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Introduction

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INTRODUCTION

CFTR, the cystic fibrosis transmembrane regulator, is a member of a family of ATP-binding cassette proteins including MDR, the multidrug resistance transporter and several other representatives in yeast, insects, and bacteria. CFTR is an approximately 180-kDa protein. Beginning at the N terminus the protein has six transmembrane-spanning domains, a first nucleotide-binding domain with Walker A and B consensus sequences, a large regulatory domain rich in *c*AMP-dependent kinase and protein kinase C phosphorylation sites, a second set of six transmembrane-spanning domains, and a second nucleotide-binding domain. At a first glance this motif is consistent with an ATP-driven transporter. But looks can be deceiving because it has been shown convincingly that CFTR functions as a Cl^- channel with distinctive properties. Two processes must occur for the channel to become and remain active, phosphorylation by PKA and hydrolysis of ATP. The CFTR protein is localized on the apical cell membrane and participates in Cl^- secretion (see the Minireview by Morris *et al.*).

Mutations in the CFTR gene resulting in defective functioning and processing of the protein cause a wide range of symptoms associated with cystic fibrosis (CF). This disease is the most common lethal, autosomal recessive disorder in North America. The hallmarks of the disease include thick, dehydrated airway mucus, chronic *Pseudomonas* lung infection, pancreatic insufficiency, bile duct obstruction, infertility in males, reduced fertility in females, high sweat Cl^-, intestinal obstruction, nasal polyp formation, and chronic sinusitis. 90% of mortality is related to pulmonary disease. Treatment of the disease continues to improve with a median survival of about 29 years.

The primary defect in CF is a reduced Cl^- permeability in affected epithelial cells. This defect has focused much attention on the Cl^- channel function of CFTR and on other Cl^- channels present in CF affected tissues (see the Minireview by Guggino). In addition to providing basic information on the unique classes of Cl^- channels uncovered during the many studies of CF, the ultimate goal of most of the studies is to provide hints either on how to restore function to mutant forms of CFTR or how to stimulate alternative Cl^- secretory pathways in CF cells. Two forms of therapy currently look most promising, gene replacement therapy (see Minireview by Terrance Flotte) to restore normal CFTR function and pharmacological therapy to stimulate alternative ion conductive pathways in airway epithelia. Both of these therapies are targeted toward correcting the primary defect in the airway, the dehydrated mucous, by increasing airway fluid production.

The most common mutation associated with the disease is the ΔF508 mutation, which is a missing phenyalanine at position 508. Although the phenotype of patients bearing the ΔF508 mutation can vary considerably, it is often associated with severe disease. The ΔF508 mutation effects the function, structure, and folding of the first nucleotide-binding domain (see the Minireview by Thomas *et al.*). These defects in the structure of the first nucleotide-binding domain have effects on the processing of the protein through the endoplasmic reticulum causing very drastically reduced levels of protein to be expressed in patients with the ΔF508 mutation. In addition to the ΔF508 mutation, many other mutations exist and are associated with either severe or milder phenotypes (see the Minireview by Cutting).

Information about CF has exploded since defective Cl^- secretion in CF tissues was first described by

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Paul Quinton. This explosion of information came primarily from interdisciplinary approaches to the study of the cellular and molecular physiology; molecular biology, cell biology, biochemistry and molecular genetics of the disease. CF research has depended heavily on collaborations among many different groups of researchers which often involves the sharing of reagents and the combining of expertise in fields of biology which previously had only limited interactions. These interactions among groups in different disciplines not only stimulated the rapid expansion of novel information, but also provided new approaches for understanding genetic diseases. The speed with which our knowledge of CF has increased is a tribute to the power of modern biology. The interdisciplinary approaches used to study CF are a model for the study of the structure, function, and processing of the protein products of other newly sequenced genes and for understanding other genetic diseases.