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Title: Proteinase 3 and its potential role in emphysema

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Body: Introduction Proteinase 3 (PR3) is an elastin-degrading proteinase similar to neutrophil elastase (NE). PR3 is the most abundant serine proteinase in neutrophils, causes emphysema in animal models & induces mucus secretion in humans. Its main circulating inhibitors are alpha-1-antitrypsin (AAT) & alpha-2-macroglobulin (A2M). Its role in respiratory disease has not been studied in detail. Aims 1) To determine how efficiently PR3 activity is inhibited by healthy (PiM), AAT deficient (PiZ) & AAT variant (PiFZ, PiIZ) sera. 2) To study partitioning of PR3 between its 2 serum inhibitors. Methods Serum from subjects with different AAT phenotypes (PiM, PiZ, PiFZ, PiIZ) was taken & AAT concentration measured. Increasing molar ratios of serum AAT to PR3 were incubated & residual PR3 activity measured. Experiments were reproduced using comparable mixtures of pure AAT & A2M. Association rate constants (Kass) of PR3 & NE with AAT variants were determined using methylamine-treated serum (A2M inactivated). Results Increasing the molar ratio of serum AAT to PR3 increasingly inhibited PR3 activity, however even in AAT excess some residual PR3 activity remained which was greater in PiZ serum compared to PiM serum. These results were reproduced using mixtures of pure AAT & A2M suggesting that PR3 bound to A2M remains catalytically active. The Kass values for AAT variants with PR3 & NE are shown in table 1.

Table 1

AAT variant	Kass with NE (25°C, M^{-1} $s^{-1)}$	Kass with PR3 (25°C, M^{-1} $s^{-1)}$
PiM	1.4×10^7	9.6×10^5
PiIZ	9.9×10^6	1.1×10^6
PiFZ	7.2×10^6	1.7×10^6
PiZ	7.3×10^6	1.5×10^6

Conclusion When serine proteinases are released from neutrophils, NE is more likely to be inhibited by AAT than PR3 (due to the lower Kass values) & binding of PR3 to A2M retains its activity.