EDITORIAL

Metalloproteolytic balance in asthma: When and how could its regulation?

Matrix metalloproteinases (MMPs) are a family of secreted and cell surface-bound neutral proteinases, active on a large array of extracellular and cell surface proteins under normal and pathological conditions. First described as proteases that can degrade extracellular matrix (ECM) components, MMPs may also act on a variety of extracellular substrates to activate latent forms of mediators, such as antimicrobial peptides, cytokines and growth factors, or alter protein functions, such as shedding of cell-surface molecules. In the lung, as in other organs, MMPs are produced by airway epithelial and mesenchymal cells, but also by a variety of inflammatory cells and their synthesis is tightly regulated, via multiple activators and repressors pathways, by hormones, cytokines, cell adhesion molecules and a variety of environmental factors. Expressed and secreted in inactive form, MMPs undergo multistep activation and inactivation processes in the extracellular milieu, the most important endogenous inhibitors being the "tissue inhibitors of matrix metalloproteinases" (TIMPs).

In health and disease, a correct balance between MMPs and TIMPs may prevent an exaggerated ECM deposition or an alteration in its composition, but may also regulate the activation and the cleavage of a variety of molecules involved in wound healing, inflammation and immunity and host defense against pathogens. Imbalance in MMPs/TIMP ratio has been detected in the acute and/or the chronic phases of a variety of respiratory disorders, including chronic obstructive pulmonary disease and asthma.

In asthma, inappropriate expression and secretion of MMP-2, MMP-3 and MMP-9 and the ADAM family were reported and thought to be part of the physiology of this disorder. Most of the studies performed have been focused on the presence and/or the activity of MMP-9 (also called gelatinase B), a protease found to be highly expressed in the airways of asthmatic patients, compared with normal individuals, and specifically in patients with severe disease or during spontaneous asthma exacerbations. In agreement with the concept that mediators released by activated parenchymal and inflammatory cells could induce MMPs secretion and activation, increase in MMP-9 activity and elevated MMP-9/TIMP-1 ratios were reported after allergen challenge in mild asthma. In addition, a significant correlation was detected between airway MMP-9 levels after allergen provocation, and the fall in FEV1 during the late-phase bronchoconstrictive response. On the contrary, under baseline conditions, a reduction in the induced sputum MMP-9/TIMP-1 ratio was observed, with almost no active MMP-9 because of the very large TIMP-1 excess. Finally, significant inverse correlations were demonstrated between MMP-9/TIMP-1 molar ratios and the degree of airway obstruction or the magnitude of high-resolution computed tomography scan lung abnormalities. All these observations suggest that in asthma the degree of MMP activity can be linked to intensity of the inflammatory processes in the airways and that the MMPs/TIMPs balance could have a role in the pathogenesis of airflow limitation and reflect the extent of structural changes in the lung.

Little information is available on the role of the other MMPs and their balance with TIMPs. Increased gelatinolytic activity linked to MMP-2 (and to MMP-9), associated with higher TIMP-1 levels were detected in patients with asthma, while elevated concentrations of MMP-3 (and of MMP-9) in active form were reported in the airways of subjects ventilated because of acute severe asthma exacerbations. Therefore, it is likely that MMPs production and activation and the balance with their inhibitors could represent a dynamic protective mechanism, finalized: a) to prevent tissue destruction, down-regulating the excessive MMPs proteolytic activity in stable conditions; b) to favor ECM degradation during wound healing, when necessary; c) to modulate the inflammatory responses, in the acute phases of an inflammatory event.

What is not known is whether molecules currently used in asthma treatments have any effect on the expression, activation and function of MMPs and/or of their major inhibitors, TIMP-1. Despite the demonstration that in asthma inhaled steroids are able to reduce various
inflammatory parameters\textsuperscript{22} and, together with β\textsubscript{2}-adrenoceptor agonists, may modulate airway epithelial cell and fibroblast activities\textsuperscript{23,24} their capability to interfere with the various MMPs activities has not yet been evaluated.\textsuperscript{13,25}

In this edition of Respiratory Medicine, Todorova L et al.\textsuperscript{26} report their results of an in vitro model on the modulation of MMPs secretion and activation by an inhaled steroid, budesonide, and a long-acting β\textsubscript{2}-adrenoceptor agonist (LABA), formoterol. They stimulated human lung fibroblasts with TGF\textbeta\textsubscript{1}, one of the most potent growth factors involved in the pathogenesis of tissue remodeling and observed: a) a significant increase in the production of proteoglycan, a major ECM component; b) an enhancement, at different levels, in the production of TIMP-1 and of three major matrix metalloproteinases, MMP-2, MMP-3 and MMP-9. The end result was a general “pro-proteolytic” environment, due to the increase of the MMP-9 or MMP-2 to TIMP-1 ratio, but not of the MMP-3/TIMP-1 ratio. Incubation with budesonide and formoterol significantly decreased proteoglycan production and dramatically reduced the increase in MMP-9/TIMP-1 ratio, while the MMP-2/TIMP-1 ratio was even further enhanced because the two drugs had no effects on MMP-2 but completely counteracted the TGF\textbeta\textsubscript{1}-induced TIMP-1 increase. The author’s conclusion was that budesonide/formoterol combination therapy may counteract excessive ECM production and deposition and thus airway fibrotic remodeling in asthma.

No question that a variety of issues stand out. Firstly, the complex regulation of the balance between the different MMPs and their inhibitors, observed in a simplified in vitro model and performed on one cell line using a single inducer, TGF\textbeta might not reflect in vivo mechanisms. Secondly, the surprising activity of budesonide/formoterol combination on the TGF\textbeta\textsubscript{1}-induced fibroblast activation, leading to opposite effects on MMP-9/TIMP-1 and MMP-2/TIMP-1 ratios has not been confirmed in human asthma. Thirdly, the limited knowledge that we have in “real life” on: a) the interaction between the mediators released in the asthmatic airways and MMPs and TIMPs production and activation; b) the specific activity of MMPs on their various targets, including cytokines, chemokines and growth factors; c) the modulation by current pharmacologic treatment of MMP/TIMP production, activation and inhibition; d) the role of MMPs and TIMPs in the various asthma phenotypes and in patients of different age. This may be even more relevant in early childhood, a period of life when a significant progressive decrease in lung function may occur.\textsuperscript{27} There is experimental evidence that MMP-9 may play an important role in oxygen-induced lung injury in bronchopulmonary dysplasia,\textsuperscript{28} while disregulation of MMP-9/TIMP-1 homeostasis in the airways may be present in infants with respiratory syncytial or parainfluenza virus induced bronchiolitis.\textsuperscript{29} In addition, extremely high levels of MMP-9 and its inhibitor TIMP-1 (about 30-fold and 35-fold) were observed in bronchoalveolar lavage cells in children with severe asthma.\textsuperscript{30} It is therefore possible that the presence of protease/antiprotease disequilibrium may have a more significant pathogenetic role early in life, in the extremely plastic, still growing lung.

Taken together, these data identify MMPs as potential therapeutic targets. However, because of the intricacy of these enzymes and their substrates, the complexity of the interaction between inflammation and remodeling and the dynamic balance with their inhibitors, it is not clear whether MMP downregulation would be beneficial or harmful and in which situations it would be of clinical help. There is no doubt that we need more information to fill the many holes that we have to provide effective treatments to our patients and to identify efficient secondary and tertiary prevention measures. The good news is that, as shown by Todorova L et al.\textit{in vitro},\textsuperscript{26} an inhaled corticosteroid/LABA combination, besides being highly effective in symptoms control,\textsuperscript{31} might also have the potential to counteract a protease/antiprotease disequilibrium induced by pro-inflammatory or pro-fibrotic mediators.

References

9. Gueders MM, Foldart JM, Noel A, Cataldo DD. Matrix metalloproteinases (MMPs) and tissue inhibitors of MMPs in the respiratory tract: potential implications in asthma and other lung diseases. Eur J Pharmacol 2006;533:133–44.


