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MMPs as therapeutic targets – still a viable option?

Barbara Fingleton
Dept of Cancer Biology, Vanderbilt University Medical Center, 734 PRB 2200 Pierce Ave, Nashville, TN 37232-6840, USA, Email: Barbara.fingleton@vanderbilt.edu, Phone: +1 (615) 936-5877, Fax: +1 (615) 936-2911

Abstract

Matrix metalloproteinases (MMPs) appear to be ideal drug targets – they are disease-associated, extracellular enzymes with a dependence on zinc for activity. This apparently straightforward target, however, is much more complex than initially realized. Although disease associated, the roles for particular enzymes may be healing rather than harmful making broad-spectrum inhibition unwise; targeting the catalytic zinc with specificity is difficult, since other related proteases as well as non-related proteins can be affected by some chelating groups. While the failure of early-generation MMP inhibitors dampened enthusiasm for this type of drug, there has recently been a wealth of studies examining the basic biology of MMPs which will greatly inform new drug trials in this field.

Keywords

Review; animal models; side-effects; inhibitors

Introduction

As we have seen from accompanying papers, there is considerable evidence implicating MMP activity in various pathologies including cancer, diseases of the central nervous system (CNS) and disorders of the immune system. Given the many physiological processes that are controlled by MMP activity, it is unsurprising that aberrant proteolysis is a significant problem in multiple disease settings. Studies using relevant disease models in MMP-deficient animals have demonstrated the contribution of MMPs to disease processes. These studies have, however, revealed some surprising, apparently protective functions of various MMP family members. Hence broad-scale MMP inhibition can have both advantageous and problematic consequences. Here we will examine some of these as well as the settings in which inhibiting MMPs can be a successful therapeutic approach. As many readers will be aware, pharmacological MMP inhibitors (MMPIs) have failed in multiple clinical trials [1;2]. However we believe that these failures should not define the field and will suggest ways in which future iterations of MMPIs could potentially be of significant therapeutic benefit.

Evidence for targeting MMPs

Proteolysis is a very effective mechanism for introducing diversity into the protein complement of an organism. Unlike many other modifications however, this is an irreversible change. For this reason, although proteases are a major group within the proteome [3], activity levels of

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proteases such as MMPs are tightly controlled [4]. This is logical since rampant proteolysis would not be an efficient way to maintain homeostasis. In disease settings however, the expression levels of individual proteases as well as the number of different expressed proteases increases. This gives us our first rationale for targeting MMPs in disease – they are primarily disease-associated enzymes and dysregulated MMP expression is associated with multiple disease types. In the cardiovascular area, MMPs have been strongly associated with aneurysms [5;6], with atherosclerotic plaque rupture [7], with myocardial infarction, left ventricular remodeling and ultimate cardiac rupture [8-10], as well as cerebral ischemia events [11]. MMP expression is raised in multiple tumor types [12] and mostly, these increases correlate with decreased survival [13]. In both rheumatoid- and osteo-arthritis, MMPs are considered to be significantly responsible for the matrix degradation that characterizes these diseases [14;15]. Respiratory disorders including idiopathic pulmonary fibrosis [16], asthma [17;18], emphysema [19;20] and acute respiratory distress syndrome [21;22] are also strongly associated with MMP activity.

A variation on simple expression correlations are those in which promoter polymorphisms that are associated with variant expression levels are also correlated either with disease susceptibility or progression [23]. In the case of MMP-9, a greater number of CA repeats or the C substitution at the -1562 promoter site is associated with increased expression of MMP-9 although the responsible factor(s) for this have not yet been identified. Interestingly, the -1562C/T substitution has been reported to have no effect on basal MMP-9 plasma levels in healthy subjects [24] but leads to greater than 5-fold increase in mRNA expression in patients with coronary artery disease [25]. In the case of the MMP-1 promoter, the biological basis of increased expression from a guanine insertion at -1607 has been well-characterized. The insertion creates a binding site for the transcription factor ets-1 which then leads to increased gene expression [26]. In the case of MMP-3, possible insertion of adenine in the promoter creates a 5A or 6A allele. The 5A allele is associated with higher expression levels, apparently through differential binding to NF-kB transcription factor family members [27]. Of these type of studies, perhaps the association between MMP3 promoter polymorphisms and coronary artery disease are the best analyzed, although the results are far from clear. While particular attributes of the study population can affect the data (e.g. gender, smoking history or ethnic group), in general the 5A polymorphism of MMP3 results in higher levels of enzyme expression which is associated with instability of atherosclerotic plaques and hence likely infarction events [27].

Some polymorphisms are considered functional i.e. related to altered expression or function of protease while others are silent i.e. in non-coding regions or changes that do not affect the amino acid sequence. The functional polymorphisms are more interesting from a biological perspective as they suggest cause and effect. There are differences in how these studies are conducted – many examine susceptibility, *i.e.* whether a particular genotype (or haplotype) is more or less prevalent in those with disease than controls. Some studies perform more complex analyses in which disease characteristics are examined. For example, in rheumatoid arthritis although the haplotype of MMP1 1G / MMP3 5A is not associated with susceptibility, it does correlate with the extent of radiographic joint destruction i.e. disease severity [28;29]. Similarly in sarcoidosis and tuberculosis, Ninomiya et al found a correlation between MMP1 1G genotype and disease severity as determined by the number of organs involved or cavity formation in tuberculosis [30].

Animal Models

Expression analyses provide evidence that a protein target is present at high levels when a disease is manifest and, ideally, absent in the healthy state. However these types of studies cannot determine whether the presence of the particular protein is in any way associated with

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the disease process or whether it is merely an ancillary event. Using animal models in which expression can be manipulated provides some evidence for the contributory effect of the particular protein to the disease process. In the case of MMPs, there are now described mouse lines that have been rendered genetically deficient in one of over 13 different proteases. In the vast majority of cases, MMP-null animals have been made as constitutive knock-outs, that is they are genetically deficient in the relevant enzyme since conception. Somewhat surprisingly, only MMP14-null mice show a significant phenotype related to total lack of the enzyme [31; 32]. MMP-2, MMP-9, MMP-13 and MMP-20 mice all have subtle phenotypes some of which resolve as the mice age [33-37]. In most cases, however, challenge with some type of pathogenic situation will induce a difference between mice proficient and deficient for particular enzymes. Many of these types of studies support roles suggested by the expression studies discussed previously. For example, the clear contribution of MMPs to tissue destruction in arthritis [15], roles for MMP-9 and MMP-3 in hemorrhagic stroke [11] and the involvement of multiple MMPs both in cardiovascular diseases [38] and in disease progression in various types of cancer [39;40]. Some surprising functions of MMPs have also been highlighted by animal studies. In particular the interaction between MMPs and immune cells or immune system proteins has been demonstrated now in multiple disease settings. In vertebral disc resorption both MMP-3 and MMP-7 are required, not for matrix degradation as initially hypothesized, but for generation of soluble signaling factors such as TNF-α that function to recruit and activate macrophages [41;42]. MMP3 is implicated in the initiation of an early and lethal cytokine response following *Salmonella typhimurium* infection [43]. MMP2 is an important processing enzyme for chemokines [44], which can have effects on pathologies as diverse as asthma [45] and AIDS-associated dementia [46]. A thorough discussion of the multiple roles for different MMPs in the immune system is given in the article by McGuire and Maniconi.

Limitations of Animal Models

Although studies in MMP-deficient animals are highly suggestive of roles for MMPs in various disease processes, there are some caveats to be aware of. Firstly, as previously noted, most of the MMP-null animals are constitutively-null. Hence some of the apparent effects of deficiency apparent in pathological situations may be reflective of an altered physiology that developed as a way to circumvent the MMP deficiency, thus the differing effect seen in the null animal is not actually due to the lack of the MMP at the time of the disease. One such change is compensatory increases in other MMPs. In the involuting uterus of either MMP3 or MMP7 null mice, there is upregulation of MMP7 or MMP3 respectively as well as MMP10 [47]. In MMP13-null mice, MMP8 expression is enhanced in healing wounds [48], while in autoimmune encephalomyelitis, MMP2-null mice have enhanced levels of MMP9 [49]. Secondly, there is a concern that mouse models are unable to replicate the complexity of any human disease. In many cases, mouse models serve to replicate specific processes or sets of processes within a disease but not the whole spectrum of physiological changes that occur in humans in the disease setting. For example, left ventricular hypertrophy is a frequently fatal sequel to myocardial infarction [8]. It is caused by the heart muscle struggling to make up for decreased blood flow due to a blocked artery by increasing pressure. A mouse model in which the heart muscle is “banded” also causes acute left ventricular hypertrophy [38] although this is in the absence of the other physiological events that would have occurred in a person with atherosclerotic-related myocardial infarction, for example. Atherosclerotic plaque rupture itself does not readily occur in animal models and thus mouse models examining effects of MMPs tend to focus on specific characteristics such as plaque diameter or thickness of the fibrous cap [50]. Finally, there are some diseases for which no adequate mouse model exists. An example is idiopathic pulmonary fibrosis for which there is significant evidence for the involvement of MMPs but no mouse model to properly test their role [16]. Use of larger animals

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including rabbits, pigs and sheep can result in more physiologically relevant disease models [51] but doesn't allow evaluation of phenotypes in genetically-deficient situations.

Results obtained with genetically-deficient animals that can be recapitulated with pharmacological agents offer the strongest evidence for involvement of MMPs in particular disease processes. This has been demonstrated clearly in various vascular disease models. Cardiac rupture after ligation of the left coronary artery was profoundly inhibited in either MMP2-null mice or wildtype mice administered an MMP2 selective inhibitor [52]. Aortic aneurysm formation induced by elastase perfusion of the aorta was suppressed in MMP9-null mice or wildtype mice treated with doxycycline, an antibiotic with MMP inhibitory activity [53]. Either genetic deletion of MMP9 or treatment with the broad-spectrum MMPI batimastat resulted in reduced lesion size in a mouse model of cerebral ischemia [54]. A number of cancer models have also passed this test. In the $Apc^{Min/+}$ mouse model of intestinal cancer development, either genetic ablation of MMP-7 [55] or treatment with the MMPIs batimastat [56] or A-177430 [57] resulted in 50-60% decrease in polyp detection. In the RIP-Tag model of pancreatic insulinoma, genetic ablation of MMP9 [58] or treatment at early stages with the MMPI batimastat [59] effectively reduced the number of angiogenic tumors. Spontaneous or experimental metastasis assays with the melanoma cell line B16-BL6 in MMP2 [60] or MMP9-null mice [61] indicated significantly attenuated numbers of metastatic tumor foci which was also seen when wild-type mice were treated with MMPIs such as BMS-275291[62]. Results from knockout murine models have also successfully transferred to drug-treated large animals. For example, mice deficient in MMPs-2 or -9 have reduced neointima formation following vascular injury in a model of restenosis [63;64]. Treatment of rabbits with the broad-spectrum MMPI GM6001 blocked stent-induced vascular wall thickening [65], while similar results were seen with the MMPI batimastat in atherosclerotic micropigs that had undergone balloon angioplasty [66].

Are there situations where MMPs should not be targeted?

When the idea of pharmacological agents that would inhibit MMP function was first suggested, there was a basic assumption that MMPs contributed detrimental activities. Therefore inhibition would be favorable. A significant finding from multiple mouse studies is that MMPs can also be beneficial. This of course should not be surprising as it would not be evolutionarily favorable for development of an entire family of proteases that are only detrimental to an organism! Rather than categorizing specific proteases as “good” or “bad”, it is more helpful to consider activities in particular contexts. In cancer models, MMP3, MMP8, MMP9 and MMP12 knockout mice have all revealed functions of these enzymes that may be considered ‘protective’ or beneficial. In the absence of MMP9, the number of tumors that develop in a transgenic model of skin cancer is reduced, however the tumors that do develop are more aggressive [67]. Similarly in a carcinogen-induced skin cancer model, tumors that develop in MMP3-null mice are more advanced and associated with pulmonary metastasis than in wildtype littermates [68]. In MMP8-deficient animals, again in a skin carcinogenesis model, tumors occur more frequently compared to wildtype controls [69]. Interestingly, in this case, the effect appears to be limited to male animals. In the case of both MMP3 and MMP8, the increased tumor aggressiveness appears related to a function of the relevant enzyme in regulating the immune system most likely through chemokine processing [68;69]. In MMP12-deficient animals, the dominant phenotype is increased angiogenesis within tumors that allows for enhanced tumor growth [70;71]. This increased angiogenesis is partly due to reduced angiostatin production from plasminogen [70], a recognized function of MMP12 [72;73]. Further protective roles of MMPs in the cancer setting have been recently reviewed [74]. Of note, expression studies in humans have also shown protective roles of certain MMPs. In particular, high levels of MMP12 correlate with better prognosis in several tumor types including hepatocellular [75] and colorectal carcinoma [76]. This is in direct contrast to the

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destructive role of MMP12 in emphysema where the elastase-degrading activity of MMP12 clearly contributes to pathophysiology [77;78].

In cardiovascular disease, functions of specific MMPs are also complex. Roles for both MMP2 and MMP9 have been shown in various models of cardiac rupture that can follow myocardial infarction [8]. Loss or inhibition of either enzyme can prevent the acute remodeling associated with disease progression, however continued inhibition can also prevent the healing and ultimate resolution since remodeling is also a physiologically necessary process [52;79]. The complex roles of MMP3 in atherosclerosis are more examples of both positive and negative contributions of a single enzyme. High MMP3 activity can prevent plaque formation however, once plaques form, high MMP3 activity can contribute to instability and ultimately plaque rupture, the problematic event that causes infarction [27;80;81].

Even within the same disease, although at different stages, specific MMPs can show both positive and negative functions. In a mouse model of the kidney glomerular disease Alport syndrome, MMP-2 or -9 null mice are protected during the early stages of disease development, but once proteinuria is evident, the MMP-deficient mice show enhanced disease progression [82]. Hence this is a situation where MMPs contribute to the pathology at the early stages but are protective during later stages. When thinking of using inhibitors in such a scenario, there would have to be careful oversight such that inhibition is only induced before proteinuria occurs and inhibitor therapy must be withdrawn as soon as there is evidence of disease progression.

Reasons for non-efficacy of early MMPIs

One of the biggest questions regarding the original MMP inhibitor clinical trials was how they could fail to show any efficacy despite data from multiple animal models suggesting they would be useful [1;2]. Of course there are always the problems of extrapolating models to the human disease setting. As discussed previously, the animal models are usually concerned with specific disease processes rather than the overwhelming sum of processes that can be present in a human patient. Additionally, in cancer models, drug treatment is usually initiated in animals with minimal metastatic disease unlike human patients with extensive metastatic burden [83]. Perhaps most importantly, it can be difficult to judge dose-limiting toxicities in animals unless they are specifically being looked for. The most frequent side-effect associated with the clinical trials of MMP inhibitors was a musculoskeletal syndrome (MSS) that manifested as pain and immobility in the shoulder joints, arthralgias, contractures in the hands and an overall reduced quality of life for patients. Although trials were initially powered with sufficient patients to be able to see differences between treated and placebo groups, frequently by the end of the trial the numbers receiving drug at adequate dosage had become too small to be able to judge any efficacy. Additionally, there have been questions as to whether even the highest doses used in clinical trials were likely to be effective as, in some cases, they approximated to only fractions of the effective dose used in animals [84]. To alleviate MSS symptoms, patients either withdrew from treatment completely, moved to a lower dose for which there was no indication of expected efficacy, or took “drug holidays”, periods without drugs during which the MSS symptoms would resolve. Multiple studies indicated that development of MSS was dose and time–related, with slightly different kinetics for the different MMPIs [84]. There has been suggestion that development of MSS was the best indicator of successful MMP inhibition since any efficacy in a trial of colorectal cancer patients of the British Biotech compound marimastat correlated with MSS symptoms [85]. This may imply that inhibition of MMPs, or related enzymes, are the reason for the side-effect syndrome or may just indicate that the MSS was the effect most easily achieved and if this didn't manifest then any other effects were unlikely to.

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Multiple reasons have been suggested as to the cause of the MSS symptoms. One early candidate was MMP-1, an enzyme thought to be required for normal collagen remodeling. However, MMPIs that had been designed to avoid inhibition of MMP-1 (e.g. prinomastat) were still associated with MSS [13]. Moreover, rats, which lack MMP-1, show evidence of joint fibrosis following MMPI administration [86]. Another potential candidate cause was members of the ADAM family of proteases, so-called sheddase type enzymes whose catalytic structure is very similar to MMPs. The mercaptoalkyl-type inhibitor BMS-275291 from Celltech/Bristol Myers Squibb was developed to avoid inhibition of the ADAM family[62], yet MSS symptoms were eventually reported in breast cancer patients receiving this drug also [87]. It should, however, be noted that two other longer term trials in prostate [88] and non-small cell lung cancer [89] did not find increased MSS associated with this drug. A current theory that appears to have some merit is that the side-effects are predominantly related to off-target metal chelation. The majority of MMPIs used clinically were derivatives of hydroxamic acid, which has potent ability to chelate zinc and other transition metals including iron III [90]. Selectivity for MMPs is carried in the peptidomimetic backbone, however it has been shown that the backbone does not sufficiently confer selectivity and other non-related metal-containing enzymes can be bound [91]. Perhaps stronger evidence for the MSS side-effects not being related to MMP inhibition *per se*, comes from the use of other drugs. A number of different compounds have been reported to have the ability to block MMP activity or expression. These include bisphosphonates [92;93], statins [94;95] and antibiotics [96]. Tetracycline-derivatives are the best studied of these with respect to MMP inhibition [97;98]. In fact, the only drug marketed for its ability to inhibit MMPs is the low-dose doxycycline periostat, which is indicated for periodontitis. So far, there has been no indication that treatment with any of these drugs is associated with MSS. In the case of the bisphosphonates or statins, large numbers of patients are exposed to the drugs chronically thus these appear to be ideal scenarios in which to examine possible links between MMP inhibition and MSS. One potential difficulty with such interpretation may be the preferred localization of these drugs in vivo – bisphosphonates accumulate in the bone [99] while many of the statin drugs are taken up by the liver [100].

A significant reason why the cause of the MSS side effects is still unknown has been their lack of detection in prevalent mouse models. A rat model that specifically focuses on development of joint effects similar in histopathology to that seen in human patients treated with MMPIs was published in 2003 [86], however no further development of this fibroplasia model has been reported. Evidence for similar effects in mice would allow simple testing of various hypotheses: 1. MSS is due to broad-spectrum MMP inhibition so that systemic TIMP-2 administration will cause the same problem; 2. MSS is related to inhibition of a specific MMP. For example neutralization of MMP14 activity will cause similar effects, given the skeletal phenotype of the MMP14-null mouse; 3. Metal chelation is the reason for the MSS pathology and specific types of zinc binding group will have different effects.

Apart from dose-limiting side-effects, the other main reason for the failure of MMPIs in phase III clinical trials may have been the broad-spectrum nature of these original drugs. As discussed previously, there is now ample evidence that MMPs have complex roles some of which can accelerate disease progression while others are protective. These “good” and “bad” roles are not enzyme-specific but related to disease stage and perhaps even genotype. Hence, optimal use of MMP inhibitors hinges on identifying the deleterious MMP activity and targeting that while sparing any non-contributory or beneficial activities. The similarity in structure of the catalytic pocket of so many of the MMPs has made design of truly specific small molecule inhibitors very difficult [101]. A recently described exception is a specific inhibitor of MMP-13 from Alantos Pharmaceuticals [102]. The actual structure of this inhibitor has not been released however it appears to bind within the catalytic pocket of MMP13 but not to chelate the zinc. This compound has shown efficacy in animal models of osteoarthritis and is poised for clinical testing. An alternative approach to designing small molecule inhibitors is to harness the power

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of antibodies to achieve exquisite selectivity with binding that can neutralize activity of an enzyme. The biotechnology company Dyax Inc have recently described a specific antibody that can neutralize MMP14 activity[1]. This is particularly interesting given the overwhelming evidence that MMP14 is rate-limiting for in vivo collagen degradation and hence tumor cell invasion [103]. However, the severe phenotype of the MMP14-null mouse [31;32] does give cause for concern and emphasizes the need for extensive pre-clinical testing of the MMP14 neutralizing antibody in appropriate settings such as the rat joint fibrosis model before any human testing can proceed.

Since antibodies are now being used frequently as therapeutics [104], there is a lot of knowledge on how best to develop and produce these type of drugs [105]. One potential problem with the antibody approach for chronic diseases is that they must be given as infusions rather than orally. This makes antibody-based therapy very expensive and unlikely to be favored by health services with limited budget resources. Thus continued investigation into small-molecule type drugs is warranted. Reports of specific inhibitors of MMP-13 [106] and of MMP-12 [107] published in the chemical literature suggest that there is continued interest in developing such agents.

Conclusion

Overwhelming evidence from animal models strongly suggests a number of therapeutic areas that would benefit from MMP inhibition. These include various cancers, cardiac remodeling post infarction, chronic obstructive pulmonary diseases, cerebral ischemia, multiple sclerosis and certain skin and eye diseases [108]. The latter two settings have the advantage of allowing local, non-systemic delivery thus potentially avoiding the MSS side-effects that have plagued clinical trials of orally-dosed agents. Until the cause of the side-effects is explained, avoiding the use of MMPIs in chronic scenarios seems wise. Once efficacy can be established in acute settings such as stroke [109;110], or to prevent cardiac rupture post-infarction [52;79], then MMPIs are more likely to be considered for chronic conditions. However, for chronic dosing, agents with minimal toxicity and that show MMP-inhibitory efficacy at achievable doses will be required. Recent reports of specific small molecule or antibody-based inhibitors suggest that this goal can be reached.

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