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Cystic fibrosis and lipoxins

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Abstract

Dysregulated neutrophilic inflammation and chronic infection lead to progressive destruction of the airways in cystic fibrosis (CF). Despite considerable recent progress in therapy, the median survival of patients with CF remains around 30 years. The lipoxins are endogenous anti-inflammatory lipid mediators that are important regulators of neutrophilic inflammation. Recent data indicate that there is a pathophysiologically important defect in lipoxin-mediated anti-inflammatory activity in the CF airway, suggesting novel approaches to pathogenesis and therapy in this lethal genetic disease.

1. Introduction

Cystic fibrosis (CF), the most common lethal autosomal recessive disorder in the US, is caused by mutations in the gene encoding the CF transmembrane conductance regulator (CFTR). The major clinical manifestations of CF include exocrine pancreatic insufficiency, male infertility, and chronic pulmonary disease [1–4]. Pulmonary disease is the main cause of morbidity and mortality. The CF airway is marked by chronic bacterial colonization and persistent neutrophilic inflammation. Bacterial colonization of the airways generally occurs within the first years after birth. There is a predisposition to subsequent chronic colonization/infection with *Pseudomonas aeruginosa*, an organism whose presence in the CF lung is associated with progressive respiratory compromise. By adulthood, 80–90% of patients with CF suffer from chronic airway infection with mucoid strains of *P. aeruginosa*. Infection is associated with an exuberant inflammatory response dominated by neutrophils and the potent inflammatory mediators that are released by activated neutrophils. The end result of this mix of infection and inflammation is progressive, bronchiectatic destruction of the lung [1,3].

2. Pursuit of the mechanistic linkage between *CFTR* and lung disease in CF

Despite the insights afforded by the identification of *CFTR* in 1989 [5], a clear understanding of the pathogenesis of pulmonary disease in CF has remained elusive [4,6,7]. *CFTR* spans 250 kb and contains 27 exons that are transcribed into a 6.5 kb mRNA that, in turn, encodes a 1480 amino acid integral membrane protein of the ATP-binding cassette family. More than 700 *CFTR* mutations are known, the most common being a 3 base pair deletion that leads to deletion of phenylalanine from position 508 (ΔF508), and to defective CFTR maturation [8]. CFTR appears to be principally expressed in epithelial cells of affected tissues, including the airways, pancreas, vas deferens, and sweat glands. In addition to direct chloride transport by CFTR, ion transport mediated by amiloride sensitive sodium channels, outwardly rectifying chloride channels, and potassium channels are altered in cells with mutant CFTR [9]. CFTR is also thought to

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conduct ATP [9]. More widely, a variety of cellular processes, including membrane recycling, protein processing, signal transduction pathways, and the secretion of immune mediators appear to be influenced by CFTR [10–13]. In turn, the expression and/or function of CFTR is modified by a variety of factors, including inflammatory mediators (e.g. IFN-γ), hormones (e.g. androgens), signaling pathways (e.g. protein kinase C), extracellular conditions (e.g. osmolarity), and pharmacological agents (e.g. genistein) [9,14–17]. The nexus of interaction with CFTR is thus wide, [7] with multiple gene products up- and downstream of CFTR, something underscored by recent functional genomic studies [18].

The theoretical and experimental focus on *CFTR* as a regulator of epithelial ion transport has provided a compelling account of the pathogenesis of gastrointestinal disease in CF as well as of the genesis of such CF-associated phenomena as high sweat NaCl content. However, the examination of altered ion and water transport alone has failed to clearly illuminate the path from gene to pathogenesis in the CF airway. Circumstantial evidence for the likely role of at least part of the above-described array of interacting gene products in the pathogenesis of lung inflammation and infection is provided by the poor correlation of genotype with phenotype in CF pulmonary disease (as opposed to pancreatic disease) [2,3]. Indeed, patients with variant CF (and chronic lung disease) with wild-type *CFTR*, and in whose families haplotype analysis reveals no linkage to *CFTR*, are well-described [19].

Several hypotheses have been advanced to explain the propensity for airway colonization and infection in CF, including alterations in mucociliary clearance due to low airway surface fluid volume and thick, viscid mucus, increased bacterial adherence and decreased bacterial phagocytosis by airway epithelial cells, and compromise of the innate immune defenses in the lung [4,7,20–28]. More recently, it has become clear that CF is marked by dysregulated airway inflammatory responses that are central to CF-associated lung disease and destruction [4,7,13,29–34].

3. Pulmonary disease in CF: a primary inflammatory disorder

The CF airway is marked by an aberrant proinflammatory diathesis. In addition to the sustained presence of activated neutrophils and neutrophil-derived secretory products (e.g. neutrophil elastase), there is significant upregulation of proinflammatory cytokine production: IL-8 (a major neutrophil chemokine), TNF, and IL-1β are all markedly elevated in bronchoalveolar lavage (BAL) fluid, sputa, and bronchial biopsies from patients with CF [13,29–34]. Conversely, production of the anti-inflammatory cytokine, IL-10, is suppressed in the CF airway [29].

Whether airway inflammation is merely an appropriate response to infection or represents a primary abnormality in CF had been unclear. Clinical studies on infants with CF have revealed inflammation in the absence of demonstrable infection [31,35,36]. Careful quantitation of bacteria and bacterial products has also revealed that inflammatory mediators, when normalized to the number of bacteria or to the concentration of endotoxin in the airway, are significantly increased in children with CF compared with children without CF with respiratory disease [37,38]. That is, CF is associated with exaggerated airway inflammatory responses that are out of proportion to the inciting infectious stimulus. Convincing evidence that CF involves a primary disorder of inflammation came from a recent elegant study using human fetal airway grafts in severe combined immunodeficient mice [13]. Such heterotopic grafts undergo histological maturation of the surface epithelium and submucosal glands after a few weeks in the host. Mature grafts also exhibit predicted differences between CF and non-CF grafts in ion transport [39]. In this (initially) pathogen-free model, IL-8 concentrations were markedly increased in airway fluids from CF compared with non-CF grafts. Immunostaining localized IL-8 production to epithelia (surface mucous and submucosal gland cells). After infection with *P. aeruginosa*, there was rapid, massive luminal transmigration of leukocytes in CF grafts, associated with mucosal damage [13]. Such damage of the normal mucosal architecture is likely to predispose to chronic bacterial colonization in the intact lung. These studies strongly suggest that the basal proinflammatory predisposition of the CF airway leads to the development of mucosal damage upon infection, damage that is integral to subsequent persistent bacterial colonization [13,39]. An inflammatory diathesis thus appears to predate infection, secondarily impairing local host defenses in ways that promote airway colonization.

Other evidence that the inflammatory response in CF isn't merely an appropriate adaptive response to ongoing bacterial infection is more indirect, if still compelling: steroids and non-steroidal anti-inflammatory drugs appear to preserve lung function in patients with CF without, however, increasing the pulmonary infectious burden [40,41]. Further, C5a receptor-deficient mice, like patients with CF, fail to clear *P. aeruginosa* from the lung despite vigorous neutrophilic infiltration, suggesting that abnormal regulation of neutrophil trafficking and activation may be important to decreased bacterial clearance and excessive inflammatory responses [42]. The interaction between inflammation and infection is clearly bidirectional, however: bacterial products themselves are paradigmatic inducers of neutrophil chemotaxis and proinflammatory responses.