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Review

Inflammation in cystic fibrosis lung disease: Pathogenesis and therapy☆

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Abstract

Lung disease is the major cause of morbidity and mortality in patients with cystic fibrosis (CF). Although CF lung disease is primarily an infectious disorder, the associated inflammation is both intense and ineffective at clearing pathogens. Persistent high-intensity inflammation leads to permanent structural damage of the CF airways and impaired lung function that eventually results in respiratory failure and death. Several defective inflammatory responses have been linked to cystic fibrosis transmembrane conductance regulator (CFTR) deficiency including innate and acquired immunity dysregulation, cell membrane lipid abnormalities, various transcription factor signaling defects, as well as altered kinase and toll-like receptor responses. The inflammation of the CF lung is dominated by neutrophils that release oxidants and proteases, particularly elastase. Neutrophil elastase in the CF airway secretions precedes the appearance of bronchiectasis, and correlates with lung function deterioration and respiratory exacerbations. Anti-inflammatory therapies are therefore of particular interest for CF lung disease but must be carefully studied to avoid suppressing critical elements of the inflammatory response and thus worsening infection. This review examines the role of inflammation in the pathogenesis of CF lung disease, summarizes the results of past clinical trials and explores promising new anti-inflammatory options.

Keywords: Lung inflammation; Cystic fibrosis; Neutrophils; Anti-inflammatory therapies; Bronchiectasis; Mucosal immunity

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1. Introduction

Cystic fibrosis lung disease is characterized by early colonization and infection of the airways. Although structural changes in the CF airways can be observed at birth in both humans and the CF pig, little inflammation is observed [1,2]. However, infection occurs very rapidly and the inflammatory response to pathogens is severe [3]. Free and bound airway neutrophil elastase is detected very early in CF infants and predicts the development of bronchiectasis later in life [4]. No other lung disease is known to induce such an early, sustained and intense inflammatory process as seen in the CF airway. Individuals with CF also suffer from an intense systemic inflammation characterized by increased serum acute phase reactants, high antibody titers to numerous exogenous and endogenous antigens, a high incidence of ileitis including Crohn's disease, atopy and heightened Th2 responses [5,6].

CF is caused by a severe functional deficiency of the cystic fibrosis trans-membrane conductance regulator (CFTR) protein [7]. CFTR is largely expressed in the apical membranes of epithelial cells that line the cylindrical structures of tissues that secrete fluids often rich in mucus and other proteins. The airways are among the tissues with the highest expression of CFTR. The lack of functional CFTR causes deficient cAMP-dependent chloride and bicarbonate secretion into airway secretions. Consequently, mucins are tethered to the bronchial apical surfaces, and airway surface fluid pH is decreased. Recent findings indicate that the degree of acidification of the CF airway surface is sufficient to induce significant defects in host anti-bacterial defenses [8]. Furthermore, defective secretion of both chloride and bicarbonate prevents the release of mucus strands from glands, leading to the tethering of mucus to the gland ducts [9]. Persistent bronchopulmonary infections with *Staphylococcus aureus*, *Pseudomonas aeruginosa* and several other pathogens ensue, leading to chronic airway and systemic inflammation, tissue destruction, and respiratory insufficiency [10–12]. But why is the inflammation so severe? The link between CFTR deficiency and inflammation likely involves several CFTR-related abnormalities (Fig. 1) that are discussed in the paragraphs below.

2. Linking the CF basic defect to inflammation

2.1. Airway surface liquid and mucociliary clearance

The airway surface liquid and mucus layer (ASLM) is a complex and dynamic structure that is continuously changing in response to signals from the environment and the host. Two of the major functions of airway mucus are to clear pathogens through the mucociliary escalator, and when needed, to provide a protective barrier against toxic endogenous and exogenous products. The former function requires a sufficiently fluid mucus layer to allow evacuation of particles and pathogens, whereas the latter requires a more abundant and viscous mucus layer. CFTR is key to defining the changing properties of the airway surface liquid and mucus layer [13].

Recent work has provided evidence supporting a model to explain how airway surface liquid and mucus hydration are regulated [14]. Tethered mucins present on the cilia of airway epithelial cells form a mesh network ensuring that the water content between cilia is constant under most conditions. The secreted mucins (primarily MUC5AC, MUC5B and MUC2) attract water and form a reservoir from which water can be drawn into the periciliary space to ensure its constant hydration. By secreting chloride and either directly or indirectly regulating sodium absorption, CFTR plays a key role in providing the water needed to balance the hydration of these compartments. The function of CFTR is also highly susceptible to cues from the environment. CFTR function is suppressed by oxidant stress (ex: cigarette smoke) and by certain bacterial products (ex: *P. aeruginosa*) [15,16]. The loss of chloride secretion from CFTR deficiency results in changes in osmotic pressures and electro-neutrality which likely lead to excessive sodium and water absorption. Loss of the critical hydration of ASLM favors chronic retention of pathogens and a secondary inflammatory response.

2.2. Mucus layer hypoxia

Histopathological examination of end stage CF lungs reveals extensive plugging of the small airways by purulent mucus. Furthermore the lung of the newborn CF pig is characterized by abundant thick mucus streaming out of goblet cells and adhering in multiple layers to the epithelial airway surface [2]. The oxygen tension in mucopurulent "masses" present in the CF *P. aeruginosa* infected airway is very low [17]. Low oxygen tensions may hinder normal host anti-bacterial defenses and favor bacterial growth. Hypoxia initiates a cascade of cell-signaling events that begin with the stabilization of the hypoxia inducible factor-1 (HIF-1), a transcription factor affecting angiogenesis, inflammation and fibrosis [18]. HIF-1 stability may be altered in CFTR-deficient cells [19], however HIF-1 has not been studied in the newborn CF airway when inflammation begins.