Public Abstract
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Title:CFTR GATING MECHANISM: THE ROLE OF DIMERIZATION OF NUCLEOTIDE BINDING DOMAINS

The chloride channel, cystic fibrosis transmembrane conductance regulator (CFTR) has two membrane spanning domains (MSD), forming the channel pore, and two nucleotide binding domains (NBD), controlling the channel gating (opening and closing). The CFTR also has a unique regulatory (R) domain. After the CFTR is phosphorylated at R domain, gating of the phosphorylated CFTR is coupled to ATP binding and hydrolysis at CFTR's two NBDs. However, the role of dimerization in channel gating is unknown.

We first investigated whether two ATP binding sites play an equivalent role in the dynamics of NBD dimerization, therefore in gating CFTR channels. By identifying two critical aromatic amino acids that coordinate the adenine ring of the bound ATP, we conclude that opening of the channel is initiated by ATP binding at the NBD2 site, and tighter binding at W401 at the NBD1 site prolongs channel open time.

We then studied the role of signature sequence in channel gating. We found that micromolar [Cd^{2+}] can dramatically increase the activity of G551D-CFTR. A specific region of the signature sequence is found to result in positive response to Cd^{2+}. We thus conclude that signature sequence serves as a switch that transmits the signal of Cd^{2+} binding to the gate opening. The Cd^{2+} effect is found to work through forming a metal bridge connecting G551D/C to unknown cysteine residue in CFTR. Our data provide the first evidence that R domain is involved in the CFTR channel opening, besides its role in PKA-dependent phosphorylation.