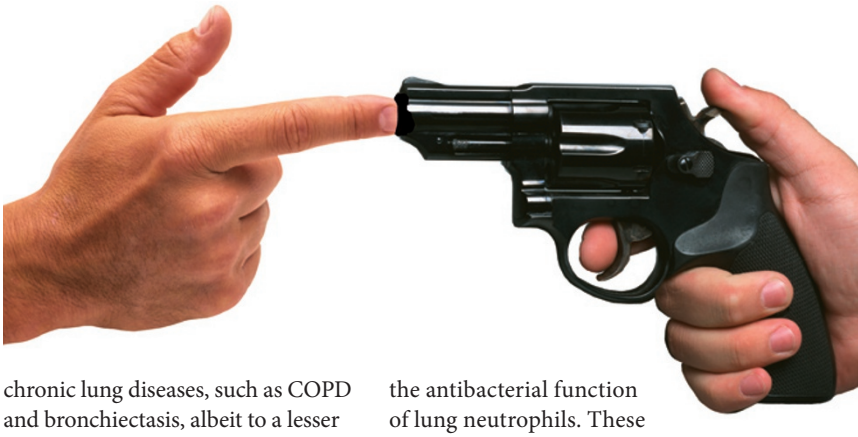
Nature Reviews Immunology | AOP, published online 14 December 2007; doi:10.1038/nri2244

LUNG INFLAMMATION

Disarming neutrophils in cystic fibrosis



The accumulation of neutrophils and high concentrations of the chemokine interleukin-8 (IL-8) in the airways is a characteristic feature of chronic lung diseases, such as cystic fibrosis and chronic obstructive pulmonary disease (COPD). However, these diseases (most pronounced in cystic fibrosis) are also associated with bacterial colonization of the airways, especially by *Pseudomonas aeruginosa*, which suggests that there is a local defect in the host defence system. Now, new research describes a mechanism by which the antibacterial function of neutrophils is disabled in the lungs of patients with this disease.

Neutrophils are recruited to the site of inflammation by IL-8 (also known as CXCL8) through their expression of CXC-chemokine receptor 1 (CXCR1) and CXCR2, and given the high levels of these factors in the lungs of patients with cystic fibrosis, the authors investigated the antibacterial functions of neutrophils within these organs.

The authors showed that in healthy individuals key IL-8-induced antibacterial functions of lung neutrophils (that is, respiratory burst and α-defensin release) are mediated through CXCR1 but not CXCR2. In the lungs of patients with cystic fibrosis the surface expression of CXCR1 by neutrophils was greatly reduced compared with that of neutrophils isolated from their blood or from the lungs of healthy individuals. This decrease in CXCR1 expression was also observed in patients with other chronic lung diseases, such as COPD and bronchiectasis, albeit to a lesser degree. The surface expression of CXCR1 by neutrophils was strongly related to their bactericidal capacity and inversely correlated with the amount of free elastase present in the airway fluid.

Further analysis showed that free elastase (which is the predominant protease in the lungs of patients with cystic fibrosis) could cleave CXCR1 from the surface of neutrophils in the lung, thereby disabling their antibacterial functions. Cleavage of CXCR1 resulted in the release of soluble CXCR1 fragments, which were shown to stimulate the production of IL-8 from epithelial cells in a Toll-like receptor 2 (TLR2)-dependent manner.

Importantly, treatment of patients with cystic fibrosis with the natural serine protease inhibitor α1-antitrypsin for 4 weeks reduced the levels of free elastase in their lungs, increased the surface expression of CXCR1 by lung neutrophils, reduced the levels of soluble CXCR1 in the airway fluids and enhanced the antibacterial function of lung neutrophils. These effects resulted in a decrease in the numbers of *P. aeruginosa* bacteria in the sputum of these patients, indicating that inhibition of free elastase has potential therapeutic benefit for patients with cystic fibrosis.

So, taken together, the authors propose that in the lungs of patients with cystic fibrosis (and possibly in patients with other chronic lung diseases) IL-8 continuously recruits neutrophils to the lung, where CXCR1 is immediately cleaved from their cell surface by free elastase, thereby disabling the antibacterial function of these cells. This cleavage step releases soluble CXCR1, which stimulates the production of IL-8 by epithelial cells, thereby initiating a feedback circuit that amplifies airway inflammation.

Olive Leavy

ORIGINAL RESEARCH PAPER Hartl, D. *et al.* Cleavage of CXCR1 on neutrophils disables bacterial killing in cystic fibrosis lung disease. *Nature Med.* 02 December 2007 (doi:10.1038/nm1690)