Protease-Antiprotease Imbalance in Inflammatory Diseases in the Lung

To the Editor:

We are very interested in the extensive research by Vernooy et al,1 who addressed the importance of matrix metalloproteases (MMPs) in the pathogenesis and/or the development of COPD. It is likely to be important to evaluate the activity of the proteases rather than the expression of MMPs. Protease/antiprotease imbalance has also been postulated to be important in the pathogenesis of COPD. However, the authors did not refer to the activity of the inhibitor of MMPs, tissue inhibitor of metalloprotease (TIMP). Thus, evaluation of the activity of TIMP will increase the understanding of the disease.

We are focusing on another protease inhibitor in several inflammatory conditions. Urinary trypsin inhibitor (UTI) is a multivalent Kunitz-type serine protease inhibitor.2 UTI has been widely used as a drug for patients with disseminated intravascular coagulation, shock, and pancreatitis, especially in Japan. UTI can inhibit proteases including trypsin, α-chymotrypsin, plasmin, cathepsin G, and leukocyte elastase as well as proteases in the coagulation cascade. Also, UTI has been reported to have anti-inflammatory properties in vitro. For instances, UTI inhibits the enhanced production of proinflammatory molecules such as thromboxane B2,3 interleukin-8,4 and tumor necrosis factor-α5 induced by lipopolysaccharide in vitro. In addition, UTI ameliorates several inflammatory models including ischemia-reperfusion injury,6 hemorrhagic shock,7 septic shock,8 and glomerulonephritis9 in vivo. We have recently exhibited the protective role of UTI in systemic inflammatory model using UTI gene knockout mice.10 The protection was characterized by the inhibition of organ (lung, kidney, and liver) injuries and the enhanced organ expression of proinflammatory cytokines and chemokines.10 More recently, we have demonstrated the protective role of UTI in acute lung injury induced by intratracheal administration of bacterial endotoxin in vivo,11 and have shown that the protection is associated with the inhibition of enhanced lung expression of intercellular adhesion molecule-1.11

Indeed, the amount of UTI in serum reportedly reflects the degree of airway inflammation in children with asthma.12 In conclusion, further investigation targeting protease inhibitors including UTI in inflammatory pulmonary diseases such as COPD may provide novel therapeutic strategies for the diseases.

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References


Patterns of Melanoma Antigen-A Expression in Lung Cancer Patients

To the Editor:

We appreciate the interest of Dr. Inoue and his group in our work. We fully endorse the importance of studying the protease/antiprotease balance rather than the expression of proteases. We therefore applied specific immunocapture activity assays that measure any active matrix metalloproteinase (MMP) but are insensitive to MMP-inhibitor complexes (such as MMP-tissue inhibitor of metalloproteinase or MMP-α2M complexes). Our finding of active MMPs in sputum is therefore indicative of a protease-antiprotease imbalance in COPD patients. The possible involvement of urinary trypsin inhibitor (UTI) is interesting, and the role of UTIs in COPD merits further study. Yet UTI (a serine protease inhibitor) does not inhibit MMP activity and will thus not influence the MMP-anti protease balance.

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Patterns of Melanoma Antigen-A Expression in Lung Cancer Patients

To the Editor:

Table 1, part (a) lists the combinations of melanoma antigen (MAGE) markers giving positive results occurring in 37 lung cancer
patterns of negative results E, BE, DE, CD, ADE, BCE, ABCD, ABCE, ABDE, BCDE, ACDE, ABCDE

(b) Observed patterns of positive results† None, A, B, C, D, E, BC, AD, ABC, ABE, ACID, ABCD

(c) Two ordered lists of markers† D, A, C, B, E

E, B, C, A, D

*A = MAGE-1; B = MAGE-2; C = MAGE-3/6; D = MAGE-4; E = MAGE-12.
†Any degree of expression (see Tables 1 and 2 of Mecklenburg et al†) has been counted as positive.
†Example: if patient P is in positions D, A, P, C, B, and E, and E, P, B, C, A, and D, then negative results to A, D, and E are predicted.

Reservations About the Data

In one sense, there seems to be a lot of variability, as any of the five markers might be the sole positive one. On the other hand, of the 32 possible patterns of positive and negative markers, only 12 were observed. These viewpoints can be reconciled by listing the results as combinations of negative results (Table 1, part [b]), and reasoning as follows. One simple form of dependence is a “negative-implies-negative” rule (ie, a single ordered list such that if there is a negative result for any marker, there is also a negative result for all markers to its left). Such a list cannot be constructed for this data set. Both BE and DE occur as combinations of negative results. Now suppose there are two ordered lists of the markers (Table 1, part [c]), that each patient has a position in both lists, and that markers to the left of the patient in either list have negative results. This pair of lists generates all except one of the observed patterns, the exception being that one patient has negative results for C and D.

It is chance that the lists are the reverse of each other.

As a concise description of the data, Table 1 (part c) is not unique. The positioning of E is ambiguous, as it could be first in the first list and last in the second list.

An alternative analysis might start from part (a) of Table 1 and employ a “positive-implies-positive” rule. This is not successful for this data set, as so many of the markers occur as the only positive result, in one patient or another.

If the lists in part (c) of Table 1 are taken seriously, they might be considered a theory and interpreted as resiliencies of the different MAGE markers, with a patient’s positions reflecting the strengths of the two systems for suppressing them. I have used the same method of summarizing data in the context of which patients do or do not succeed at various neuropsychological tests, and which chemicals do or do not kill various microorganisms. Interpretations could be made in terms of systems damaged to lesser or greater degrees, with a rule either saying both components are needed or saying one component is sufficient for a certain outcome. The method has disadvantages, admittedly. It is silent about degrees of response, dealing only with a 0/1 dichotomy, and there is no random element.

Reservations About the Data

Treating Tables 1 and 2 of the study by Mecklenburg et al† as a single data set is questionable. They refer to induced sputum and BAL fluid, respectively. Moreover, the level of MAGE expression is reported as being much higher in Table 2. It is arguable that marker C should have been excluded from consideration, since it is a confound of MAGE-3 and MAGE-6 (see page 253 of the article by Kufer et al†). Repeated observations from the same patient are not available, so allowance cannot be made for possible errors.

I hope that part (c) of Table 1 is thought-provoking despite the preceding paragraph, and that the proposed method of summarizing patterns of expression may be useful with other data sets.

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REFERENCES

3 Hutchinson TP. Analysis of datasets showing which compounds kill which organisms: inferring two systems. Eur J Med Chem 2004; 39:107–111

To the Editor:

We thank Dr. Hutchinson for his detailed statistical review of our described melanoma antigen (MAGE) expression profiles in sputum and bronchial fluid of lung cancer patients. We definitely agree to his notion that different MAGE expression patterns need further attention, as the distinct expression of individual markers might have particular prognostic impact or may be used for further subclassification of disease.

However, comprehensive analysis of large cohorts of patients with different types of cancers have not yielded any transparent order of distribution yet. Moreover, the additional qualitative assessment of MAGE expression by real-time polymerase chain reaction displays a rather arbitrary gene activity of individual markers in different types of tumors (unpublished data), and the sensitivity threshold of the utilized assay markedly affects the formation of the expression pattern.

The biological function and the physiologic role of individual cancer/testis antigens is still obscure; therefore, we are currently tracking prospective data for a correlation of the course of
To the Editor:

We read with interest the article by Choi et al (November 2004) concerning the incidence and risk factors of delayed pneumothorax after transthoracic fine-needle aspiration (FNA) of pulmonary lesions guided by a variety of radiologic techniques. The article is both well written and informative. As the authors indicate in their discussion, it is a common practice to obtain a postprocedure chest radiograph after CT-guided FNA. Instruction to seek medical attention in the event of symptoms of pneumothorax appears to be a more effective method of addressing this potential complication.

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Pneumothorax Following Transthoracic Fine-Needle Aspiration of the Lung

To the Editor:

In our study (November 2004),1 most transthoracic needle biopsies were performed by fluoroscopic and ultrasonography guidance. Only 4.5% of the transthoracic needle biopsies (21 of 458) were performed with CT scan guidance. Therefore, it is difficult to compare our data to the data of Byrd et al2 and Shantaveerappa et al.3

Definitely, CT scanning is more sensitive than a posteroanterior chest radiograph for the detection of pneumothorax. After the analysis of our data, we had a suspicion that a delayed pneumothorax was simply so small and localized that it would go undetected by a posteroanterior chest radiograph at 4 h but would be detectable by CT scan if one were performed. However, according to his previous work, delayed pneumothorax still occurred in 4 of 158 patients (2.53%) even though a CT scan was performed after the CT scan/fine-needle aspiration.3 This rate is not so different from that in our study1 (3.3%; 15 of 458). The study by Shantaveerappa et al3 helps us to resolve our suspicion. Furthermore, the rate of intervention was even higher (all patients, 1.7% [2 of 138]; patients with delayed pneumothorax, 50% [2 of 4]) in their study3 than that in ours (all patients, 0.65% [3 of 458]; patients with delayed pneumothorax, 20% [3 of 15]).1 I think that the two studies showed quite similar data but different interpretations.

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REFERENCES