CFTR is a modulator of airway inflammation

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Although it has been 17 years since the identification of the cystic fibrosis transmembrane ion receptor (CFTR) gene and protein, it remains enigmatic how abnormalities in CFTR can cause chronic and persistent pulmonary infection and inflammation that lead to bronchiectasis and end-stage lung disease (9). Because CFTR regulates transepithelial chloride and sodium conductance, the most prominent hypotheses have related to changes in the salt and water composition of the periciliary fluid causing isotonic dehydration of the airway surface (11). This is thought to make it more difficult to clear infected secretions from the airway, leading to chronic obstruction and bacterial infection with biofilm forming gram-negative organisms, especially Pseudomonas aeruginosa. The excessive inflammation in the CF airway is largely responsible for the development of bronchiectasis, but it has not been clear if this hyperinflammatory milieu is the result of the chronic infection or if it is primary to the pathology of CFTR dysfunction (5).

The CFTR protein has many functions, and there are several lines of evidence suggesting that the CFTR mutation itself can produce a proinflammatory milieu in the airways, suggesting that inflammation may precede infection. Some studies support the concept of increased NF-κB activation and IL-8 production in unstimulated CF epithelial cells, whereas other in vitro studies have demonstrated increased secretion of proinflammatory cytokines by CF airway cells only after exposure to pathogenic bacteria (1, 4, 8). Although this supports the concept that there is sustained and exaggerated inflammatory response in the CF airway, a problem in all of these studies has been that primary human CF airway cells may already be primed to respond differently. Furthermore, comparing cultures derived from normal and CF individuals can be difficult to interpret due to genetic differences other than CFTR.

This controversy is difficult to resolve in vivo because almost all people who have CF also have chronic bacterial infection. Infection has been shown to cause intense neutrophilic inflammation in CF (6). Studies of bronchial lavage fluid from subjects with CF show that neutrophilic inflammation is present even in infancy and perhaps before overt airway infection (3). Although the CF knockout mouse does not spontaneously develop chronic infection, the inflammatory response after infection with Pseudomonas appears to be significantly increased in these mice (10). A more intense neutrophilic response to bacterial simulation has also been reported in the CF airway and in cultured CF cells. When denuded trachea are seeded with primary CF or non-CF bronchial epithelial cells and implanted below the skin of athymic mice, there is increased airway inflammation in those airways populated by the CF cells (12). Despite the strong evidence for hyperinflammatory responsiveness in the CF airway, it has been difficult to link this directly to inhibition of the CFTR protein.

Perez and colleagues, in one of the current articles in focus in this issue (7), report that primary non-CF human bronchi epithelial cells have a significantly increased basal secretion of proinflammatory cytokines and stimulated secretion when these cells are first treated by a specific inhibitor of CFTR chloride conductance, CFTRinh-172. These investigators used CFTRinh-172 to create a CF cell culture model with its own control for testing the hypothesis that CFTR inhibition alone is sufficient to produce an exaggerated inflammatory response.

They demonstrated that when CFTR chloride conductance was inhibited by CFTRinh-172, there was a significant increase in IL-8 secretion that did not depend on stimulation by Pseudomonas, and this was associated with a decrease in Sma3 expression, an increase in RhoA expression, and an increase in NF-κB nuclear translocation after stimulation with TNF-α. This response was directly related to inhibition of CFTR protein because there was no increase in epithelial sodium channel activity, and withdrawal of CFTRinh-172 quickly led to a reversion to the normally lower inflammatory phenotype of these airway cells. Also, CFTRinh-172 did not appear to produce increased IL-8, IL-6, or granulocyte/macrophage colony-stimulating factor secretion in cultured CF-derived airway cells where CFTR was defective and thus chloride conductance was constitutively abolished. These results are the strongest evidence to date that inhibition of CFTR in itself is sufficient to produce an exuberant inflammatory response to bacteria as well as an increased constitutive secretion of IL-8.

What does this mean for our understanding of the pathogenesis of CF lung disease and the development of potential therapies? It appears that the CF airway may be exceptionally vulnerable to infection by biofilm-forming gram-negative organisms, perhaps through a process of failing to prevent bacterial adherence to the epithelium or to clear bacteria through an effective mucociliary clearance and by failing to prevent transformation of the bacteria from planktonic to a biofilm-producing phenotype. In association with this, there is a profound inflammatory response that not only activates and recruits neutrophils but through chronic stimulation leads to neutrophil necrosis rather than clearance through apoptosis. This in turn leads to the accumulation of polymeric DNA and cellular debris in the airway along with bacteria and bacterial products and a reduction in the amount of mucus (2). Thus the CF airways fill up with secretions that are indistinguishable from pus, and this poorly cleared purulent material exacerbates the vicious cycle of infection and inflammation. Breaking this cycle will require eradication of infection and appropriate neutralization of the inflammatory response. This may be far more important than restoration of ion transport or water content of the airway surface liquid in isolation.
REFERENCES