. In this case identifying the cellular sources of different MMPs and the regulatory mechanisms underlying their excessive production comes to the forefront. Both approaches are considered in detail below. This short perspective cannot be comprehensive. For more details the reader is referred to other recent reviews of the function [8–11] and regulation [12,13] of MMPs and TIMPs.

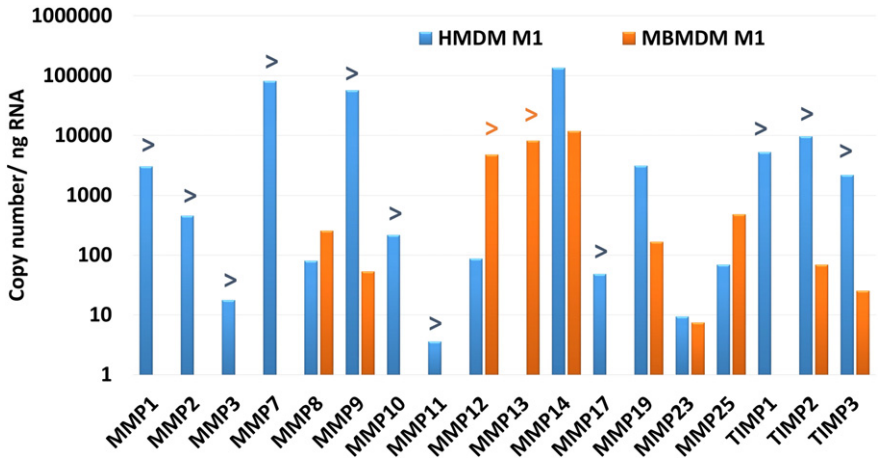

Fig. 1. Comparison of MMP and TIMP mRNA expression in human and mouse macrophages. Steady-state levels of mRNA for human monocyte-derived macrophages (HMDM) differentiated in CSF-1 and stimulated with LPS and IFNγ for 18 h are compared to those for mouse bone-marrow derived macrophages (MBMDM) under the same conditions. The symbol > indicates a difference of at least 10 times in the published values between human [20] and mouse [21] macrophages.

Complexities within the MMP family and beyond

As reviewed before [14] and elsewhere in this focussed issue, MMPs comprise a family of at least 23 active proteinases. Most MMPs are secreted proteins but the six membrane-type MMPs (MT-MMPs) are either integral membrane proteins or contain membrane anchors. Because of their overlapping substrate preferences there is ample possibility for redundancy and compensation that would frustrate selective drug intervention. Moreover, other classes of proteinase, including serine proteinases and cysteinyl cathepsins act in concert with or in parallel to MMPs [14]. Furthermore, MMPs have many non-matrix substrates [15] and their individual activities therefore result in surprisingly complex degradomes [16]. Finally, MMPs may have pleiotropic actions in different physiological and pathological processes, which are well illustrated by the breadth of articles in this focussed issue. In looking for therapies, one hopes to target a specific adverse effect of MMPs whilst leaving intact essential physiological functions, thereby avoiding a narrow or non-existent therapeutic window.

Lack of adequate preclinical models — a mouse is not a man

None of the current mouse models of plaque rupture has gained unequivocal acceptance [17]. Spontaneous plaque ruptures have been described in fat-fed ApoE null mice [18]. However, the nature of the mouse ruptures is so different morphologically from that in humans that many authors have preferred to use the term intra-plaque haemorrhage [19]. Other mouse models have been developed that use extreme haemodynamic or genetic interventions to increase the rate of plaque disruption [17]. Whether these replicate the human disease accurately and are therefore useful for intervention studies is yet to be established. In the absence of direct models of plaque rupture, most animal studies record the same histological surrogates as used in human plaques. These include bigger plaques, larger lipid cores, less collagen, an increased ratio of macrophages to VSMCs and thinner plaque caps, although fewer VSMCs and thin caps could also indicate less advanced plaques. These limitations need to be borne in mind when considering the effects of genetic manipulation of MMPs summarized below and in more detail elsewhere [7].

Another problem is the possibility that mice and men regulate a different spectrum of proteinases, including MMPs, during physiological responses. There is a huge difference in relative expression levels of different MMP mRNAs between human [20] and mouse [21] monocyte-derived macrophages isolated and differentiated under very similar conditions (Fig. 1). The MMP-1 gene is lacking from the rat and mouse genomes and therefore MMP-1 mRNA is undetectable in mouse macrophages, whereas it is abundant in human macrophages (Fig. 1). Conversely, another collagenase, MMP-13, is undetectable in human but abundant in mouse macrophages, which implies that collagenolysis is mediated by different proteases in the two species. Similarly, MMP-12 may be the most important elastase in mouse macrophages but MMP-7 in humans [22]. Indeed, MMP-12 is much more abundant in mouse than human macrophages whereas the opposite is true for MMP-7 (Fig. 1). The mRNAs for gelatinases, MMP-2 and MMP-9 are also much more abundant in