Editorial

How Can We Target Pulmonary Inflammation in Cystic Fibrosis?

With each year our enhanced understanding of the pathogenesis of cystic fibrosis (CF) is challenged by new discoveries related to the increasingly complex nature of this disorder. Originally described as a genetic disorder principally due to defective chloride ion conductance at epithelial surfaces and a predisposition to bacterial colonization have been moved into the category of an inflammatory disorder because of increasing research efforts. As our knowledge of the molecular and cellular events associated with CF has burgeoned, we now have a greater appreciation of its protean inflammatory manifestations. This Mini-Hot Topic on "Mechanisms of Pulmonary Inflammation in Cystic Fibrosis" presents a series of comprehensive review articles in which the authors describe novel mechanisms regulating inflammation in the CF lung and propose and dissect the potential benefits and side-effects of diverse treatments aimed at ameliorating the inflammatory consequences of CF lung disease.

CF is the most common serious inherited metabolic disorder among Caucasians. It is a recessive condition with a known gene defect, which is invariably fatal. CF affects the liver, pancreas and intestinal tract but the major causes of morbidity and mortality are the lung disease. This generally begins in childhood with the production of thick mucus, chronic airway infections and inflammation leading to progressive decline in lung function and death from respiratory failure. Although gene therapy heralded great promise for the treatment of CF, this approach, whilst likely to repair the chloride ion secretion defect in CF, has no effect on the chronic pulmonary inflammatory manifestations of the disorder.

Current treatments for CF are broad ranging. In addition to exercise regimes and nutritional supplementation strategies, a number of CF therapies targeting mucus overproduction, inflammation and infection, along with gene therapeutics, protein assist/repair and salt transport restoration drugs are either fully developed or in Phase I, II or III trials. Continuous cycles of infection lead to increased morbidity and mortality in the setting of CF. Prompt antibiotic therapy is associated with reduced decline in lung function and improved patient outcomes. Symptomatically, inhaled/ nebulised bronchodilator therapy provides relief from breathlessness, and mucolytic therapy can be very useful in enabling patients to expectorate sputum. Both are associated with improvements in lung function. Now there is an increasing focus on the therapies targeting the underlying pathogenesis, and in particular underlying inflammation which is central to the disease process in CF. In this respect non steroidal anti-inflammatory medications (NSAIDS), steroids and azithromycin have proved to be useful but their chronic use is associated with long term sequelae including osteoporosis, peptic ulcer disease and cataracts.

Recently, a number of novel mechanisms regulating the pulmonary inflammatory manifestations of CF have been reported. Teichgraber *et al*. described an age-dependent relationship between ceramide generation and lung inflammation, cell death and infection in CF knockout mice [1]. Their study highlighted acid sphingomyelinase as a potential therapeutic target in CF. JE Blalock's group identified the new collagen-derived proinflammatory tripeptide molecule, proline-glycine-proline (PGP), detectable in CF sputum that is chemotactic for neutrophils [2]. They also described a role for high mobility group box protein-1 (HMGB1) in the ENaC overexpressing Scnn1b+ mouse model [3]. Taggart *et al*. have proposed secretory leucoprotease inhibitor (SLPI) as a multifunctional therapeutic for chronic inflammatory lung disease characterised by a high protease burden [4-6]. Their studies showed how SLPI acts not only as an antiprotease but also as an anti-inflammatory by directly inhibiting toll-like receptor (TLR) signalling and NFκB activation in macrophages. Their thesis promotes the idea that antiprotease therapies are likely to have significant benefit for CF.

Protease-mediated lung destruction is a hallmark feature of CF lung disease. In their article Quinn *et al*. outline the major protease families present in the CF lung and the various antiproteases that have been proposed as their possible therapeutic inhibitors. Therapies targeting the serine protease neutrophil elastase (NE) are described however, as NE is not the only culprit causing the lung damage in CF, other major proteases in the CF lung including metalloproteases (MMPs), cysteinyl cathepsins and bacterial-derived proteases are also addressed as potential targets. Antiprotease strategies to dampen the pulmonary inflammation in CF and halt further damage to the airways are certainly an attractive therapeutic option and Quinn *et al*. expound the use of antiproteases themselves rather than small synthetic molecule protease inhibitor drugs, due to their additional therapeutic properties. For example the antibacterial and anti-inflammatory properties of SLPI are discussed. Finally the feasibility of using appropriate cocktails combining inhibitors of classes of proteases, which may form part of the future of personalised medicine programmes, is also considered.

In their review Gaggar *et al*. examine the potential impact of two new small molecule inflammatory mediators in CF lung disease, PGP and HMGB1. These novel molecules are described as playing an important and heretofore underappreciated role in pulmonary inflammation in CF. PGP, a collagen-derived peptide generated *via* prolyl endopeptidase, MMP-8 and MMP-9 activity, although by no means the only chemotactic molecule in the CF lung, according to Gaggar *et al*. may fulfil a role as significant as IL-8. HMGB1, possibly more familiar as a late mediator of inflammation in sepsis, is a DNA-binding protein which once released from its intracellular location can activate the receptor for advanced glycation end products (RAGE) and TLRs 2 and 4. Various strategies are proposed that have the potential to antagonise HMGB1 and PGP in the CF lung.

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Becker *et al*. believe that ceramide plays an important role in the pathogenesis of CF and that pharmacological or genetic inhibition of acid sphingomyelinase, the enzyme responsible for generating ceramide, has therapeutic potential for the treatment of CF. Their mouse models have generated convincing data that ceramide is important in promoting inflammation and pathological changes in the CF lung yet they freely admit that its role in the development of fibrosis remains to be determined. Furthermore they are quick to point out that in addition to its undesirable proinflammatory effects ceramide is actually required for the effective removal of bacteria from the lung during acute infection. Accordingly their favoured approach is to use aerosolised agents such as amitryptyline to partially inhibit ceramide production thereby restoring normal pulmonary ceramide concentrations.

The usefulness of any particular therapeutic for the pulmonary inflammatory manifestation of CF must be suited to the context of CF lung disease. Any particular treatment must have a clearly defined use – should it be given at the onset of an exacerbation or is it more suited for long-term administration to quell chronic inflammation? These are considerations which should be addressed in the evaluation of the novel therapeutic strategies described here.

Notwithstanding the veracity with which each of the authors expound the importance of their chosen therapeutic targets and their respective roles in the pathogenesis of CF lung disease, it is clear that this disease is dependent not only on the factors described in this series of articles but on additional known, and no doubt yet to be discovered, processes. Some of the major determinants of CF lung disease include a decreased airway surface liquid volume, increased mucus viscosity, chronic microbial colonisation, an impaired protease-antiprotease balance and increased pulmonary inflammation mediated in part by proinflammatory lipid- or collagen-derived molecules such as ceramide and PGP. However, other idiosyncratic factors including genotype, gender, colonisation status, co-morbidities, other organ involvement, treatment regimens and exacerbation history all play their part too.

With respect to the novel targets discussed here I look forward to the rapid development and proven success of therapies directed at these targets in our ongoing challenge to enhance the health and quality of life for individuals with CF.

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