Innate and Adaptive Immunity in Cystic Fibrosis

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KEYWORDS

• Innate immunity • Adaptive immunity • Lung hyperinflammation • Bacterial infection

KEY POINTS

- Innate and adaptive immunity is dysregulated in individuals with cystic fibrosis (CF).
- Immune dysregulation in CF is driven by inherited and acquired factors.
- Both CF airway epithelium and CF immune cells contribute to immune dysregulation in CF.
- Therapies that reduce inflammation or boost the anti-inflammatory response may prevent the progression of CF lung disease.
- An effective, long-term therapy for CF should ameliorate the defective immune response.

INNATE IMMUNITY

Altered Barrier Function Impairs Host Defense in Cystic Fibrosis

The airway epithelium works as a physical barrier between the external environment and internal structures, which represent the lung's first defense against inhaled microorganisms. The barrier function of airway epithelium is accomplished by (1) mucociliary transport, which traps and removes inhaled foreign particles in the airways[1]; (2) secreted antimicrobial molecules that kill inhaled pathogens[2]; and (3) cell-cell connections that regulate epithelial paracellular permeability.[3] The integrity of the airway epithelium in individuals with cystic fibrosis (CF) is often disrupted at several levels, thus playing a central role in dysregulated innate immunity.

Reduced mucociliary clearance

The major macromolecular components of lung mucus are mucins, which are secreted by various cells of the conducting airway epithelium. Mucins are folded in an organized manner so as to reach a specific viscosity necessary for efficient release and transport. The cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is defective in CF, produces a protein whose basic function regulates ion transport on the surface of the airways that contributes to mucus hydration and periciliary transport, which are altered on mucosal surfaces in CF.[4] Recent studies in the CF pig, which models the intrinsic human disease, revealed that CF mucosal properties (eg, elasticity and tenacity) are abnormal, leading to defective mucus detachment from the submucosal gland ducts of piglet tracheal tissues, thus impairing mucociliary transport. Alterations of mucosal proprieties are directly linked to reduced CFTR-dependent chloride and bicarbonate secretion,[5] which result in increased acidity of the airway surface liquid.[6] A similar scenario may compromise the gastrointestinal function.[7] As the disease

Disclosures: None.

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Clin Chest Med 37 (2016) 17–29
http://dx.doi.org/10.1016/j.ccm.2015.11.010

progresses, increased absorption of sodium, via epithelial sodium channel (ENaC) will further contribute to airway surface liquid dehydration, decreased periciliary liquid transport, and impaired ciliary function, thus exacerbating defective mucociliary transport in CF airways.[8] The biophysical properties of CF mucus may also be altered because of epithelial production of adenosine,[9] and neutrophilic oxidative stress.[10]

A number of microorganisms (including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Haemophilus influenza* have been implicated in CF. These pathogens bind to mucins secreted by the respiratory tract, which normally is cleared by mucociliary clearance. However, it is clear that in a disease such as CF, in which mucociliary transport is altered, this essential and basic innate immune defense is compromised. Reduced mucociliary clearance and stagnating mucus will affect the innate immune response by several potential mechanisms including:

- Favoring the trapping of bacteria in the airways, which has been observed in lung tissue sections of patients with CF.[11]
- Altering the airway microenvironment (eg, oxygen tension, glucose, and iron concentrations), which may benefit bacterial adaptation. For example, *P aeruginosa* evolves from a nonmucoid to a mucoid strain, which is more resistant to antibiotics.
- Altering the behavior and function of lung immune cells. Impaired lung mucus may alter function of lung macrophages (MΦ),[12] compromising their production of anti-inflammatory and repair mediators (also discussed in the section on macrophages/monocytes, later in this article).

Intensive research is ongoing to identify novel drugs to improve mucus hydration and mucociliary clearance in CF. These therapies may also assist to reestablish basic barrier function in CF, which has additional therapeutic implications.

Altered airway surface liquid composition

There are several factors (summarized in the following sections) that have been linked to altered airway surface liquid (ASL) composition.

Airway surface liquid acidification The acidic pH of the CF ASL neutralizes the activity of several enzymes/peptides that normally provide protection against pathogens. The antimicrobial peptides β-defensin-3 and cathelicidin (LL-37) are downregulated in the lungs of pigs and patients with CF.[13] Lysozyme and lactoferrin are additional proteins that are abundantly secreted by lung epithelial cells and immune cells, and perform important host defense functions. Lactoferrin, which sequesters iron, may be low in CF.[14] As a consequence, iron may accumulate in the lavage and lungs of patients with CF, favoring microbial growth and viral infection.[15,16] Reduced concentrations of lactoferrin in CF lungs also may be a result of suboptimal degranulation of secondary and tertiary granules in CF neutrophils.[17]

In normal airways, the secreted protein Short Palate Lung and Nasal epithelial Clone 1 (SPLUNC1) plays an important role in innate immunity by binding bacterial products[18] and inhibiting sodium absorption in a pH-dependent manner.[19] Thus, in the CF airways, in which pH is lower, SPLUNC1 is inactive, further compromising innate immune functions.

Increased protease activity Increased lung neutrophil recruitment, which reflects persistent inflammation, is a hallmark of CF lung disease. In normal lung, neutrophils migrate to the airways in response to chemokines, and are activated, programmed for cell death, and removed from the airways by MΦ or by expectoration (see also the sections titled Neutrophils and Macrophages/monocytes). This coordinated process is altered in CF lungs, which results in lung neutrophilia causing the accumulation of neutrophil proteases. CF sputum has high concentrations of neutrophil elastase,[20] which correlates with more rapid decline in lung function in individuals with CF.[21] Elevated neutrophil elastase activity in the airways, degrades structural airway matrix proteins (eg, collagen and elastin)[22] and cleaves plasma membrane receptors/proteins involved in immune regulation. For example, the interleukin (IL)-8 receptor CXCR1,[23] MΦ phosphatidylserine that mediates apoptotic cell clearance[24] (see also the section Macrophages/monocytes), complement (C3, C5, and dC3bi), complement receptors (eg, CR1), and lymphocyte receptors (CD4 and CD8)[25] are all affected by elastase. Increased neutrophil elastase activity also has been associated with increased mucin expression, secretion,[26] and activation of Toll-like receptor (TLR)4 signaling.[27]

All of these changes exacerbate inflammation, interfere with efficient bacterial clearance, and compromise lung tissue integrity. Unfortunately, ivacaftor treatment, which improves mutation-specific CFTR function, is not associated with improvements in neutrophil elastase or sputum inflammation,[28] suggesting that anti-inflammatory therapies may still be necessary for patients with CF to reduce lung tissue damage over time. Other neutrophil proteases, such as cathepsin G,[20]