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The Evolution of Cystic Fibrosis Care

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Cystic fibrosis (CF) is the most common life-limiting inherited illness of whites. Most of the morbidity and mortality in CF stems from impaired mucociliary clearance leading to chronic, progressive airways obstruction and damage. Significant progress has been made in the care of patients with CF, with advances focused on improving mucociliary clearance, minimizing inflammatory damage, and managing infections; these advances include new antimicrobial therapies, mucolytic and osmotic agents, and antiinflammatory treatments. More recently, researchers have targeted disease-causing mutations using therapies to promote gene transcription and improve channel function, which has led to impressive physiologic changes in some patients. As we develop more advanced, allele-directed therapies for the management of CF, it will become increasingly important to understand the specific genetic and environmental interactions that cause the significant heterogeneity of lung disease seen in the CF population. This understanding of CF endotypes will allow for more targeted, personalized therapies for future patients. This article reviews the genetic and molecular basis of CF lung disease, the treatments currently available, and novel therapies that are in development.

CHEST 2015; 148(2):533-542

ABBREVIATIONS: CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; ENaC = epithelial sodium channel

Cystic fibrosis (CF), which is an autosomal recessive defect occurring in approximately one in 3,500 live births based on data from neonatal screening,[1] is the most common, life-shortening inherited disease of whites. The life expectancy of a child born with CF has improved steadily, largely because of advances in disease surveillance and more aggressive treatment strategies. Nevertheless, patients with CF die too young, with much of the early morbidity and mortality from CF resulting from progressive airway involvement. Universal adoption of newborn screening in the United States[1] has led to earlier diagnosis and treatment of CF, which has sparked hope that lung disease can be averted even before it begins, especially with the advent of newer agents that target the basic cellular defect and have the potential to radically change clinical outcomes. The use of defined endotypes, phenotypic subtypes that rely on a combination of genetics, biomarkers, environmental exposures, clinical outcome measures, and infectious and inflammatory factors to characterize disease, may better

Manuscript received August 13, 2014; revision accepted February 12, 2015; originally published Online First March 12, 2015.

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FUNDING/SUPPORT: The authors were supported by the Cystic Fibrosis Foundation Therapeutics (Dr Pittman), the Children's Discovery Institute (Dr Ferkol), and the National Institutes of Health (NIH) [Grants HL101465 (Dr Ferkol), HL116211 (Drs Pittman and Ferkol), HL096458 (Dr Ferkol), and K12 HL120002 (Dr Pittman)].

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DOI: 10.1378/chest.14-1997

direct therapeutic interventions by targeting specific populations with CF. In this article, we review the pathophysiology of CF lung disease and describe how current and emerging therapies can both treat and possibly prevent this progressive lung disease.

Genetics and Pathophysiology of CF Airway Disease

To fully understand the current and newer therapies for CF, physicians must have a working knowledge of the basic pathophysiology of the disease. CF is clinically characterized by chronic sinopulmonary and GI manifestations, which are caused by abnormalities in the cystic fibrosis transmembrane conductance regulator (CFTR), a channel located at the surface of the cells lining the airway epithelium and in the submucosal glands that mediates cyclic adenosine monophosphate (cAMP)-regulated transport of chloride and other anions.[2-6] The CFTR is functionally linked to the epithelial sodium channel (ENaC) and alternative apical chloride channels; thus, the CFTR defects lead to not only reduced chloride conductance but also dysregulation of ENaC activity. This failure of chloride secretion and sodium hyperabsorption leads to desiccation of the periciliary fluid layer and viscous mucus on the airway surface. The dehydrated secretions and excess solids in airway mucus impair mucociliary clearance, obstruct the airways, allow bacterial infection to become established, and subsequently incite an intense inflammatory response.[7] Impaired activity of bactericidal proteins produced by airway epithelia related to altered bicarbonate secretion in the CF airway creates gaps in innate airway defenses and contributes to chronic infection (Fig 1).[8]

Nearly 2,000 disease-causing mutations in *CFTR*, a 27-exon gene on chromosome 7,[9-11] have been identified. Although racial and ethnic differences exist, the most common mutation is c.1521_1523delCTT, or delF508, which accounts for > 70% of mutant alleles in the CF population.[11,12] Mutations are usually grouped into six classes based on the protein product. Class 1 mutations consist of frameshift or nonsense variants that cause altered or impaired *CFTR* transcription, producing either messenger RNA that decays before nuclear export or truncated, nonfunctional protein. Class 2 mutations, such as delF508, result in misfolded protein that is trafficked to degradation pathways, has abnormal function, and is more rapidly cleared from the cell membrane. Mutations from both of these classes typically lead to more severe lung disease and pancreatic insufficiency. Class 3 mutations, including G551D, commonly called gating mutations, lead to a CFTR that is poorly responsive or nonresponsive to ATP activation of the nucleotide-binding domains, resulting in defective chloride conductance across the apical cell membrane. The clinical phenotypes and severity associated with class 3 mutations vary. Class 4, or conducting, mutations have impaired chloride conductance or transport caused by alterations in size and ion selectivity of the channel pore. Class 5 mutations are frequently splice mutants that reduce the rate of synthesis of functional CFTR and include intron 8 polythymidine variants. Class 6 mutations involve genetic defects that are near the N- or C-terminus and lead to aberrant membrane insertion, stability, or trafficking (Fig 2).[2,6,13-18] Some mutations defy classification. For instance, delF508 acts as a class 2 (altered processing), class 3 (impaired gating), and class 6 (rapidly degraded) mutation, which potentially

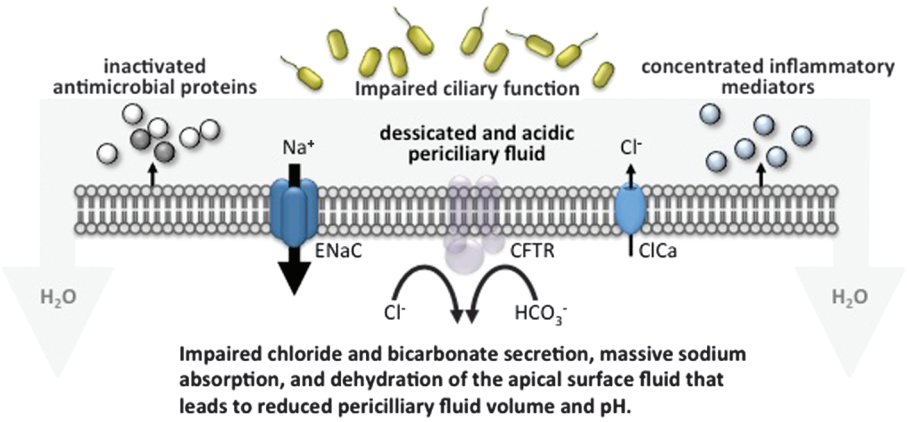

Figure 1 – *Epithelial pathophysiology in cystic fibrosis, characterized by altered anion secretion, sodium hyperabsorption, and dehydration of the apical surface fluid that leads to reduced periciliary fluid volume and pH, which interferes with mucociliary clearance and innate defenses, resulting in chronic infection. The decreased periciliary fluid volume also concentrates inflammatory mediators at the immediate epithelial surface. CFTR = cystic fibrosis transmembrane conductance regulator; Cl^- = chloride; ClCa = alternative chloride channel; ENaC = epithelial sodium channel; HCO_3^- = bicarbonate; H_2O = water; Na^+ = sodium.*