**Targeting S100A9 signaling reduces lung cell death and inflammation in alpha-1 antitrypsin deficiency**

We previously reported that S100 calcium-binding protein A9 (S100A9), a damage-associated molecular pattern protein, is increased in lungs and plasma of COPD and alpha-1 antitrypsin (AAT) deficient patients, and inhibition of S100A9 signaling preserves lung function in animal models of cigarette smoke-induced COPD and AAT deficiency. We also observed higher inflammation in primary human bronchial epithelial (HBE) cells treated with S100A9. Here, we hypothesize that targeting S100A9 signaling could alter inflammation and cell fate in AAT-deficient animals and HBE cells. Male and female age-matched Serpina1a-e knockout mice were orally administered the S100A9 inhibitor, paquinimod, daily for 4 months. Inflammation responses were examined using Luminex assays. Lung apoptosis was quantified in the lungs of the animals by quantifying the positivity of TUNEL staining. Primary human bronchial epithelial (HBE) cells were treated with AAT protein before S100A9 stimulation. Downstream TLR4 and RAGE signaling and Annexin V staining were recorded. We previously presented that paquinimod treatment reduced airspace enlargements, and loss of lung function in the Serpina1a-e knockout mice. Here, we observed that inhibition of S100A9 signaling is accompanied by reduced immune cell infiltration, reduced inflammatory markers (CCL2, CXCL1, IL6, and TNFα), reduced ERK and c-RAF phosphorylation, and decreased lung cell death. HBE cells exposed to AAT had reduced TLR4 and RAGE-associated signaling following stimulation with S100A9; with AAT impacting ERK phosphorylation, IRAK1 and IκBα degradation, NFκB activation, and inflammation (CCL2, CXCL1, IL6, and TNFα). AAT also reduced S100A9-induced apoptosis determined by Annexin V staining using flow cytometry. In conclusion, inhibition of S100A9 reduced AAT deficiency-associated inflammation and lung cell death. Therefore, S100A9 signaling plays a major role in several mechanisms associated with AAT deficiency emphysema.