

Editorials

Matrix metalloproteinases: a role in emphysema?

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The combined observations that (1) an inherited deficiency of the major serum neutrophil elastase inhibitor, α_1 -proteinase inhibitor (α_1 -PI; α_1 -antitrypsin) predisposes to development of emphysema¹ and (2) intratracheal instillation of elastolytic enzymes into rodents causes emphysema led to the elastase/anti-elastase imbalance hypothesis for the development of the disease. This suggests that increased neutrophil influx and release of neutrophil elastase (NE) causes the tissue destruction and loss of elastic tissue integrity that characterises emphysema.¹ However, although NE is probably the pathological agent in α_1 -PI deficiency, most of those with emphysema are smokers with normal levels of α_1 -PI. Cigarette smoke inactivates α -PI in vitro² and may induce environmental pulmonary α_1 -PI deficiency in vivo, but the evidence for this is conflicting. Increased levels of neutrophils and extracellular NE are found in the bronchoalveolar lavage (BAL) fluid of smokers, but again the evidence that this is related to interstitial tissue damage is unclear.³ Although some have demonstrated a direct link between interstitial NE and degree of disease,⁴ others have not.^{5,6} There is no definitive evidence that NE is directly related to emphysema in smokers.

The search is on for alternative candidates. A protease with elastolytic activity of neutrophil or macrophage origin would be a strong contender. Neutrophils store the serine proteinases, NE, cathepsin G and proteinase 3, and a metalloproteinase, gelatinase B, which is released in its active form.^{7,8} Macrophages also produce gelatinase B, and other metalloproteinases, macrophage metalloelastase and stromelysin, but they require activation.⁸ Macrophages synthesise cysteine proteinases, cathepsins L and S, although it is unclear whether these are secreted in large quantities in vivo.^{9,10} These proteases all degrade elastin. Finally, neutrophils and macrophages release latent collagenases, metalloenzymes, distinct from each other, that degrade interstitial collagens but not elastin.⁸ In combination, neutrophil and macrophage proteases degrade most of the extracellular matrix, an event that seems likely to occur during emphysema.

Thus, the situation now is complex compared with the simple hypothesis formulated over 30 years ago.¹¹ Technological advances have enabled a fuller understanding of protease/anti-protease interactions and have highlighted the interdependence of the different classes of enzyme. Clearly, a fine balance exists between proteases and their inhibitors that may become pathological when tipped in favour of proteases. In this issue of *Thorax* Finlay *et al*¹² have investigated the relationship between BAL fluid levels of collagenase, gelatinase, and NE and emphysema. They have found a consistent relationship between BAL fluid levels of collagenase and emphysema. A similar but less consistent relationship exists for gelatinase B. NE

activity was found to be most strongly related to smoking, confirming previous studies. Interestingly, there was no quantitative relationship between the enzyme levels, loss of lung function, or degree of emphysema. Since their study suggests that these are largely neutrophil-derived enzymes, these findings may simply reflect non-specific neutrophil degranulation. The absence of NE in the non-smokers or ex-smokers with emphysema (six of 10 were non-smokers), in whom lung function should stabilise, suggests that NE is a significant contributory factor in the progression of emphysema. It would be interesting to know whether BAL fluid levels of collagenase are increased in early emphysema, and also whether it might be active and therefore cause tissue damage, rather than inactive, or raised in the face of tissue repair/remodelling.

Why are neutrophil-derived proteases prevalent, even in the face of a macrophage:neutrophil ratio of 45:1. What happens to macrophage-derived proteases? Are they released interstitially, rapidly removed from the site of action, and therefore overlooked? Are they important? Recent observations by Shapiro and colleagues suggest that macrophage metalloelastase and gelatinase B expression are significantly upregulated in the lungs of smokers.⁷

Unfortunately, emphysema is usually studied at an advanced stage. Interstitial damage and tissue of interest has already disappeared and analysis of BAL fluid can only indicate what processes might be occurring interstitially. Nevertheless, as the authors suggest, a combination of neutrophil (and macrophage) proteases may represent the most pathological scenario in the development of emphysema.

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- Snider GL. Emphysema: the first two centuries and beyond. Part II. *Am Rev Respir Dis* 1992;146:1615-22.
- Evans MD, Pryor WA. Cigarette smoking, emphysema, and damage to alpha-1 proteinase inhibitor. *Am J Physiol* 1994;266:L593-606.
- Stockley RA, Burnett D. Bronchoalveolar lavage and the study of proteinases and antiproteinases in the pathogenesis of chronic obstructive lung disease. *Monaldi Arch Dis Chest* 1993;48:245-53.
- Damiano VV, Tsang A, Kucich U, Abrams WR, Rosenbloom J, Kimbel P, *et al*. Immunolocalisation of elastase in human emphysematous lungs. *J Clin Invest* 1986;78:482-93.
- Fox B, Bull TB, Guz A, Harris E, Tetley TD. Is neutrophil elastase associated with elastic tissue in emphysema? *J Clin Pathol* 1988;41:435-40.
- Morris SM, Stone PJ. Immunocytochemical study of the degradation of elastic fibers in a living extracellular matrix. *J Histochem Cytochem* 1995;43:1145-53.
- Shapiro SD. The pathogenesis of emphysema: the elastase:antielastase hypothesis 30 years later. *Proc Assoc Am Physicians* 1995;107:346-52.
- O'Connor CM, FitzGerald MX. Matrix metalloproteinases and lung disease. *Thorax* 1994;49:602-9.
- Chapman HA, Munger JS, Shi G-P. The role of thiol proteases in tissue injury and remodelling. *Am J Respir Crit Care Med* 1994;150:S155-9.
- Reddy VY, Zhang QY, Weiss SJ. Pericellular mobilization of the tissue-destructive cysteine proteinases, cathepsins B, L, and S, by human monocyte-derived macrophages. *Proc Natl Acad Sci USA* 1995;92:3849-53.
- Tetley TD. New perspectives on basic mechanisms in lung disease. 6. Protease imbalance: its role in lung disease. *Thorax* 1993;48:560-5.
- Finlay GA, Russell KJ, McMahon KJ, D'arcy EM, Masterson JB, FitzGerald MX, *et al*. Elevated levels of matrix metalloproteinases in bronchoalveolar lavage fluid of emphysematous patients. *Thorax* 1997;52:502-6.