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Title: Inflammation induced conformational changes in Z alpha-1 antirypsin promotes lung Z-AT cell damage

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Body: Severe deficiency of the major anti-elastase α1-antitrypsin (AT) due to the Z (Glu342Lys) variant (Z-AT) is the commonest genetic reason for the development of COPD. There is however, significant variability in disease expression in Z-AT homozygotes. We postulated that Z-AT are prone to exaggerated lung damage compared to normal AT (M-AT) during LPS infection. Lung epithelial (A549 and NHBE) cells transfected with human M-AT or Z-AT (M-AT/Z-AT cells) were treated with LPS(20ng). Plasma native AT (N-AT,0.3mg/ml) was used to probe the effect of LPS. At 24h LPS Z-AT cells was compared to M-AT (unless stated) using ELISA, immunoblot or RT-PCR. Z-AT had significantly increased secretion of TNF-α; (mean±SEM) 87±5pg/ml vs. 28±2, IL-6; 296±52pg/ml vs. 40±10, IL-8; 14215±2857pg/ml vs. 1743±227 and MCP-1; 20769±1769pg/ml vs. 3025±161 and their respective mRNA at 0.5h, P<0.001 for all. Z-AT had significant HLE activity (OD at 405nm, 1.95±0.2 vs. 0.35±0.1, P<0.001. Development of pZ-AT; 1559±195ng/ml and Ox-pZ-AT; 1078±143ng/ml were detected in Z-AT only, P<0.001 for both. Z-AT had significantly activated NF-κB, P<0.001 at 0.5h. In LPS Z-AT treatment with N-AT significantly inhibited all activity, P<0.001 for all, P=0.047 for Ox-pZ-AT. N-AT treatment had no effect on pZ-AT formation (P=0.940). These findings were confirmed on NHBE cells. Monomeric AT has novel anti-inflammatory and anti-elastase properties. During LPS infection induced lung inflammation the conformationally labile Z-AT monomer is converted to Ox-pZ-AT, which by further reducing protective monomeric AT, predisposes to increased lung damage. This process may explain some of the observed variability of the PiZZ clinical phenotype.