Public Abstract

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Title:Functional and pharmacological importance of the composite ATP binding site 1 in CFTR chloride channels

Dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR), an ATP binding cassette (ABC) protein serving as a chloride ion channel, causes the most common lethal genetic disease cystic fibrosis (CF) in the Caucasian population. Investigating the mechanism of CFTR function could potentially promote the development of therapeutics to treat cystic fibrosis as well as help us understand how other ABC proteins work. Here, I demonstrate that opening and closing of the CFTR channel, catalyzed by ATP binding and hydrolysis respectively, is coupled to the dimerization and partial separation of CFTRâ€™s two cytoplasmic nucleotide binding domains (NBDs). This novel finding provides insight into the structural basis underlying an ABC proteinâ€™s function. At the NBD dimer interface are two composite ATP binding sites, called site 1 and site 2. I have discovered several mutations that optimize ATP binding in site 1. These mutations drastically improve the activity of wild type (WT) channels and the 1st and 3rd most common CF-associated mutant, Î”F508- and G551D-CFTR. Therefore, a small molecule compound designed to bind to site 1 tightly could be a strong CFTR potentiator to treat patients with cystic fibrosis.