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The paradox of matrix metalloproteinases in infectious disease

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Summary

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that perform multiple roles in the normal immune response to infection. MMPs facilitate leucocyte recruitment, cytokine and chemokine processing, defensin activation and matrix remodelling. However, excess MMP activity following infection may lead to immunopathology that causes host morbidity or mortality and favours pathogen dissemination or persistence. Here, we review the normal functions of MMPs in immunity and then discuss viral and bacterial infections where excess MMP activity has been implicated in pathology, specifically examining HIV, HTLV-1, hepatitis B, endotoxin shock, *Helicobacter pylori* and *Mycobacterium tuberculosis*. Tissue destruction may be exacerbated further by bacterial-derived enzymes which activate the host pro-MMPs. Finally, the potential for therapeutic targeting of excess MMP activity in infection is considered.

Keywords: HIV, immunopathology, infection, matrix metalloproteinase, tuberculosis

Introduction

Successful eradication of infection by the host requires the influx of effector cells, killing of the pathogen, resolution of inflammation and finally remodelling of the extracellular matrix (ECM). Host-derived matrix metalloproteinases (MMPs) are necessary for the successful execution of these events. However, excessive inflammation following infection may cause tissue damage and MMPs are implicated in causing this immunopathology. Tissue destruction may favour pathogen dissemination or persistence, by breaking down barriers to spread or by creating an immunoprivileged site that is poorly accessed by host immune cells. Here we will overview the role of MMPs in the normal immune response and then consider how MMPs may contribute to infection-related pathology.

Matrix metalloproteinases

MMP activity was first described in the tail of metamorphosing tadpoles, subsequently identified as interstitial collagenase (MMP-1) [1]. Since then, a total of 24 vertebrate MMPs have been described [2], all containing a zinc-binding catalytic domain. A role for MMPs in normal physiological function has been described in development, the menstrual cycle and bone remodelling, and in diseases where aberrant ECM turnover predominates, such as arthritis, tumour invasion and atherosclerosis [3]. Although MMPs were considered initially as purely matrix-degrading enzymes, their known functions have expanded beyond ECM remodelling to include multiple mechanisms of immunomodulation. For example, MMPs may cleave cytokines either to augment or to inhibit their functional activity.

Collectively, MMPs are able to degrade all components of the ECM and they share extensive substrate overlap. MMPs can be classified broadly by substrate specificity into collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10, -11), elastases (MMP-7 and -12) and membrane-type MMPs (MT-MMPs, MMP-14, -15, -16 and -17), which are surface anchored by either a transmembrane domain or a glycosyl-phosphatidylinositol anchor. The catalytic domain is highly conserved and determines substrate specificity, which may be enhanced considerably by the a haemopexin-like domain [3]. However, correlation of *in vitro* proteolysis with activity *in vivo* is often challenging [2]. Furthermore, the substrates of each enzyme may be both cell- and organ-specific.

As one would predict for enzymes that may cause host damage, MMPs are tightly regulated. First, they are rarely stored but instead require increased gene transcription to

drive secretion, the exceptions being neutrophil MMP-8 and -9, which can be released immediately. Secondly, they are secreted as pro-enzymes that undergo proteolytic cleavage for activation, releasing a cysteine residue in the pro-peptide domain from the catalytic zinc, known as the cysteine switch [4]. Thirdly, after secretion MMPs are compartmentalized in close proximity to the cell [5,6]. Finally, their activity is regulated by secretion of specific inhibitors, the tissue inhibitors of metalloproteases (TIMPs), which bind in a non-covalent manner to the catalytic domain [7]. The balance between matrix catabolism and anabolism is complicated further by the ability of MMPs to degrade non-specific protease inhibitors such as α-1 antiproteinase [8,9], thus swinging the local environment further to matrix breakdown.

MMPs are secreted by both inflammatory and stromal cells in response to both exogenous insults and inflammatory cytokines such as tumour necrosis factor (TNF)-α [10] and interleukin (IL)-1β [11]. Additionally, cell contact-dependent signalling may drive MMP up-regulation [12,13]. MMP secretion is down-regulated by diverse cytokines including IFN-γ, IL-4 and IL-10 [14–16], although the regulation of secretion is cell- and stimulus-specific. Intracellularly, signal transduction pathways involving the mitogen-activated protein kinase (MAPK) and prostaglandin E_2/cyclic AMP pathways are key [17–19].

MMPs in normal immune responses to infection

When the host immune system is challenged by an invading organism, it must first recruit leucocytes to the site of infection, eradicate the pathogen and then dampen the response to allow the resolution of inflammation. Matrix metalloproteinases play an important role in this process both by degrading components of the extracellular matrix and by modulating cytokine and chemokine activity. The migration of immune cells to sites of inflammation from the bloodstream requires proteolysis of the basement membrane. *In vitro*, T cell and dendritic cell migration is in part MMP-9-dependent [20–22]. In mice, MMP activity is required for lymphocyte transmigration across high endothelial venules into lymph nodes [23], where antigen will be detected, and MMP-3-deficient mice have deficient neutrophil migration to inflamed lung tissue [24]. Although not proved *in vivo*, it is likely that the migration of all inflammatory cells will require MMP activity.

In addition to opening a path through the ECM for cell migration, MMPs modulate the chemokine and cytokine gradients that drive inflammatory cell recruitment. MMP-1, -2, -3, -7, -9 and -12 can release active TNF-α from the membrane-anchored precursor by a similar mechanism to TNF-α converting enzyme [TACE, A disintegrin and metalloprotease (ADAM)-17] [25]. MMPs can both activate pro-IL-1β proteolytically and cleave the activated form of IL-1β to an inactive form, thereby providing both positive and negative regulation [26,27]. MMPs also modulate chemokine activity. MMP-9 cleaves CXCL8 (IL-8) to a fragment with 10 times the potency of the parent molecule [28]. Conversely, CCL7 monocyte chemoattractant protein (MCP)-3 is cleaved from an active to an inactive form by MMP-2, and the CCL7 fragment acts as a receptor antagonist [29]. This down-regulating mechanism is not limited to MMP-2/CCL7. CCL2 (MCP-1), CCL8 (MCP-2) and CCL13 (MCP-4) are cleaved variously by MMP-1, -3, and -8 to produce receptor antagonists [30]. In addition, MMP-9 cleaves the specific CXC chemokines CXCL1 (GRO-α) and CXCL4 (PF-4) [28]. The full number of interactions described between MMPs and chemokines is beyond the scope of this review. This mechanism of antagonist-producing chemokine degradation may provide an elegant negative feedback loop that dampens inflammatory cell influx and permits the timely resolution of inflammation [30].

MMP-7 knock-out mice demonstrate a deficit of neutrophil migration that led to the identification of a third mechanism whereby MMPs regulate leucocyte recruitment. MMP-7 releases the cell surface proteoglycan syndecan-1, which is complexed with the mouse chemokine CXCL1 (KC). This creates a chemokine gradient that regulates neutrophil influx to the lung alveoli, whereas in MMP-7 knock-out mice neutrophils did not progress beyond the interstitium [31]. Thus MMP-7 is needed to release of a chemokine from its cell surface anchor to allow it to exert a biological activity.

Finally, a fourth role of MMPs in immunity to infection is the activation of defensins, antibiotic peptides that kill bacteria by membrane disruption. MMP-7 in the gut cleaves pro-α-defensins to their active form and MMP-7 knock-out mice take longer to clear infection with pathogenic bacteria [32]. Direct infection of pulmonary epithelial cells by *Escherichia coli* causes MMP-7 up-regulation [33]. Bacterial components such as flagellin also increase MMP-7 in the absence of viable bacteria [34], suggesting that epithelial cell MMP-7 secretion is an early component of the host response to infection [2].

MMPs and pathology in infectious disease

The data outlined above demonstrate that MMP activity is required for the normal immune response to infection. Paradoxically, these host-derived enzymes may also cause infection-related immunopathology (Fig. 1). While appropriate MMP secretion facilitates an effective immune response, host tissue damage may be caused by excess MMP activity, resulting from either increased MMP secretion or decreased TIMP secretion. The number of infectious syndromes where MMPs may be adversely affecting the host is long and an exhaustive review is beyond the scope of this paper (Table 1). We shall now focus on specific aspects of six infections to illustrate the diverse mechanisms by which excess MMP activity has been implicated in pathology.

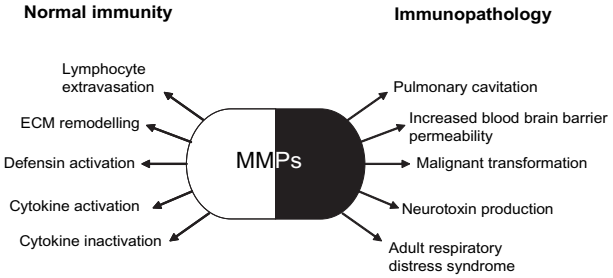

Fig. 1. The paradox of matrix metalloproteinases (MMPs) in infectious disease. MMPs are responsible for numerous functions in the normal immune response, but in infection excess MMP activity results in immunopathology by multiple mechanisms.

HIV infection

HIV dementia is a devastating complication of chronic HIV infection, marked by widespread neuronal death accompanied by the influx of activated macrophages and microglia. The exact mechanisms underlying the neuronal death are unknown but several lines of evidence implicate MMPs. The cerebrospinal fluid (CSF) levels of MMP-9 relate to HIV-associated neurological diseases and dementia [35–37]. HIV infection of monocytes increases MMP-9 secretion *in vitro*, the activity of which results in increased endothelial cell monolayer permeability, which may explain the increased blood–brain barrier permeability that occurs in HIV infection [38]. Soluble HIV-Tat protein alone can up-regulate monocyte MMP-9 secretion [39] and HIV-1 envelope glycoprotein 120 increases MMP-9 secretion by T cells and glioma cells [40]. Intracisternal injection of the HIV Nef protein in a rat model of HIV causes a breakdown of the blood–brain barrier that parallels the changes in CSF MMP-9 levels [41]. Furthermore, pretreatment with an MMP inhibitor abrogates the increased vascular permeability.

Interstitial cells may contribute to the excess MMP activity within the brain, either through directly secreting MMPs or reducing secretion of TIMPs that counteract the MMPs. Astrocytes may be a key source of MMP-9 in the inflamed brain [42], but also prolonged astrocyte activation suppresses TIMP-1 secretion [43]. This correlates with reduced TIMP-1 levels in the CSF of patients with HIV-associated dementia [43], illustrating the importance of the balance between proteases and their inhibitors. Interestingly, anti-HIV medication, which prevents the development of HIV-associated dementia, reduces MMP-2 and -9 secretion by LPS-stimulated astrocytes [44].

HIV envelope diversity is an important determinant of neurovirulence and MMP up-regulation by envelope fragments correlates closely with neuropathology. HIV clones containing brain derived envelope fragments from patients with HIV-associated dementia cause more MMP-2 and -9 secretion from macrophages than clones from non-demented patients [45]. MMP mRNA and protein levels are increased in infected brain tissue from affected patients [45]. Furthermore, inhibition of MMP activity in animal models of HIV neurotoxicity prevents the development of neurological deficits [46,47].

Recently, a novel mechanism of MMP-mediated neurotoxicity in HIV has been identified. Infection of macrophages with HIV increases MMP-2 secretion, which then cleaves a chemokine secreted by astrocytes, stromal cell derived factor-1 (SDF-1, CXCL12), to a highly neurotoxic protein [48]. Neuronal death caused by the SDF-1 fragment is demonstrated both *in vitro* and *in vivo*, while inhibition of MMP activity is neuroprotective. Thus, MMPs are implicated in HIV neuropathology by causing a breach in the blood–brain barrier, by increasing inflammatory cell influx and also by generating neurotoxic products.

Table 1. Infections and syndromes where matrix metalloproteinase (MMP) activity is implicated in causing pathology (this list is not exhaustive).

	References
Viral	
HIV	[35–48]
Hepatitis B	[53,54,56]
HTLV-1	[50–52]
HSV	[94]
Viral meningitis	[95]
Bacterial	
Bacterial meningitis	[87,96–99]
Endotoxic shock	[57–59,61–67]
Periodontal disease	[84,93,100]
H. pylori peptic ulcer disease	[69–73]
Hospital acquired pneumonia	[101]
Chlamydia pneumonia	[102]
Tuberculosis	[19,75–81]
Spirochaetal	
Lyme disease	[103–106]
Protozoal	
Cerebral malaria	[107]
Fungal	
Fungal meningitis	[108]
Parasitic	
Schistosomiasis	[109,110]
Angiostrongylus	[111,112]

Human T lymphotrophic virus (HTLV-1)

HTLV-1 is another retrovirus that leads to infection-related neuropathology, causing tropical spastic paraparesis. The lifetime risk of developing tropical spastic paraparesis in an HTLV-1 infected individual is 1–2%. MMP-9 is detected in the CSF of patients with HTLV-1-induced neurological disease [49]. Astrocytes stimulated by HTLV-1-activated $CD4^+$ T lymphocytes secrete increased MMP-3 and MMP-9, mediated through both soluble factor and integrin-

dependent pathways [50]. Increased MMP-9 expression is demonstrated in neural cells in the perivascular space in biopsies from patients with HTLV-1 infection and neurological disease, implicating MMP-9 in the local breakdown of the blood–brain barrier [50]. Excessive gelatinolytic activity is implicated further by the finding that polymorphisms of the MMP-9 promoter are associated with the development of neurological disease in HTLV-1 infection [51].

A second complication of HTLV-1 infection is adult T cell leukaemia (ATL), with a 1% lifetime risk of development in infected individuals. Leukaemia can progress to organ invasion and HTLV-1 infected T cell lines secrete high levels of MMP-9, driven by the viral transactivation factor, Tax [52]. Malignant cells from patients with adult T cell leukaemia secondary to HTLV-1 secrete increased MMP-9, and plasma MMP-9 levels are elevated compared to control. Interestingly, MMP-9 levels in ATL patients with disseminated organ involvement were higher than in ATL patients with limited disease, suggesting that MMP-9 activity facilitates tissue invasion by malignant cells [52].

Hepatitis B

Chronic hepatitis B virus infection is associated with hepatocellular carcinoma, which worldwide is one of the most prevalent infection-related malignancies. The hepatitis B virus X protein (HBx) is essential for the development of hepatocellular carcinoma and the induction of MMP secretion may be vital for tumour invasiveness. HBx drives MMP-14 expression and this correlates with increased invasiveness *in vitro* and *in vivo* [53]. MMP-14 may increase invasiveness not only through a direct effect on the extracellular matrix but also by activation of MMP-2, illustrating the complexity of proteolysis regulation. HBx also up-regulates MMP-9 secretion via the ERK MAPK and phosphatidylinositol 3-kinase (PI-3K) signalling pathways and this drives increased invasiveness [54]. Prognostic importance of the increased MMP activity was demonstrated by the finding that patients with hepatocellular carcinoma who have a higher serum TIMP-2 level, which would counteract the increased MMP secretion, had a better 2-year survival than those with low TIMP-2 levels [55].

In acute hepatitis B infection, excessive inflammation leads to foci of necrosis, with the recruitment of antigen-non-specific lymphocytes to the liver parenchyma. This recruitment is associated with MMP-8 and -9 expression. In a mouse model of acute hepatitis, enhanced TIMP-1 expression in the liver reduces the excessive cell influx and the severity of disease, while leaving chemokine expression unchanged [56]. The specific cytotoxic T lymphocyte recruitment was intact, suggesting that appropriate modulation of MMP activity in hepatitis can reduce immunopathology without adversely affecting the clearance of the virus.

Endotoxic shock

Bacterial lipopolysaccharide (LPS) initiates uncontrolled activation of the innate immune system, known as endotoxic shock. Organ failure is associated with increased vascular permeability and MMPs may contribute to this breakdown of the endothelial barrier. Type IV collagen is a primary component of the endothelial basement membrane and is degraded by MMPs: widespread compromise of the endothelial barrier results in the systemic syndrome of septic shock and multiple organ failure. LPS is known to up-regulate MMP-1, -7 and -9 secretion by monocytes and macrophages [57–59] and MMP-9 release by neutrophils [60]. The inflammatory cascade may be exacerbated by the catecholamines released in septic shock amplifying monocyte MMP-9 production [61]. LPS endotoxaemia in mice induces multiple MMPs and causes increased gelatinolytic activity in affected organs, and a lethal LPS dose drives greater and more prolonged MMP gene expression [62]. In patients with endotoxic shock, the serum levels of MMP-9 parallel the severity of illness [63] and increased MMP-9 levels are found in bronchoalveolar lavage fluid from patients with the acute respiratory distress syndrome, one of the main complications of endotoxaemia [64].

The functional importance of MMP activity is suggested by the observation that MMP-9-deficient mice have reduced mortality in endotoxin shock compared to wild-type animals [65]. Furthermore, lack of MMP inhibition is disadvantageous, as mice deficient in TIMP-3 had exacerbated pulmonary pathology compared to wild-type animals in a model of sepsis [66]. Ethanol abuse is known to increase the mortality of septic patients, and in ethanol-fed rats the activation of MMP-2 and MMP-9 is increased in endotoxaemia, secondary to glutathione depletion [67]. Therefore, although MMP-9 is proposed as a tuner of immune responses [68], in endotoxic shock it appears to exacerbate pathology.

Helicobacter pylori

Chronic *H. pylori* infection of the stomach is associated with peptic ulcer disease and gastric cancer, both involving aberrant breakdown of the extracellular matrix. Biopsies from patients with *H. pylori* infection demonstrate increased MMP-7 expression and cell infection *in vitro* increases MMP-7 secretion [69,70]. The Cag pathogenicity island of *H. pylori* is associated closely with virulence. Only Cag^+ isolates up-regulate MMP-7 expression in cultured gastric epithelial cells via the ERK MAPK pathway, further implicating MMP-7 in disease progression [69,71]. Gastric epithelial cells also secrete MMP-1 and MMP-3 in response to TNF-α and IL-1β, inflammatory cytokines induced by *H. pylori* [72,73]. This demonstrates the diverse mechanisms through which bacteria may up-regulate MMPs, both directly and via intercellular networks, to cause either local tissue destruction or malignant invasion.

Mycobacterial infection

Mycobacterium tuberculosis (*MTb*) infection results in a disease which is characterized typically by extensive tissue destruction in multiple organs. *MTb* infects a third of the world's population [74] and ECM breakdown with cavitation in the lung is vital to the transmission of the bacteria. Consideration of the lung biochemistry predicts a role for MMPs, as the lung's tensile strength comes from type I collagen and only specific MMPs can degrade this at neutral pH. The water soluble fraction of *M. smegmatis* can increase collagenase secretion by guinea pig macrophages [19]. Mycobacterial lipoarabinomannan (LAM), a major antigenic cell wall component, increases MMP-1 and MMP-9 secretion in the human THP-1 cell line and MMP-9 mRNA accumulation was demonstrated in broncho-alveolar lavage fluid cells isolated from two patients with active pulmonary tuberculosis (Tb) [75]. Mice infected by MTb have increased levels of MMP-2 and MMP-9 in infected tissues [76] and murine macrophages increase secretion in response to infection [77]. In patients with Tb circulating MMP-9 levels correlate with disease severity [78].

In Tb meningitis, we demonstrated a matrix-degrading phenotype in the CSF where increased MMP-9 concentrations are unopposed by a compensatory increase in TIMP-1 concentrations [79]. Furthermore, CSF MMP-9 concentrations correlated with markers of local tissue destruction, such as unconsciousness or a neurological deficit, and with death. In contrast, CSF MMP-9 concentrations did not relate to systemic signs of illness. Extensive tissue destruction occurs in tuberculosis despite a relatively low bacterial load, suggesting that host immunity and specifically intercellular networks drive MMP secretion. Consistent with this, immunohistochemistry of granulomas from patients infected with MTb demonstrates extensive MMP-9 staining with minimal TIMP-1 expression despite the presence of only small numbers of bacilli [80]. In a cell culture model, we demonstrated that monocyte–monocyte networks drive MMP-9 secretion via TNF-α and G protein-linked receptor signalling pathways [80]. In mice infected with *MTb*, MMP inhibition leads to reduced blood-borne *MTb*, suggesting that MMP activity may contribute to erosion from the alveolar space into capillaries that facilitates the dissemination of mycobacteria around the body [81]. Together, these data suggest that MTb subverts the host immune response to promote its own transmission by causing unopposed MMP expression in inflammatory cells and that increased MMP activity may be associated with pathology (Fig. 2).

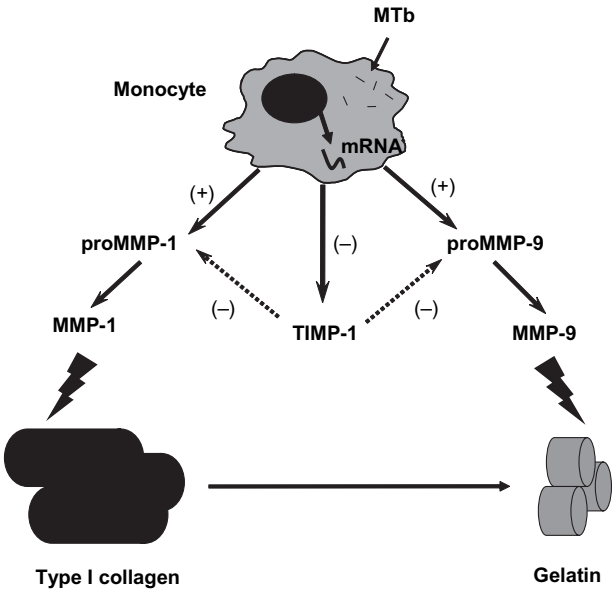

Fig. 2. Schematic representation of *Mycobacterium tuberculosis* (MTb)-driven tissue destruction. MTb infection of monocytes increases matrix metalloproteinase (MMP)-1 and MMP-9 gene expression and secretion. However, no compensatory increase in secretion of the tissue inhibitor of metalloproteinase (TIMP)-1, occurs. After activation, MMP-1 cleaves type I collagen fibrils to gelatin, which is in turn degraded by MMP-9.

MMP activation by bacterial proteases

In addition to inducing MMP secretion by host cells, pathogens may further skew the immune response towards tissue destruction by secreting proteolytic enzymes that activate host pro-MMPs. This would represent a biochemically efficient way for the pathogen to cause pathology by operating at the apex of a proteolytic cascade. An example of this is the wide range of proteases of the thermolysin family secreted by *Pseudomonas aeruginosa* and *Vibrio cholera* that activate pro-MMP-1, -8 and -9 [82]. Serine proteases associated with LPS preparations also activate MMP-9 [83], while proteases from the oral pathogen *Porphyromonas gingivalis* activate MMP-1, -3 and -9 [84]. *Streptococcus pneumoniae*, the major cause of severe pneumonia, secretes a zinc metalloproteinase ZmpC which cleaves MMP-9 *in vitro*. In a murine pneumonia model ZmpC- mutants caused 75% less mortality than wild-type pneumococci, confirming a role of ZmpC in pathogenesis [85]. Where bacterial-derived proteases are required for virulence, they are attractive pharmacological targets as they may be inhibited while leaving normal host MMP function intact.

MMPs as therapeutic targets

The evidence outlined above suggests that excess MMP activity may contribute to host damage in infectious diseases; therefore, the question arises whether modulating MMP activity can improve outcomes. Initial interest in therapeutic manipulation of MMPs focused on cancer progression, but the results of clinical trials to date have been disappointing [86]. Preliminary data suggest that targeting MMPs in infectious disease may be beneficial. In a rat model of pneumococcal meningitis, inhibition of MMP and TNF-α converting enzyme activity reduced mortality [87], while

inhibition of MMP activity by a chemically modified tetracycline reduces mortality in a rat model of sepsis [88,89]. Alternatively, MMP-9 activity can be reduced by inhibition of the MAPK pathways [90]. In humans, chronic periodontitis is caused by excess MMP release in response to bacterial LPS [91], and the combination of a subantimicrobial dose of doxycycline, which inhibits MMP activity [92], with cyclooxygenase inhibition reduces collagenolytic and gelatinolytic activity in the gingival cleft [93]. Therefore, MMP activity can be regulated both by direct inhibitors and by targeting the signalling pathways that up-regulate MMP expression. We hypothesize that a combination approach to regulating excess MMP activity may have benefits in many of the diseases discussed above.

Conclusion

Over the past decade, there has been increasing evidence demonstrating a role for MMPs in normal immunity. However, it is now becoming apparent that MMP activity can contribute to the development of immunopathology. This paradox results from the fine line between normal MMP function and MMP-related host tissue damage. The range of infectious diseases, the organs involved and the nature of resulting tissue damage are diverse. Certain MMPs are preferentially up-regulated by different infections. The key area for research is to understand the points which determine whether MMP activity is appropriate or destructive. Future therapeutic approaches will have to be targeted specifically to individual infections.

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