Serum Amyloid A opposes lipoxin A_4 to mediate glucocorticoid refractory lung inflammation in chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) will soon be the third most common cause of death globally. Despite smoking cessation, neutrophilic mucosal inflammation persistently damages the airways and fails to protect from recurrent infections. This maladaptive and excess inflammation is also refractory to glucocorticosteroids (GC). Here, we identify serum amyloid A (SAA) as a candidate mediator of this GC refractory inflammation in COPD. Extrahepatic SAA was detected locally in COPD BAL fluid, which correlated with interleukin-8 and neutrophil elastase, consistent with neutrophil recruitment and activation. Immunohistochemistry detected SAA was in close proximity to airway epithelia, and *in vitro* SAA triggered release of interleukin-8 and other pro-inflammatory mediators by airway epithelial cells in an ALX/FPR2 receptor-dependent manner. Lipoxin A_4 (LXA_4) can also interact with ALX/FPR2 receptors and led to allosteric inhibition of SAA initiated epithelial responses (pA_2 13 nM). During acute exacerbation of COPD, peripheral blood SAA levels increased dramatically and were disproportionately increased relative to LXA_4. To determine its direct actions, SAA was administered into murine lung, leading to induction of CXCL chemokines, neutrophil recruitment and an acute inflammatory response that could be inhibited by 15-epi-LXA_4 but not the GC dexamethasone. Human lung tissue macrophages (CD68+) colocalised with SAA and *in vitro* dexamethasone led to a marked and paradoxical increase in macrophage SAA production (THP-1, pEC_{50} 43 nM). Together, these findings identify SAA as a therapeutic target for inhibition and implicate SAA production as a mediator of GC resistant lung inflammation that can overwhelm organ protective signaling by lipoxins at ALX/FPR2 receptors. Of note, these findings in COPD differ from the defective lipoxin generation seen in severe asthma and represent distinct pathogenetic mechanisms for these common airway diseases.

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