

## Degradation of the Antimicrobial Screen in the Cystic Fibrosis Lung

One of the major problems associated with Cystic Fibrosis (CF) lung disease is bacterial colonisation of the airways, which is chronic in duration. Although the use of antibiotics has helped reduce colonisation and therefore, the excessive inflammatory response associated with infection, persistence of bacteria is still a major problem facing individuals with this inherited disease. In addition, it has now been realised that bacteria such as *Pseudomonas* can form complex communities of bacteria called biofilms that are notoriously resistant to antibiotic treatment.

The lung itself produces its own range of natural antibiotics, called antimicrobial proteins that can kill invading microorganisms. However, in CF this natural killing mechanism appears to be defective allowing infection to take hold at an early stage. In our laboratory in the Department of Medicine in the Royal College of Surgeons in Ireland Education and Research Centre, we have demonstrated that a group of proteins called cathepsins can inactivate and degrade some of the more abundant antimicrobial proteins of the respiratory tract including lactoferrin. Lactoferrin is important because it can also prevent bacteria such as *Pseudomonas*, which is an important colonising pathogen of the CF lung, from forming antibiotic-resistant colonies called biofilms. However, incubation of lactoferrin with cathepsins reduces its ability to kill *Pseudomonas* and to prevent biofilm formation. We have also demonstrated that CF sputum samples that are *Pseudomonas*-positive also contain more cathepsin activity, less lactoferrin and are less able to prevent *Pseudomonas* biofilm formation compared to sputum samples that are negative for *Pseudomonas*. We have recently published these findings in the Journal of Infectious Disease (Rogan et al, *J Infect Dis.* 2004; 190:1245-53).

In another strand to this study we have shown that the respiratory tract antimicrobial protein, secretory leucoprotease inhibitor (SLPI), is also susceptible to degradation by cathepsins. However, apart from being an antimicrobial protein, SLPI also possesses anti-inflammatory properties. SLPI has previously been used in clinical trials for CF and has been shown to decrease the neutrophil burden in patients and to increase the anti-elastase capacity of the CF lung. We are now investigating SLPI's anti-inflammatory activity with particular emphasis on how it inhibits activation of inflammatory cells by bacterial products. We have previously shown that SLPI can inhibit activation of a group of inflammatory cells, called monocytes, by bacterial cell wall products such as lipopolysaccharide and lipoteichoic acid (Greene et al, *Infect Immun.* 2004, 72:3684-7; Taggart et al *J Biol Chem.* 2002, 277:33648-53).

We envisage that the results obtained from these studies may highlight the need to inhibit cathepsin activity in CF in order to preserve antimicrobial function. In addition, elucidation of SLPI's anti-inflammatory mechanism may indicate the potential of SLPI as a future mainstream therapy to prevent the excessive inflammatory response associated with CF lung disease.