MOLECULAR UNDERSTANDING OF CFTR'S PORE DOMAIN SUGGESTS POSSIBLE EVOLUTIONARY DIVERGENCE BETWEEN CFTR AND ABC TRANSPORTERS

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ABSTRACT

Cystic Fibrosis Transmembrane conductance Regulator (CFTR) is the culprit behind Cystic Fibrosis (CF), a genetic disease highly occurs among Caucasians. Studying the structure/function of CFTR chloride channel not only facilitates our understanding of the molecular nature of this protein, but also potentially provides cures for the debilitating disease. In my study, by adopting site-directed mutagenesis and Patch Clamp as well as other various molecular biology techniques, I focused my efforts in CFTR's pore domain and made the following revealing findings: First, the first transmembrane segment (TM1) contributes to CFTR's pore lining with its whole length and the restrictive region identified in TM1 confirms that CFTR's pore is constituted by three main components: a narrow region flanked by the internal and external vestibules. Second, while TM1 and TM6 contribute to pore lining for CFTR in a relatively symmetrical manner, a lack of symmetry between TM6 and its topological counterpart—TM12 suggests the two-fold pseudo-symmetry seen with other ABC proteins does not apply in CFTR's TMDs. At last, the gate of CFTR resides in a region (337 – 344 in TM6) that encompasses the above mentioned narrow region (338- 341 in TM6) which may also serve as the selectivity filter for this anion channel, challenging the prevailing degraded ABC transporter hypothesis that states CFTR evolves from an ABC transporter by simply degenerating the intracellular gate.