Ten Years With CFTR

RAYMOND A. FRIZZELL

Department of Cell Biology and Physiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

This is the second single-topic supplement to *Physiological Reviews*. In introducing the first supplement, Daniel Gardner indicated that the articles reported on the progress of a revolution, first recognized by the series of papers on membrane currents in nerve published by Hodgkin, Huxley, and colleagues. This supplement reports on another revolution in cell physiology and on what is probably one of the most intensely studied proteins in biomedical science: the cystic fibrosis transmembrane conductance regulator (CFTR). It is now 10 years since identification of the gene responsible for cystic fibrosis (CF) was announced (2, 7, 8); these papers reported not only the chromosomal mapping and sequence of the gene and its protein product but also an amazingly accurate prediction of CFTR’s secondary structure (7). Lap Chee Tsui, John Riordan, and Francis Collins included in their appellation, CFTR, the terms conductance and regulator, descriptors that the subsequent years’ investigations, and the articles in this supplement, show aptly to apply.

In the period B.C., that is, before cloning of the CFTR gene, our understanding of the cellular implications of CF gene mutations was fairly well developed. We understood that CF was a disease of epithelial cells and that its cellular phenotype omitted a cAMP-regulated chloride conductance pathway that was crucial for the salt and water secretory response of many epithelial tissues. We understood that the impairment of epithelial chloride conductance extended to channels localized in membrane fragments at the ends of patch pipettes. The pioneering work of Quinton (6), Knowles et al. (4), and other colleagues created a sea change, not only in our understanding of the CF phenotype but also in the numbers of skilled scientists willing to devote significant effort to this protein and the disease that it defines. In the period A.C., after cloning, this momentum has exploded, as a tangible and manipulatable entity was provided to explore the array of cellular processes on which CFTR touches. Indeed, this proliferation is so extensive that detailed chapters can now be written on subjects as focused as the conduction and gating properties of CFTR. Evidence supporting the idea that CFTR functions as a regulated chloride channel quickly emerged in the period A.C., largely as a result of our existing understanding of the physiology of CF epithelial cells. To be sure, we are still trying to fully appreciate how the loss of this chloride channel pathway contributes to the multiple manifestations of CF in diverse organ systems. In this collection of works, we attempt to remain focused on essential physiological issues concerning the function of CFTR. Therefore, little information is provided on CF genetics, and there is only a brief treatment of human genotype-phenotype correlations (5). For these subjects, the interested reader is referred to several excellent reviews (1, 3, 9). Rather, we focus on the “nuts and bolts” of CFTR and its contribution to epithelial cell function.

Paul Quinton begins this series with a personal account of the physiological basis of CF that includes not only historical perspectives but also valuable reflections on the complex events that attend deletion of the cAMP-regulated chloride conductance pathway of CFTR chloride channel. They provide a functional survey of the significant domain structures of CFTR and the manner in which they relate to chloride channel gating. David Dawson, Steven Smith, and Monique Mansoura provide us with a detailed look at CFTR’s conduction pathway for chloride ions. They describe the structural basis of anion selectivity and the way in which both disease and experimental mutations have contributed to our current understanding of the conduction pathway. David Gadsby and Angus Nairn focus their review on the control of CFTR channel gating by phosphorylation and nucleotide hydrolysis. Their review details the unique position occupied by the CFTR chloride channel in the ABC (ATP-binding cassette) superfamily of transporters; they provide a model that utilizes coordinated nucleotide hydrolysis to effect channel opening and closing rather than organic solute transport. They also review the control of CFTR by kinase and phosphatase-mediated R-domain phosphorylation in relation to its channel-gating functions. Bruce Schultz, Ashvani Singh, Daniel Devor, and Robert Bridges describe the pharmacology of CFTR. Their detailed overview of compounds that modulate the chloride channel activity of CFTR should be a valuable field guide for those who are brave enough to approach studies.
of CFTR function with drugs in hand. Ron Kopito provides an overview of the biosynthesis and degradation of CFTR. His chapter reviews the role of molecular chaperones and degradation pathways in the processing of the common CFTR mutant ΔF508. Eric Schwiebert, Dale Benos, Marie Egan, M. Jackson Stutts, and William Guggino provide a review of CFTR’s function as a regulator of other ion channels. This important aspect of CFTR function has been appreciated since the early findings of elevated sodium absorption across CF airways (5), but it has been reborn in recent years and is likely an important issue regarding the complex clinical manifestations brought on by CFTR mutations. Neil Bradbury provides a review of the intracellular functions of CFTR, including both the localization and activity of CFTR in intracellular compartments. This chapter reviews accumulating evidence for a role of CFTR in membrane traffic regulation and in the acidification of intracellular compartments in epithelial cells. Barbara Grubb and Richard Boucher review the physiology of CF mouse models, which began to emerge about 3 years after the CF gene was cloned. This chapter beautifully highlights the organ-specific phenotypes associated with CFTR deletion or mutation and the role of alternate pathways in complementing CFTR activity. Finally, Joseph Pilewski and I consider the question of how CFTR mutations cause lung disease. We attempt to relate CFTR’s activity as an anion conductance to the properties of the airway surface liquid, whose volume and composition are thought to control mucus and bacterial clearance, leading to infection and inflammation, processes that govern the progression of CF airway disease.

The CF field has witnessed a revolution also in the sense that it has provided a paradigm for multidisciplinary interactions among molecular geneticists and physiologists concerning the way in which genetic diseases can be approached experimentally. Indeed, CFTR may be one of the most intensely studied proteins during the last 10 years, yet we can anticipate many more and important revelations from the continuing studies of this complex protein. We can all hope that our growing understanding of the way in which CFTR contributes to epithelial physiology will elucidate its role in the pathophysiology of CF and that this will serve as a substrate for more effective disease treatment. Finally, I want to take this opportunity to formally thank the many contributors, both the authors and their assistants, whose effort in generating this volume indicates that they share this hope.

REFERENCES


