

## Journal club

### Human neutrophil chemotaxis regulation by $\alpha$ -1 antitrypsin

$\alpha$ -1 Antitrypsin (AAT) has anti-inflammatory roles beyond regulation of proteases. Chronic lung disease in  $\alpha$ -1 antitrypsin deficiency (AATD) is characterised by neutrophilic inflammation. This series of experiments investigated the effects of AAT on neutrophil chemotaxis by comparing neutrophils from patients with AATD with controls, both in vitro and in vivo.

Chemotaxis to both IL-8 and soluble immune complexes was increased in neutrophils from AATD patients when compared with controls, but chemotaxis was inhibited by exogenous AAT, with a dose–response effect. Similarly, in vivo, the increased chemotaxis of neutrophils from patients with AATD was normalised when they were treated with AAT augmentation therapy.

To investigate the mechanism behind this, further experiments identified that glycosylated AAT binds directly to IL-8, preventing the latter binding to its specific CXCR1 receptor, with consequent reduction in calcium influx into the cell and protein phosphorylation, components of the cascade of intracellular events which precede chemotaxis. In a second line of experiments, AAT was found to co-localise on the neutrophil membrane with the Fc $\gamma$ RIIIB receptor. Shedding of this receptor is required for neutrophil chemotaxis, and this process is activated by the metalloproteinase ADAM17. AAT inhibited the shedding of the Fc $\gamma$ RIIIB receptor via inhibition of ADAM17.

This study demonstrates that AAT inhibits neutrophil chemotaxis by two mechanisms: binding of IL-8 and inhibition of shedding of the Fc $\gamma$ RIIIB receptor via ADAM17, providing new insight into its anti-inflammatory roles. As these effects were also seen in vivo, they increase our understanding of the therapeutic role of AAT augmentation therapy.

► **Bergin DA**, Reeves EP, Meleady P, *et al.*  $\alpha$ -1 Antitrypsin regulates human neutrophil chemotaxis induced by soluble immune complexes and IL-8. *J Clin Invest* 2010;**120**:4236–50.

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