

Matrix Metalloproteinases and Infection

with

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What are the normal physiological roles of Matrix Metalloproteinases (MMPs)?

Jon S. Friedland: Matrix metalloproteinases (MMPs) are a family of zinc-containing enzymes. The first MMP was identified as the enzyme involved in the involution of the tadpole tail as it developed into a frog (1). Together, MMPs are able to degrade all components of the extracellular matrix. They have extensive substrate overlap. In particular, MMPs are the only enzymes known to be able to digest the triple helix of collagen which is one of the main structural substances in the body

and in the lung maintains lung architecture. MMPs are important in any physiological process involving tissue remodelling such as embryonic development and would repair after minor injury. In addition, MMPs may activate defensins. MMPs are secreted both by leukocytes and stromal cells including fibroblasts and astrocytes in the brain. However, in many instances, *in vitro* activity of MMPs has been hard to reconcile with apparent *in vivo* effects.

How are MMPs regulated?

Jon S. Friedland: Unrestricted MMP activity is potentially fatal since they are destructive enzymes. They are rarely stored within cells although MMP-8/9 in the neutrophil are exceptions to this. More commonly, MMPs are tightly regulated initially at a transcriptional level where nuclear binding factors such as NF- κ B and AP-1 have a critical role(2). MMPs are initially secreted as pro-forms which are inactive and require enzymatic

activity (sometimes by other MMPs) for cleavage and activation. Next, MMPs are regulated by ensuring that their secretion is compartmentalised and being local does not cause systemic injury. Finally, MMP activity is countered by 4 Tissue Inhibitors of Metalloproteinases (TIMPs) which are often co-secreted from the same cell type(3). The MMP / TIMP ratio may be very important in determining net tissue protein breakdown.

What is the potential involvement of MMPs in the pathophysiology of infection?

Jon S. Friedland: MMPs have important immunological functions essential in host defence to infection. They are involved in the very localised tissue damage required to facilitate leukocyte migration to sites of inflammation. For example, MMP-3 deficient mice have impaired neutrophil recruitment to the lungs(4). In addition, they cleave a range of cytokines and chemokines and as a result, may either activate or inactivate a range of

autocrine, paracrine and endocrine signalling molecules(5). A large number of MMPs including MMP-1, -2, -3, -7, -9 and -12 can all activate TNF α from its membrane bound precursor(6). MMP-9 activates CXCL8 whereas MMP-2 results in CCL7 becoming both inactive and a receptor antagonist.

Thus, it is clear that MMPs have the potential to regulate the human response to infectious agents and determine

outcome. Although research on the role of MMPs in infection has lagged investigation in other areas such as cancer, it is now becoming apparent that MMPs are involved in the immune response to a range of bacterial,

fungal, parasitic and viral infections. HIV, endotoxic shock due to gram negative infection and hepatitis B have provided some of the most compelling data demonstrating a central role for MMPs in host defence to infection(7).

Is there any influence of Mycobacterium tuberculosis on MMP expression?

Jon S. Friedland: Tuberculosis is a disease characterised by extensive local tissue destruction which in the case of lung cavitation, is essential for transmission of the pathogen and also is the major cause of morbidity and mortality. *Mycobacterium tuberculosis* (MTb) kills an estimated 2 million people each year. MMP activity is driven by components of MTb such as cell wall lipoarabinomannan. In murine models of Tb, increased MMP activity is detected although such models are somewhat problematic since they are not cavitory. Furthermore in man, circulating MMP-9 concentrations have been reported to be related to disease severity.

We reported the development of a matrix-degrading phenotype in patients with Tb meningitis(8). MMP-9 activity was relatively unopposed by TIMP-1 and local central nervous system (CNS) concentrations were associated with local signs of tissue damage and death. Subsequently, we have demonstrated MMP-1, MMP-7 and MMP-9 secretion in Tb patient granulomas. The regulation of MMP activity in Tb is complex and appears different in leukocytes, fibroblast, respiratory epithelial cells and CNS astrocytes. Some of our data points to p38 mitogen activated protein kinase having a key regulatory role(9).

Why do you believe that MMPs might be a therapeutic target in tuberculosis?

Jon S. Friedland: There is every reason to believe that MMPs may be therapeutic targets since much of the pathology, tissue damage and mortality caused by MTb is a result of the host response rather than direct pathogen activity. MMP inhibitors have already reached the clinic and although this first generation of inhibitors were not successful in the treatment of cancer, it does indicate that MMPs can be targeted in man by drugs. In future, it may be feasible to combine immunologic and pharmaceutical approaches to therapy to bring down treatment times from their current minimum of 6 months to a few weeks. The rise of multi-drug resistant MTb gives urgency to investigation of new treatment approaches.

There are good clues already to indicate that targeting MMPs has a beneficial effect in other infections such as in the rat models of pneumococcal menin-

gitis and of septicemia. In man, subantimicrobial doses of tetracyclines which inhibit MMP activity, have been shown to have a beneficial effect in chronic periodontitis. Furthermore, the existence of apparent switch points in signalling pathways and at the level of transcriptional control which inhibit MMP and increase TIMP secretion, indicate that there are a number of potential therapeutic targets. It is likely that a combination approach to therapy which is MTb disease specific will be the way forward.

REFERENCES

- Gross J et al. PNAS USA 48, 1014, 1962
- Parks WC et al. Nat Rev Immunol 4, 617, 2004
- Nagase H et al. Cardiovasc. Res 69, 562, 2006
- Warner RL et al. Am J Respir Cell Mol Biol 24, 537, 2001
- McQuibban GA et al. Science 289, 1202, 6, 2000
- Gearing AJH et al. Nature 370, 555, 1994
- Elkington PT et al. Clin Exp Immunol 142, 12, 2005
- Price NM et al. J Immunol 166, 4223, 2001
- Elkington PT et al. J Immunol 175, 5333, 2005