#206 Bakr Jundi Advisor(s): Patrick Geraghty

Elevated S100A9 Levels in Alpha-1 Antitrypsin Deficiency Contributes to Lung Inflammation

Alpha-1 antitrypsin deficiency (AATD) is characterized, in part, by a dysregulation of lung inflammation and protease responses. S100A9 is a potent inflammatory protein that is increased in plasma and bronchoalveolar lavage fluid of COPD patients. We recently demonstrated that inhibiting S100A9 signaling prevented smoke-induced emphysema in mice. However, its role in immune responses in human AATD remains to be identified. Here, we hypothesize that the loss of AAT will result in elevated S100A9 levels and AAT may counter-regulate S100A9-mediated signaling. In this study, plasma AAT was purified from healthy AAT deficient subjects (PiZZ) not receiving AAT augmentation therapy and aged-match PiMM controls by affinity chromatography. Global proteomic profiling was performed on equal concentrations of PiMM and PiZZ AAT protein and bound unknown protein utilizing an ultra-high-pressure liquid chromatography approach coupled to a high resolution, high mass accuracy quadrupole-Orbitrap MS. Total plasma and AAT purified from PiMM (n=10) and PiZZ (n=10) individuals were also quantified for S100A9 levels by immunoblots and ELISA. Finally, primary human bronchial epithelial (HBE) cells were treated with plasma purified AAT isolated from PiMM and PiZZ prior to S100A9 stimulation. Immune responses were quantified by qPCR.The purified AAT protein bound to peptides associated with 201 proteins. Interestingly, 79 proteins interacted with the PiMM AAT but not the PiZZ AAT protein. One of these proteins was S100A9. We confirmed that only PiMM AAT bound to S100A9 by ELISAs and immunoblots. Total plasma levels of S100A9 were also elevated in PiZZ subjects relative to PiMM subjects. AATD patients receiving AAT had reduced plasma S100A9 levels. Treatment of HBE cells with PiMM AAT prevented S100A9 induction expression of CXCL1/GROα, CXCL8/IL8. In conclusion, non-mutated AAT binds directly to S100A9 and decreases S100A9 signaling and counter-regulates the immune dysregulation in AATD.

Additional contributors to this project:
Kanza Zahid
Alnardo Lora
Christopher Railwah
Zeeshan Sattar
Abdoulaye J. Dabo
Robert Foronjy
Michael Campos
Edward Eden
Patrick Geraghty