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Title: Effects of α1-antitrypsin on neutrophil extracellular traps formation

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Body: Neutrophils belong to the innate immune response and are essential for elimination of invading pathogens. Apart from phagocytosis and secretion of anti-microbials, neutrophils are also capable of producing neutrophil extracellular traps (NETs) to kill pathogens extracellularly (NETosis). Neutrophil elastase (NE) is a critical initiator of NETosis and also is one of the main components of NETs. The acute phase protein α_1-Antitrypsin (AAT) is a potent inhibitor for NE released from the activated neutrophils. Therefore, we asked a question if AAT inhibits NETosis? We induced NETosis in neutrophils isolated from healthy donors by applying phorbol myristate acetate (PMA, 10 ng/ml) alone or together with purified AAT protein (1 mg/ml). To our surprise, AAT did not inhibit NETs formation but make the structures less adherent to the surface. Remarkably, using anti-AAT antibodies we detected AAT in the NETs either separately or in co-localization with elastase. In the next set of experiments, we isolated neutrophils from emphysema patient with inherited ZZ (Glu342 Lys) AAT deficiency before and after AAT augmentation therapy. In response to PMA, neutrophils isolated before augmentation therapy formed NETs similar to those observed in healthy donors. However, after augmentation therapy, NETs contained large cell aggregates some of which were detached from the specimen. Again, exogenous AAT did not inhibit NETs. We suggest that an increased risk for development of chronic obstructive pulmonary disease (COPD) in subjects with inherited AAT deficiency results from both-increased elastase activity and uncontrolled NETosis.