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| **Recombinant Alpha-1 Antitrypsin as a Potential Therapy for Chronic obstructive pulmonary disease** |
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| **Introduction/Aim:** The excessive production of proteases such as neutrophil elastase (NE) drives inflammation and the development of chronic obstructive pulmonary disease (COPD); the main anti-protease is alpha-1 antitrypsin (AAT). AAT has been used for the treatment of COPD/emphysema but has significant issues with lack of availability, high cost and instability. We have therefore developed a recombinant form of AAT (rAAT) to address these issues. The aim of this study was to assess the effect of the rAAT on lung inflammation.  **Methods:** rAAT produced by protein engineering was used. The effect of additional recombinant DNase 1 (dornase alfa/Pulmozyme) was also assessed. In vitro experiments were performed using blood and bronchoalveolar lavage (BAL) samples from human subjects, that were infected with influenza A virus (IAV) to induce NE activity and expression of neutrophil extracellular traps (NETs). In vivo experiments were performed in mice infected with IAV and administered inhalational AAT and DNase 1 daily; mice were culled at 3 days (peak inflammation) and 10 days (resolving infection).  **Results:** Samples were obtained from 24 adults (mean age of 51± 15 years). IAV infection increased NE activity/NET expression, which was reduced by the addition of AAT (p<0.0001), and further reduced by the addition of DNase 1. AAT reduced inflammation in infected mice as assessed by body weight, BAL white cell counts (both neutrophils and macrophages) and lung weight, (n=18 mice, p<0.0001); this effect was enhanced by the addition of DNase 1. The combination of the rAAT and DNase also reduced lung inflammatory cytokine expression (e.g., interleukin 8). Similar effects were obtained with other models of lung inflammation, including bacterial infection and cigarette smoke exposure.  **Conclusion:** Our recombinant alpha-1 antitrypsin reduces lung inflammation and this effect is enhanced by the addition of DNase 1.  **Grant Support:** United States Department of Defence Grant |