ALPHA-1 ANTITRYPSIN (AAT) POLYMERIZATION IN ALVEOLAR MACROPHAGES OF AAT DEFICIENT INDIVIDUALS AND IN SMOKERS

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Alpha-1 antitrypsin (AAT) is a potent serine-protease inhibitor known as the serpins (Carrel et al. 2002). Genetic deficiency of alpha-1 antitrypsin is a rare autosomal codominant disease characterized from reduced or absent blood levels of the protein, mainly due to the accumulation of polymerized protein into hepatocytes, the main producing cells (Lomas et al., 2002). This deficiency is also associated with early onset of lung emphysema (Baraldo et al., 2015). It's known that Alveolar macrophages(AM) produce AAT(Wout et al., 2012),however it is not known if AAT could polymerize in AM, decreasing its defensive role, and promoting lung inflammation. The aim of this study is to investigate if AAT polymerizes in the AM and study the possible relation between polymerization and degree of lung inflammation. We used the 2C1 monoclonal antibody(mAb)(provided by prof Lomas,UCL,UK) which is specific for polymerized AAT,to perform immunohistochemical analysis of sections from 33 lungs with severe COPD,of which 9 with AAT deficiency(AATD) and 24 with normal AAT levels,and in 24 lungs without COPD,of which 11 smokers and 13 nonsmokers. AM positive for AAT polymerization were counted and expressed as percentage of total AMs in lung section. Polymerization of AAT was detected in [27(5-55)%]of AMs in AATD patients,but also in AMs of smokers with COPD [24(0-54)%] and in smokers without COPD [24(0-46)%], while in non smokers AMs did not show polymerization [0(0-2)%] ($p<0.0001$). The percentage of polymerized AMs was correlated with amount smoked ($r:0.53$; $p=0.0001$), number of CD8+T in the alveolar walls ($r:0.51;p=0.002$) and FEV1 ($r:-0.44;p=0.002$). In this study we have shown the presence of alpha-1 antitrypsin polymers in alveolar macrophages, which causes a local deficiency of the protein in lung parenchyma. This occurs not only in patients with genetic deficiency of the protein, but also in patients with pulmonary emphysema without deficiency and in smokers without COPD. This suggests that smoking itself induces conformational changes in the AAT predisposing to polymerization,with consequent loss of the AAT protective effect in the lung. These results contribute to move beyond the traditional elastase/antielastase paradigm and to open to new and more complex functions of alpha-1 antitrypsin, involving the adaptive immune response.

Carrel et al (2002). N Englan J Med.346: 45-53

Lomas et al (1992). Nature.357:605-607

Baraldo et al (2015). Am J Respir Crit Care Med.191:402-9

Wout et al (2012). Am J Respir Cell Mol Biol.46:607-13