Editorial

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Targeting Inflammation in Cystic Fibrosis

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Cystic fibrosis (CF) lung disease starts early in life and is characterized by chronic infection and inflammation. Long-term evidence shows that inflammation is a hallmark of and key contributor to the pathophysiology of CF lung disease, and is associated with the progressive destructive changes that are responsible for most of the morbidity and mortality in CF [1]. Despite the identification of the gene mutation that causes CF, the exact relationship between the basic gene defect and the pathophysiology of the disease still remains unclear. In particular understanding the inflammatory response of the host and the association between infection and inflammation is subject of ongoing debate and research [2, 3]. This is especially important as anti-infectious therapy is the mainstay of CF treatment and anti-inflammatory therapy could represent a major therapeutic target [4].

Several anti-inflammatory agents including corticosteroids and ibuprofen have been investigated for treatment of CF lung disease. Pioneer trials with long-term alternate-day use of oral prednisone in CF patients reported a decrease in lung disease progression and morbidity with maintenance of lung function [5]. However, side effects of systemic corticosteroids have limited their use as a standard therapy, prompting trials with inhaled corticosteroids, which showed no significant benefits [6]. High-dose ibuprofen has been shown to reduce the amount of neutrophils in the lung [7] and slow the decline in lung function and disease progression [8]. However, due to unfavourable side effects, its clinical use is subject to debate [9]. Other anti-inflammatory agents for CF lung disease, such as n–3 polyunsaturated fatty acids, receptor antagonists of the cysteinyl leukotrienes, macrolides, *N*-acetylcysteine, and α-1 antitrypsin have shown clinical efficacy or potential for clinical use, but to date no ideal anti-inflammatory agent for CF lung disease has been found [10].

Because of the notable side effects of broad-spectrum anti-inflammatory drugs, a more targeted approach to control inflammation in CF lung disease is needed [4]. The ideal anti-inflammatory drug should efficiently combat deleterious inflammatory components without adverse effects such as impairment of innate immunity. In order to find such treatment, a thorough understanding of the mechanisms of inflammation in the CF lung as well as of the mechanisms of action of anti-inflammatory drugs is warranted.

Unfortunately, our knowledge on the mechanisms of inflammation in the CF lung is limited. One of the most striking characteristics of airway inflammation in CF is the predominance, continuous influx, and sustained accumulation of neutrophils with impaired bacterial-killing capacity upon changes due to unopposed proteolytic activity or host-derived stress signals upon entering CF airways [11, 12]. Neutrophils are recruited to the lungs by chemokines and cytokines, amongst which IL-8 is of key importance [13]. IL-8 is produced by airway epithelial cells endogenously or in response to pathogens via activation of the transcriptional regulatory complex NF-κB signalling, suggesting a central role of this pathway in the pathophysiology of inflammation in CF lung disease [14].

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However, the exact pathways leading to the overt inflammation in the CF epithelium have been poorly described. We know even less about the mechanisms of anti-inflammatory drugs used in CF. Corticosteroids are amongst the best studied drugs, and it has been shown that one of their ways of action is to inhibit cytokine release by airway epithelial cells by acting on the NF-κB pathway [15].

In this issue of *Respiration*, Dauletbaev et al. [16] explore possible anti-inflammatory mechanisms of ibuprofen in CF. Using two different CF airway epithelial cell lines, they demonstrate a modest suppression of NF-κB transcriptional activity by ibuprofen in cytokine-stimulated CF airway epithelial cells, without effect on IL-8 production by these cells, whilst they show an effect of dexamethasone, a widely used corticosteroid, on both NF-κB transcriptional activity and IL-8 production. These unexpected findings suggest that both ibuprofen and dexamethasone may act on the CF airway epithelium by molecular mechanisms other than NF-κB inhibition. Dauletbaev et al. speculate that pathways such as the transcription factor C/EPB homologous protein or the activated protein-1 pathway could be involved. Indeed, recent evidence has shown that NF-κB is not the only signalling pathway implicated in pro-inflammatory molecular mechanisms in the CF lung epithelium [17]. Alternative hypotheses suggested by the authors to explain their findings include direct effects on CF transmembrane regulator function, suppression of cAMP-dependent pathways, or effects on other cells such as neutrophils.

Thus, although the article of Dauletbaev et al. in this issue of *Respiration* provides us with interesting information regarding mechanisms of anti-inflammatory drugs in CF, it raises more questions than it answers. Perhaps a first step in the quest for the ideal anti-inflammatory drug in CF should be to get a proper understanding of the molecular effects of anti-inflammatory drugs on the normal airway epithelium before studying mechanisms in CF cells that possibly harbour inherent dysregulated inflammatory responses [2, 17].

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