

SYMPOSIUM SUMMARIES

S1.2

REGULATION OF CFTR ACTIVITY VIA PROTEIN-PROTEIN INTERACTIONS

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The ATP-binding cassette (ABC) superfamily proteins are important functional transporters in both prokaryotes and eukaryotes, playing primary roles in mediating the entry and exit of a variety of molecules. The CFTR protein is a member of the ABC transporters. The interactions of the CFTR with other structural and regulatory proteins are essential for the proper function of the CFTR in health and disease.

Protein-protein interactions are intrinsic to virtually every cellular process. At the biochemical level, protein-protein interactions have been found in multi-subunit proteins, assembled functional protein complexes, and transient protein-protein contacts. Consequently, these interactions lead to a broad spectrum of biological outcomes that include alteration of kinetic properties and/or activity of an enzyme, substrate channeling, and formation of a new binding site and/or changes of its substrate. Because the degree of regulation that protein-protein interactions confer is large, investigation of their physiological implications requires (i) identification of the different interactions and the molecular components, (ii) determination of the extent to which they take place in the cell, and (iii) determination of the consequences of the interaction. Recent progress in this area has revealed a class of very interesting proteins whose function is dedicated to the spatial and stoichiometric organization of various signaling and transport proteins. The primary structure of these scaffold proteins usually contains multiple protein interaction modules; each often interacts with a given target protein. As a result, they are capable of recruiting and organizing protein machinery with defined composition and stoichiometry, thereby providing high specificity and efficiency to the corresponding biochemical reactions such as ion transport and signal transduction.

Using molecular and biochemical approaches, a number of scaffolding proteins have been identified on the basis of their ability to interact with the C-terminus of the CFTR. These scaffolding proteins include CAL (CFTR-Associated Ligand), NHE-RF (Na⁺-H⁺ Exchanger Regulatory Factor) and CAP70 (CFTR-Associated Proteins 70Kd). In addition to their potential role in trafficking the interaction proteins, purified recombinant proteins of CAP70 and NHE-RF have been shown to directly potentiate the chloride channel activity of CFTR via a stoichiometric interaction that is consistent with the inductive formation of a CFTR dimer by CAP70 or NHE-RF. This evidence supports the notion that in addition to the conventional role of PDZ domain in spatial positioning of binding protein to specific subcellular locations or to other functionally coupled proteins, PDZ domain containing proteins may also play a role in regulating functionality of their target proteins by defining the stoichiometry and geometry of a functional unit.

References

1. Bezprozvanny I, Maximov A (2001). PDZ domains: more than just a glue. *Proc Natl Acad Sci U S A*. 98: 787-789.
2. Raghuram V, Mak DD, Foskett JK (2001). Regulation of cystic fibrosis transmembrane conductance regulator single-channel gating by bivalent PDZ-domain-mediated interaction. *Proc Natl Acad Sci U S A*. 98:1300-1305.
3. Wang S, Yue H, Derin RB, Guggino WB, Li M (2000). Accessory protein facilitated CFTR-CFTR interaction, a molecular mechanism to potentiate the chloride channel activity. *Cell*. 103:169-179.

S1.3

CFTR REGULATION BY INTERMOLECULAR AND INTRAMOLECULAR INTERACTIONS

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The opposing cytoplasmic tails of CFTR are engaged in distinct sets of protein-protein interactions. PDZ domain-mediated interactions with the carboxy terminal tail of CFTR can modulate the intracellular location and

functional activities of CFTR channels. We have determined that the amino terminal tail (N-tail) also participates in intermolecular and intramolecular interactions that govern CFTR channel activity. Three topics will be