



## EDITORIAL

# MMPs are regulatory enzymes in pathways of inflammatory disorders, tissue injury, malignancies and remodelling of the lung

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**M**embers of the matrix metalloproteinase (MMP) family of zinc-dependent proteolytic enzymes regulate physiological and pathophysiological events in development, injury and repair, such as morphogenesis, vasculogenesis, remodelling of the extracellular matrix, cell migration, cleavage of cytokines, and activation of mediators and defensins. They are synthesised as secreted or transmembrane proenzymes and processed to their active forms by the removal of amino-terminal propeptides. Their activation by the cleavage of the prodomain from the latent proenzyme and the presence of natural inhibitors, such as tissue inhibitors of metalloproteinases (TIMPs), are important mechanisms that restrict the action of secreted MMPs to the micromilieu of their origin. This tight control of activation and the redundant design of the MMP system, points to their importance in the named processes. In most tissues, their constitutive expression is low and their overexpression at sites of inflammation or other pathogenic events was thought to be due the classical role of extracellular matrix degradation.

However, MMPs are no longer thought of as just matrix-degrading proteins. Rather, proteolysis should be viewed as an important post-translational principle of regulating a fast spectrum of biological processes, and the functional redundancy in combination with a wide substrate overlap underscores the pivotal roles of MMPs not only as effectors but also in regulatory mechanisms. Thus, MMPs are essential in many physiological events and the increasing interest in their function originates from their contribution to inflammatory and remodelling processes, in which they regulate physical barriers, release bioactive factors, participate in membrane shedding, modulate chemokine gradients that regulate leukocyte motility, activate cells *via* triggering of proteinase-activated receptors (PAR), and alter the activity status of other proteases, including other MMPs. Consequently, the majority of MMP substrates are non-matrix proteins, which underscores their critical roles in regulatory processes [1, 2]. Reports implicating MMPs in destructive pathogenic processes of pulmonary disorders are found in the literature from the early 1990s; more recently it has been recognised that the clinical

outcome of these processes is the result of an imbalance between MMP action and its inhibitors.

In humans, 24 MMPs have been identified and a cluster of nine MMP genes is located on chromosome 11q22, which are likely to be derivative of a single ancestor gene. The 24 MMP genes can be found on 10 different human chromosomes and their gene products are integrated in a redundant network, which can be seen by analysis of murine MMP knockout mutants. The phenotypes of these mutants are surprisingly benign, with pathologies in growth and ossification indicating functional redundancy and a rather limited activity in health [3]. Proteolysis, such as cleavage by MMPs, is a very effective mechanism which enables an organism to react very rapidly to pathologic events. Several types of lung cells, such as macrophages, neutrophils, epithelial cells and stroma cells, are capable of releasing MMPs in response to endogenous or exogenous stimuli, leading to complex roles of MMPs in health and disease; this is the topic of a new series that commences in the current issue of the *European Respiratory Journal (ERJ)* with a review by LÖFFEK *et al.* [3], which provides an overview of the physiological roles of MMPs. The *ERJ* has always disseminated advances in knowledge about MMPs and commits to doing so consistently. To this end, in the forthcoming months, the *ERJ*'s new series on MMPs will provide in-depth coverage of the biological role of MMPs in pulmonary health and distinct disorders. Tuberculosis, cystic fibrosis (CF), acute lung injury (ALI), adult respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), lung cancer, pulmonary hypertension, and MMPs as drug targets will be addressed.

Fibrillar collagens, which are highly resistant to enzymatic cleavage, are important constituents of the pulmonary extracellular matrix. However, collectively, MMPs are able to degrade all components of the extracellular matrix, resulting in cavities [4], and about a decade ago it was recognised that lung extracellular matrix destruction by MMPs was essential to tuberculosis [5]. The destruction of extracellular matrix by MMPs allows mycobacteria to spread from the interstitium to the airways, and results in cavities with an immunodeficient milieu in which mycobacteria can proliferate as a consequence of a missing protective immune response. These events are initiated by mycobacterial MMP activation within the monocytes/macrophages hosting the mycobacteria in the pulmonary

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interstitium, as discussed by ELKINGTON *et al.* [6] in a forthcoming article in this series, and elsewhere [7].

Animal and clinical studies demonstrate an increased expression of MMPs in ALI and ARDS. However, different MMP and TIMP levels are found over time. Their role in destructive pathologies and tissue repair needs to be balanced in order to identify new therapeutic intervention points for these devastating disorders, as the role they play as pathogenic factors or compensating mechanisms remains to be established. This is considered in a later article in the series by DAVEY *et al.* [8].

Increased expression of MMPs has been demonstrated in almost all inflammatory diseases, including IPF [9]. A microarray study previously demonstrated that MMP-7 was the most significantly overexpressed gene in IPF and that MMP-7-deficient mice were protected from bleomycin-induced fibrosis [10]. However, MMP-7 and its inhibitor are not only found in IPF but also in cryptogenic organising pneumonia, a disease which generally responds well to anti-inflammatory therapy. These observations lead to the hypothesis that MMP-7 overexpression represents an attempt of the body to control the fibrogenic processes, rather than being a pathogenic factor [11]. A better understanding of these processes is necessary for the development of new treatment strategies manipulating the biology of MMPs, as discussed by DANCER *et al.* [12] later in the series, and elsewhere [13].

Similar considerations, whether MMP overexpression is a pathogenic mechanism or a compensating response of the body, apply to CF. For pulmonary CF manifestations, however, abundant evidence points to a pathogenic role [14] and clinical studies targeting the protease/anti-protease imbalance can now be designed along the lines of pharmacological anti-elastase studies performed in CF [15].

Around 2,000 years ago, Aulus Cornelius Celsus described the classical symptoms of inflammatory tissue responses to harmful stimuli as rubor (redness), tumor (swelling), dolor (pain), and calor (heat), which are the result of the exudation of plasma proteins, degradation of extracellular matrix, activation of mediators, and recruitment of leukocytes, as observed in the airways of patients with asthma and COPD. MMPs have shown to be critically involved in all these processes [16, 17], and in particular phenotypes presenting with the overlap of asthma and COPD are associated with risk alleles of variant MMP genes with differences in the expression of their gene products [18, 19].

In lung cancer, the expression of a number of MMPs and their inhibitors is exaggerated and may be causally linked to enhanced tumour progression and metastasis [20–23]. This will be the focus of a later instalment in the series by H. MCGARRY and N. KAMINSKI.

Unsurprisingly, this broad involvement of MMPs in the pathologies of pulmonary disorders has developed interest in pharmacological manipulation of the balance between MMPs and their inhibitors, including TIMPs, and several established drugs have been shown to influence MMP activity. In this context, it is interesting to note that p-amino salicylic acid, a drug used to treat tuberculosis, is derived from the original cyclooxygenase inhibitor salicylic acid and inhibits mycobacteria-driven prostaglandin E<sub>2</sub> accumulation, thereby suppressing

MMP-1 secretion. This mode of drug behaviour blocks the mycobacterial exploitation of MMP-1 for tissue destruction and cavity formation [24]. Furthermore, doxycycline, an antimicrobial drug with some immunomodulatory behaviour, has been shown to inhibit MMP-9, in part explaining its non-antimicrobial actions [25]. MMP-2 and MMP-9 expression can be reduced by pentoxifyline to 30 and 56%, respectively [26]; this to some extent explains the immunomodulatory action of this drug. Other inhibitors of MMP-9 preventing adverse remodelling are the angiotensin converting enzyme (ACE) inhibitors, which act on zinc-dependent endopeptidases such as ACE and MMP-9 [27, 28]. These molecules may be the basis for more specific MMP inhibitors to come. Unfortunately, studies using currently available MMP inhibitors have not reached their therapeutic endpoints, but third-generation MMP inhibitors are in development that will specifically inhibit individual MMPs to manipulate the MMP/MMP inhibitor imbalance. This is further discussed in the series article by VANDENBROUCKE *et al.* [29].

The series on MMPs in health and disease that begins in this issue of the *ERJ* aims to summarise current knowledge on the importance of these molecules for lung health. A more detailed understanding of physiologic and pathophysiologic roles of MMPs will have a substantial impact on the pathogenic concepts of most pulmonary disorders, which will influence our therapeutic approach. MMP research will gain momentum in the near future and this series offers a basis for a thorough discussion of future advances.

#### STATEMENT OF INTEREST

None declared.

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