

Public Abstract

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Title: Structure/Function Studies of CFTR's Pore-forming Domain Reveal Evolutionary Divergence between CFTR and ABC Transporters

Cystic Fibrosis (CF), clinical manifestations of which include chronic lung infections, pancreatic insufficiency and infertility, is a genetic disease that afflicts mostly people of Caucasian descent. The culprit behind the disease—Cystic Fibrosis Transmembrane conductance Regulator (CFTR)—is a chloride channel protein mainly expressed in epithelial cells lining the airway, the gastrointestinal tract and the pancreas. Like many other protein molecules, CFTR possesses several different domains, including two transmembrane domains that craft a gated pathway (or a pore) for chloride ions, two nucleotide binding domains that serve as an engine to power the conformational changes leading to opening of the gate, and a regulatory domain whose main function is to work as a master switch that enables proper actions of the other domains. My studies are aimed to elucidate the structural mechanism underpinning the function of CFTR's two transmembrane domains. Specific findings made include: First, I identified a pore-lining component in the first transmembrane domain, and hence broadened our molecular understanding of the constituents of the pore of CFTR. Second, my studies also led to the identification of specific amino acid residues that compose the gate. Third, by using a biochemical strategy that allows us to gauge the relative positioning of several pore-lining components, I was able to specify the amino-acid compositions in the part of CFTR's pore that plays the most critical functional roles: selecting the chloride and controlling the ion flow across the pore. Collectively, my studies have greatly facilitated our fundamental understanding of CFTR's ion permeation pathway, and the new data presented in this dissertation could shed light on the mechanism regarding how mutations in CFTR cause CF pathology.