Milestones in Drug Therapy
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Treatment of Cystic Fibrosis and Other Rare Lung Diseases

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Preface

Some of the most exciting discoveries in pulmonary medicine have come from studying rare diseases. Insights gained from uncommon lung diseases often shed light on normal physiology as well as the mechanism of more common lung diseases. For example, investigations into cystic fibrosis (CF) have clarified the role of innate defense and mechanism of mucociliary clearance in the airway, as well as the function of the cystic fibrosis transmembrane conductance regulator protein in maintenance of airway surface liquid. The study of lymphangioleiomyomatosis (LAM) has led to an understanding of genes that control cell energy utilization, growth, and movement, potentially lending insights into the cellular and molecular basis of cancers. An understanding of the role of granulocyte macrophage colony-stimulating factor (GM-CSF) in the regulation of surfactant and other components of the complex biological systems in lung host defense as seen in pulmonary alveolar proteinosis (PAP) has led to GM-CSF being developed as an immunity-enhancing treatment for several other diseases.

Drug development for these conditions has been limited by a lack of understanding of the underlying mechanisms of disease and the relative unavailability of subjects for clinical trials, as well as the prohibitive cost of investing in novel pharmaceutical agents with poor market potential. Over the last several decades, however, legislation has been created in the USA (1983), Japan (1993), Australia (1998), and Europe (2000) to provide incentives for the commercial development of new "orphan drugs" to treat rare diseases, including those of the lung. In the USA, the National Institutes of Health has established the Rare Lung Diseases Consortium within its Office of Rare Diseases, and patient advocacy organizations such as EURORDIS are valuable allies in the fight against rare lung disease, by educating, supporting, and organizing patients and families in a manner that facilitates research. Central databases, registries, and research networks such as the Rare Lung Diseases Consortium in the USA and Orphanet in Europe are also useful adjuncts. With such rare disorders, international cooperation is critical for accumulating sufficient numbers of patients for research.

This volume of Milestones in Drug Therapy is dedicated to a discussion of a somewhat arbitrarily chosen group of rare lung disease—we must point out that many others, in which exciting new research is currently being performed, could have been chosen, but were not, in the interest of keeping the volume from being too overwhelming. We have included introductory chapters on the pathogenesis and current standard treatment of the diseases of interest, followed by chapters discussing the biologic basis of current and new investigational treatments for those conditions. We pay special attention to CF, which incidentally serves as a special example of successful alignment of governmental, academic, foundational, and pharma resources; research into this condition has led to extraordinary advances in our understanding of the underlying genetic and molecular basis of this disease and to dramatic improvements in survival and quality of life for affected individuals. Chapters in Part II focus on treatments directed toward the sequential well-defined steps in the pathogenic pathway of the disease. Additional chapters in Parts I and III discuss diffuse panbronchiolitis, for which the salutary effect of macrolides has been brought to attention due to their anti-inflammatory effect and potential benefit in a host of other inflammatory conditions; idiopathic pulmonary fibrosis, a previously untreatable condition that is now becoming better characterized and for which several effective drugs have become available, with others on the horizon; PAP, a disease for which the discovery of the underlying abnormality related to GM-CSF offers promise of effective treatment; and LAM, for which identification of the key role of dysregulation of the mTOR pathway has identified multiple novel therapeutic targets.

We wish to thank Jutta Lindenborn, our editorial contact from Springer, for keeping us on track and assisting in the organization of contributions from our valued chapter contributors, who of course did most of the “heavy lifting” for this volume. We hope this contribution will be of benefit to clinicians, students, and researchers looking for an introduction into the current investigations that are taking place in regard to the diseases discussed.

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Part I
Etiopathology and Genetics of Rare Lung Diseases

Chapter 1
An Introduction to Clinical Aspects of Cystic Fibrosis

Nauman Chaudary and Michael S. Schechter

Abstract Cystic fibrosis (CF) is the most common life shortening inherited disease in people of Northern European background. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR is a 1480 base protein belonging to the ABC transporter family. It acts as a cAMP-activated chloride and bicarbonate channel and also regulates Na reabsorption through its effect on the epithelial sodium channel (ENaC). The loss of CFTR-mediated inhibition of ENaC leads to excess sodium and water reabsorption, resulting in dehydration of airway surface materials, and dehydration of airway surface materials. Concomitant loss of chloride efflux prevents the epithelium from correcting the low airway surface water volume. The subsequent decrease in periciliary water volume results in a reduction in the lubricating layer between the epithelium and mucus, causing inhibition of normal ciliary clearance of mucus. In addition to abnormalities in ion transport, dysregulation of the host inflammatory response appears to play an important role in cystic fibrosis. It is characteristic of CF that the airways become infected with pathogenic bacteria. Compounding the inability to clear infection, patients with CF also exhibit abnormal inflammatory signaling and an excessive inflammatory response. With persistent infection and periodic exacerbations of the chronic infection, progressive lung disease develops. Thus, in spite of the progress in treatment that has been made, the overwhelming majority of patients still die from respiratory failure. Treatment has traditionally focused on the downstream effects of CFTR dysfunction, and includes therapies that correct altered airway secretions (physical airway clearance therapy, dornase alfa, hypertonic saline, and the recently approved inhaled mannitol); anti-inflammatory

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therapies (high-dose ibuprofen and alternate-day azithromycin); anti-infective therapies (inhaled anti-pseudomonal antibiotics such as tobramycin and aztreonam, along with intermittent treatment with systemic antibiotics of episodic pulmonary exacerbations), and when lung damage is severe, lung transplantation. The recent development of first generation CFTR modulating agents to treat CFTR dysfunction (ivacaftor, a potentiator that activates defective CFTR at the cell surface, and lumacaftor, a CFTR corrector that facilitates transport of class II mutations to the apical cell surface) marks the beginning of a new era of mutation- specific therapies to improve the function of defective CFTR protein. A number of next-generation modulators and other agents are currently moving through the drug development pipeline, offering hope for increased optimism regarding continuing improvements in the long-term outlook of this difficult disease.

Keywords Cystic fibrosis • Genetics • Pathophysiology • Diagnosis • Gene therapy • Ion transport

1.1 Introduction

Cystic fibrosis (CF) has been previously described as the most common *lethal* inherited disease in people of Northern European background, but in view of how much the outlook has changed over the last half-century, we now describe it as *life shortening*. The incidence in affected populations is about 1/3000 births overall, but there is significant variation by region, ethnicity, and race. The incidence is 1/1400 in Ireland. In the USA, CF is reported to occur in 1/3200 Caucasian births, compared with 1/15,000 African American births and 1 in 10,000 Latin American and Native American births. The prevalence in East Asians is considerably lower but hard to ascertain due to likely underdiagnosis (Bobadilla et al. 2002; O'Sullivan and Freedman 2009).

This chapter will serve as an overall introduction to the disease, its pathogenesis, pathophysiology, and treatment in order to provide a background for the chapters to follow.

1.2 Genetics

CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Of the >1900 CFTR mutations that have been identified, the functional abnormality of a relatively small number is known (Table 1.1) (O'Sullivan and Freedman 2009; Gallati 2014; Mickle and Cutting 1998). Class I mutations lead to the complete absence of any functional CFTR, either due to the presence of a premature stop codon resulting in the production of a truncated protein (so-called nonsense mutations) or the presence of splicing defects with no

Table 1.1 Classification of CFTR mutations

	Effect on CFTR	Functional CFTR present	Example mutations
Class I	Lack of protein production	No	G542X, 711 +1G→T
Class II	Protein trafficking defect	No	F508del
Class III	Defective regulation	No	G551D
Class IV	Reduced chloride transport	Yes	A455E, R117H
Class V	Splicing defect with reduced production	Yes	IVS8-5T
Class VI	Accelerated turnover	Yes	4326delTC

protein production. Class II mutations are associated with the production of a CFTR molecule that may retain some chloride channel function but is misfolded and degraded shortly after synthesis, before it can reach its site of action at the cell surface. The most important example of this mutation class is Fdel508 (in which the protein lacks a phenylalanine residue at position 508), as it is present in approximately 60–70 % of defective CFTR alleles and 80–90 % of all patients with CF. CFTR produced by class III mutations assumes the correct position at the cell surface but fails to be appropriately activated by ATP or cAMP to regulate ion transport. Class IV mutations are associated with reduced (but not absent) chloride transport through the normally positioned CFTR molecule; as a result of the small amount of residual CFTR function, these patients will usually have normal pancreatic function, at least initially. Class V mutations lead to a splicing defect that causes decreased production of CFTR protein; these mutations are especially important if associated with another mutation that causes the production of a CFTR molecule with decreased function. Class VI mutations produce a molecule that reaches the cell surface but is unstable and short lived.

The different mutation classes compromise CFTR function to varying degrees, with class I–III mutations typically associated with virtually no CFTR function and class IV–V mutations allowing some residual CFTR function (Mickle and Cutting 1998). Class VI mutations are variable in their expression. The organ that appears to be most sensitive to CFTR dysfunction is the vas deferens; men with mutations that retain residual function (most notably R117H) may exhibit congenital bilateral absence of the vas deferens (CBAVD) as their primary or only clinical manifestation of CF, depending upon the nature of the coexisting IVS8 polythymidine tract allele (Mickle and Cutting 1998; Gilljam et al. 2004). Pancreatic function is typically well predicted by genotype; patients with class I–III mutations are reliably pancreatic insufficient, while those with class IV–V mutations are pancreatic sufficient. In contrast, a looser genotype–phenotype correlation is seen for lung disease. While lung function, on average, is less severe in patients with class IV–V mutations, this is not uniformly the case due to the important role that both modifier genes and environmental factors play in determining the extent and severity of airway dysfunction (Collaco and Cutting 2008; Cutting 2010; Schechter 2011; Vanscoy et al. 2007).

1.3 Pathophysiology of CF

CFTR is a 1480 base protein belonging to the ABC transporter family (Fig. 1.1). It acts as a cAMP-activated chloride and bicarbonate channel and also regulates Na reabsorption through its effect on the epithelial sodium channel (ENaC) (Anderson et al. 1991; Quinton 2008; Collawn et al. 2012; Collawn and Matalon 2014). In addition, CFTR impacts transport of adenosine triphosphate (ATP) out of the cell activating outwardly rectifying chloride channel (ORCC) and regulation of chloride/bicarbonate transport, and it may inhibit calcium-activated chloride channels (CaCCs) due to lack of ATP at P2Y2 required to activate CaCC (Collaco and Cutting 2008; Cutting 2010; Schechter 2011; Vanscoy et al. 2007; Anderson et al. 1991).

There are four hypotheses regarding how CFTR dysfunction leads to the clinical manifestations of cystic fibrosis, and it may be possible that aspects of all four contribute to the pathogenesis of the disease.

The low-volume hypothesis postulates that the loss of CFTR-mediated inhibition of ENaC leads to excess sodium and water reabsorption, resulting in dehydration of airway surface materials (Matsui et al. 1998, 2006; Boucher 2007). Concomitant loss of chloride efflux prevents the epithelium from correcting the low airway surface water volume. The subsequent decrease in periciliary water volume results in a reduction in the lubricating layer between the epithelium and mucus, causing inhibition of normal ciliary clearance of mucus (Fig. 1.2). According to this hypothesis, mucus on the epithelium forms plaques with hypoxic niches that can harbor bacteria, particularly *Pseudomonas aeruginosa (PA)* (Boucher 2007; Worlitzsch et al. 2002).

A less well-accepted alternative "high-salt hypothesis" argues that in the absence of functional CFTR, excess sodium and chloride are retained in airway surface liquid (Smith et al. 1996; Zabner et al. 1998). The increased concentration of chloride in the periciliary layer disrupts the function of important innate antibiotic molecules (e.g., human β-defensin 1), allowing bacteria that are cleared by

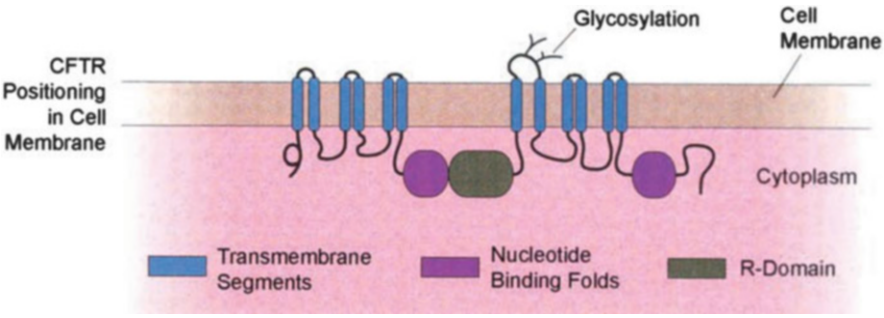

Fig. 1.1 Structure of the cystic fibrosis transmembrane conductance regulator (CFTR) molecule, consisting of transmembrane segments, nucleotide-binding folds, and a regulatory (R) domain. Adapted from Gibson et al. (2003)

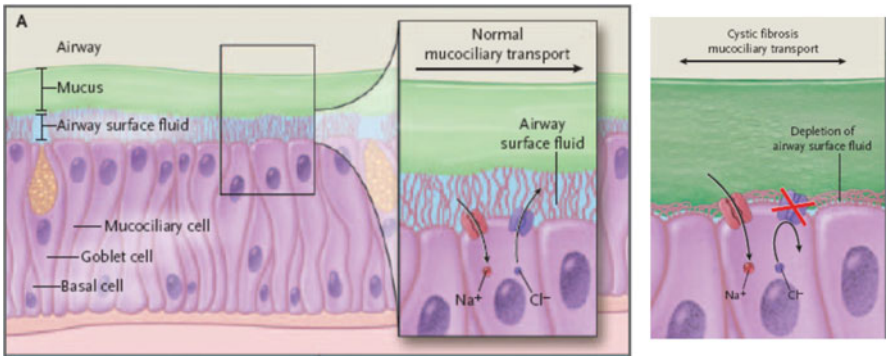

Fig. 1.2 Normally functioning CFTR determines airway surface fluid depth by regulating Cl^- (and bicarbonate) secretion and Na^+ reabsorption [the latter indirectly through its influence on the epithelial Na channel (ENaC)]. CFTR dysfunction and the resulting abnormalities in ion transport lead to reduced airway surface fluid and pH, inhibiting mucociliary clearance and innate defenses to lead to chronic infection and concentrating inflammatory mediators at the epithelial surface. Adapted from the *New England Journal of Medicine* 2006

normal airways to persist in lungs (Goldman et al. 1997). Studies in the CF knockout pig have indicated that depletion of airway surface liquid is not present in CF pig airways (Chen et al. 2010), lending some support to the "high-salt" hypothesis. The CF pig also has reduced CFTR-dependent bicarbonate secretion in the airways (Chen et al. 2010), and it has been suggested that reduced bicarbonate secretion leads to reduced airway surface pH which impairs innate bacterial defense mechanisms (Pezzulo et al. 2012).

In addition to abnormalities in ion transport, dysregulation of the host inflammatory response appears to play an important role in cystic fibrosis. Abnormally high concentrations of inflammatory mediators are seen in CF cell cultures and uninfected ex vivo tissue samples (Carlstedt-Duke et al. 1986; Tirouvanziam et al. 2000; Karp et al. 2004; Machen 2006). Furthermore, findings from lung lavage studies show that inflammation is present in children as young as 4 weeks of age who are apparently free of infection (Khan et al. 1995). An increase in proinflammatory molecules such as interleukin-8, interleukin-6, tumor necrosis factor-α, and arachidonic acid metabolites has been found in patients with CF (Freedman et al. 2004; Zaman et al. 2004; Colombo et al. 2005). Stimulation of the nuclear factor-kB pathway, platelet hyperreactivity, and abnormalities in neutrophil apoptosis has also been reported (Carrabino et al. 2006; O'Sullivan and Michelson 2006; Rottner et al. 2007). At the same time, low concentrations of native anti-inflammatory substances such as interleukin-10 and lipoxin favor unabated inflammation.

In addition, there may be a primary predisposition to infection due to CFTR dysfunction. In normal hosts, *PA* binds to functional CFTR and initiates an innate immune response, which is rapid and self-limiting. In patients with CF, an increase in asialo-GM1 in apical cell membranes allows increased binding of PA and