PATHOPHYSIOLOGY AND THERAPEUTIC TARGETS*

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ABSTRACT

One of the most common genetic disorders resulting in early death, cystic fibrosis (CF) is believed to be caused by a defect in the CF gene, which results in an absence or deficiency of a fully functional CF transmembrane conductance regulator (CFTR) protein. Although life expectancy of patients with CF has significantly increased over the last few decades as a result of modern-day treatment, therapeutic research and development remain critical. Current drug discovery efforts are focused on a 3-pronged approach involving discovery of new therapeutic agents to treat or replace the underlying defective protein, discovery of new therapies to treat secondary consequences of the dysfunctional CFTR protein (e.g., inflammation and infection), and identifying approved therapies that may benefit patients with CF. This discussion explores new research approaches and new therapeutic targets, most notably those that involve targeting abnormal genes, abnormal CFTR protein production, altered ion transport/abnormal mucus secretion, and infection/inflammation.

(Cystic fibrosis [CF], a complex multi-organ disease in which lung function accounts for nearly 85% of mortality, is one of the most common genetic disorders causing early death. Although this disease remains devastating, significant strides made in the understanding of CF, availability of multiple therapies, and aggressive management of CF lung disease have resulted in great improvements in length and quality of life. Unlike patients with CF in the past, who often died in early childhood, today’s patients can be expected to reach adulthood, surviving to nearly 40 years of age. But in order to further increase life span and improve quality of life, research into new treatment strategies and therapeutic targets is critical.

OVERVIEW OF PATHOPHYSIOLOGY

Although the pathogenesis of CF is not entirely understood, current belief is centered on a cascade (Figure 1) that is initiated by a defect in the CF gene, which results in an absence or deficiency of a fully functional CF transmembrane conductance regulator (CFTR) protein. In broad terms, the presence of the deficient CFTR protein results in defective respiratory transepithelial ion transport (accelerated rate of sodium absorption, inefficient chloride secretion), airway surface liquid depletion, and defective mucociliary clearance. Airway surface liquid depletion, considered a central driver of CF pathogenesis, results in dehydration and accretion of mucus, which predisposes the airway to colonization and infection with a restricted spectrum of microbial pathogens. These conditions eventually lead to development of the hallmark CF lesions, consisting of occlusion and severe inflammation in and around conducting airways. Inflammatory plugs found in the airways commonly contain mucus, a large number of neutrophils, and a high prevalence of bacteria. The alter-
ations that occur in the upper and lower airways lead to a perpetuating cycle of bronchial obstruction, infection, inflammation, and ultimately, lung destruction. The actual temporal sequence of inflammation and infection is not currently known (as indicated by their cyclical positions in the Figure 1 cascade), but it is expected to have future therapeutic implications in regard to which agents patients are initially treated with and the combination therapy that may be most effective.4,5

**NEW RESEARCH APPROACHES**

Current research efforts are focused on a 3-pronged approach involving discovery of new therapeutic agents to treat or replace the underlying defective protein, discovery of new therapies to treat secondary consequences (eg, inflammation and infection) of the dysfunctional CFTR protein, and identification of approved therapies that may benefit patients with CF. As researchers continue to develop new therapies to treat the primary defect in CF, it is important to continue searching for already approved drugs that are not currently being prescribed in the CF community. Drugs such as ibuprofen and azithromycin treat secondary complications (eg, inflammation and infection) of CF, and they carry the obvious advantages of decreased cost and time from a research and development perspective, immediate availability to the patient, and a well-defined safety profile. Nevertheless, drug development remains critical because, thus far, there is no currently available disease-modifying drug for CF.

In examining potential therapeutic approaches, it is useful to consider the robust research that has historically linked forced expiratory volume in 1 second (FEV1), a measure of lung function, with survival in CF. The US Food and Drug Administration (FDA), which is largely focused on outcomes that affect patient performance, survival, or subjective feeling, has accepted FEV1 as a valid surrogate end point for clinical trials because it predicts survival outcome. With traditional therapy, improvement in lung function normally follows initiation of treatment. But when lung function is examined over time, that initial clinical improvement does not appear to change the slope of decline that occurs in CF, indicating that therapy may be effective but it is not resulting in disease modification. Ideal future interventions would arrest the disease and, if initiated soon after birth, would preserve lung function and structure. At this time, however, a more realistic disease-modifying approach would be to slow the decline and alter the downward slope of this disease. But accomplishing even this goal requires researchers to intervene at an earlier stage in the disease. In considering the events that occur between birth, development of persistent symptoms of lung disease, and loss of lung function (as measured by spirometry), several phenomena may be placed on a time line...
(Figure 2) and identified as occurring before FEV₁ loss (as a result of events occurring earlier and because FEV₁ cannot be reliably measured before age 5 or 6). As indicated in Figure 2, targeting the disease upstream, at a much earlier point than the studies that have validated chronic therapies, would produce considerably better outcomes.

Historically, drugs (eg, azithromycin and hypertonic saline) were validated in clinical trials by their ability to increase FEV₁, but because many of the studied patients already had abnormal lung function, the validation (FEV₁ improvement) occurred later in the disease process. Thus, essentially, the strongest evidence for therapeutic benefit is derived from patients who have already experienced considerable lung damage. Current CF pulmonary guidelines, which recommend 6 drugs (azithromycin, dornase alfa, inhaled tobramycin, hypertonic saline, ibuprofen, and β₂-agonists), are all based on evidence of established disease in clinical trial patients with baseline loss of lung function (as measured by spirometry). But therapeutic intervention should be considered in early stages, before lung disease is established, in order to provide the most benefit. Although there has been a general shift in management to earlier intervention, treatment is still largely based on the presence of signs or symptoms of disease. But pathologic sequelae precede loss of lung function, and there is no consensus on the optimum time to intervene and on which therapy to utilize initially.

By using already approved drugs (the so-called “low hanging fruit”) for persistent symptoms and/or pulmonary exacerbations, clinicians are already intervening earlier in the disease process than researchers conducting clinical trials. Interventions that begin even earlier, as well as the use of nontraditional biomarkers (eg, structural lung changes on computed tomography [CT] imaging or early occurrence of bacterial infection) that are not currently considered accepted surrogates for new drug approval, may be helpful in improving outcomes. Although the FDA may not approve a drug for CF based on a study utilizing, for example, the presence of Pseudomonas aeruginosa in a throat culture as a biomarker, clinicians may incorporate biomarker-driven interventions into practice if they feel this information may ultimately help the patient. In the future, potentially helpful markers may include cytokines or cells in the bronchoalveolar lavage or induced sputum (in evaluating anti-inflammatory agents), the immune response (early indication of infection prior to culture detection), certain risk factors (eg, nutritional and growth indices) that precede loss of lung function, and early pulmonary physiologic or structural changes.

Structural analysis, as conducted by high-resolution CT, may provide qualitative and quantitative parameters that are more sensitive than routine pulmonary function tests in estimating structural lung changes in CF. CT scanning may, therefore, provide more sensitive outcome measures to assess new therapies. It may also be used to detect subtle indications (eg, air trapping) of early lung damage, prior to occurrence of spirometric loss, so that a preventive intervention may be considered before major changes in lung function or structure are detected.

Figure 3 depicts proposed staging of structural damage in CF (as it progresses from birth to adulthood), along with potential stage-specific therapeutic interventions.

NEW THERAPEUTIC TARGETS

Potential therapeutic approaches currently in development involve targeting abnormal genes, abnormal CFTR protein production, altered ion transport/abnormal mucus secretion, infection/inflammation, tissue/organ destruction, and respirato-

![Figure 3. Defining CF Patient Populations for Therapeutic Interventions: Staging Structural Damage](image-url)
ry failure. Several investigational therapies (eg, CFTR potentiators, ion channel agents, gene therapy, and CFTR correctors) may ideally target the initial, silent component of CF lung disease and these therapies should be tested in the later stages of lung disease as well. In reality, all of these therapies target underlying processes (obstruction, inflammation, and infection) that drive lung damage at the earliest stages of CF.

In developing genotype-specific therapeutic targets, researchers have been closely examining molecular consequences of nonsense CFTR mutations (no synthesis or synthesis of truncated CFTR) and missense CFTR mutations (block in processing, block in regulation, altered conductance, and reduced synthesis). Up to 90% of patients are affected by the F508del mutation involving a block in CFTR processing; thus a therapeutic approach targeting this defect, which is currently in phase II studies, would be considered a tremendous breakthrough.

A more general therapeutic approach involves targeting volume depletion of the airway surface liquid. Mucus clearance, which is dependent on adequate surface liquid volume, is considered a key component of normal lung defense. In CF, there is a loss of the periciliary fluid, which results in diminution of mucociliary clearance. There are several potential enhancers of mucociliary clearance (Figure 4), each focusing on a different level of activity within the overall process of mucociliary clearance. These investigational agents may target alterations in chloride transport that do not involve CFTR, modulate ion transport, hydrate the airway without relying on channels, or nonspecifically enhance mucociliary clearance. Some agents (osmotic drugs) are being evaluated for their ability to affect airway hydration without having an effect on ion transport, whereas others may enhance mucociliary clearance through other mechanisms (eg, surfactant or lubricant secretion, alteration of ciliary beat). One compound in development (denutosol) appears to have multiple modes of action, acting on alternative chloride transport, and exhibiting independent activities on sodium transport inhibition, surfactant secretion, and ciliary beat frequency.

Other investigational efforts are focused on bacterial lung infection in CF. In terms of the pathogenesis of CF-related infection, it is important to realize the link between loss of periciliary fluid, stasis, increase in immobile mucus plaques within the airway, trapping of bacteria, and the ability of certain bacteria (particularly P aeruginosa) to grow in an environment that is progressively hypoxic and nutrient-lacking. As a result, evidence of early lung disease in patients with CF can be seen in samplings of bronchoalveolar lavage fluid, with most patients demonstrating infection with at least one of the common pathogens (Haemophilus influenzae, Staphylococcus aureus, and P aeruginosa) in infancy. P aeruginosa status has a tremendous impact on patient outcomes, with chronic colonization of the airways associated with a more rapid decline in lung function.

The natural course of P aeruginosa infection in patients with CF usually starts early in life with transient, non-mucoid P aeruginosa infections, which may occasionally self-resolve or be eradicated with aggressive antibiotic interventions. Eventually, however, Pseudomonas is known to adapt from a single-cell planktonic life form to an anaerobic biofilm or macrocolony mode of living, which becomes impermeable to eradication. The resultant chronic infection leads to escalating inflammation and an accelerated loss of lung function. Investigational therapeutic approaches involve using vac-

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**Figure 4. Potential Enhancers of Mucociliary Clearance by Mechanism of Action**

![Diagram showing potential enhancers of mucociliary clearance by mechanism of action.](image)

CFTR = cystic fibrosis transmembrane conductance regulator; Cl⁻ = chloride.

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cines that target CF pathogen colonization, antibiotics that are effective against biofilm *P. aeruginosa* adapted to anaerobic environments, agents that remove hypoxic mucus plugs, and anti-inflammatories for ineffective host defense and inflammation.

In examining anti-inflammatory opportunities, it is important to consider evidence indicating that, in CF, the inflammation that accompanies any degree of infection is excessive and is thought to be a major cause of airway destruction, ultimately leading to bronchiectasis and severe obstructive airway disease.\(^{4,12}\) Currently, oral ibuprofen appears to be the only approved agent that has been shown to reduce the rate of FEV\(_1\) decline. Oral corticosteroids have been associated with some improvement in lung function, but steroid-related side effects limit long-term use.\(^6\) Inhaled corticosteroids have not been shown to have any clear benefits, yet more than 50% of patients with CF are being treated them. These gaps reflect a significant unmet need in this important therapeutic area.

**CONCLUSIONS**

The advances made in pulmonary therapeutics and the outcomes derived from day-to-day management of CF have resulted in identification of several new therapeutic targets and research approaches. Current drugs in the pipeline offer the promise of a more “upstream” disease-modifying approach of arresting or slowing lung damage in the early stages of CF. Perhaps, one day, these therapies will come to fruition and prevent the devastating lung destruction that occurs inevitably in this disease. Some of the agents are in phase II/III studies, while others, such as gene therapy and regenerative medicine with progenitor cells (used to repopulate damaged airways), remain more distant in the research and development process. Clearly, research is critical in improving patient outcomes. However, at this time, it is equally important to optimize currently available therapeutic strategies through early intervention and comprehensive use of already approved drugs.

**REFERENCES**