Perspective

The Basic Defect in Cystic Fibrosis

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CYSTIC FIBROSIS (CF) WAS PERHAPS THE FIRST CONGENITAL disease for which an accurate diagnosis was available at birth: historical anecdote tells us that the midwife would lick the forehead of the newborn, and if the sweat tasted abnormally salty the infant was destined to die of pulmonary congestion and its side effects. Today our diagnostic tests are more sophisticated, but CF remains the most common lethal congenital disease among Caucasians, with a prevalence of about 1 in 2000 live births.

There is much stirring in CF research these days. The science is becoming exciting, and with the aggressive and enthusiastic support of the Cystic Fibrosis Foundation many new investigators are being recruited to the field and are bringing novel approaches to the understanding of this devastating disease. The two areas generating the most excitement are the quest for the gene and the search for the basic defect. The race is on to find and clone the gene defective in CF; several groups are within striking distance of the gene and may already have it in hand. One might think that with the gene available the CF problem will be solved, but any prospects for gene therapy remain far in the future. Certainly highly accurate prenatal diagnostic tests will become available, but there is reason to believe that only a small proportion of prospective parents told that they have conceived a CF fetus will choose to abort it. Thus CF is likely to be with us for some time, and this makes the ongoing search for the basic defect far more than simply an interesting academic exercise: by understanding the disease at the molecular level, it may be possible to devise rational treatments that prolong and improve the quality of life of CF patients. Four papers in *Science*, two last week (*1, 2*) and two in this issue (*3, 4*), describe important advances in the effort to understand the basic defect.

CF is a disease of secretory epithelia, tissues that mediate the transport of water, salt, and other solutes between the blood and the outside world. Epithelial cells exhibit anatomical and functional polarity; the basolateral membrane, which faces the blood, and the apical membrane, which faces the lumen (the outside world), mediate different transport events, which together give rise to net chloride transport across the epithelium from blood to lumen. Sodium and water accompany the transported chloride, resulting in secretion of a solution of sodium chloride into the lumen. This secretion requires activation of the secretory pathway by hormones or neurotransmitters, which utilize the intracellular second messengers adenosine 3′,5′-monophosphate (cyclic AMP) or calcium.

What do we know about the basic defect in CF? The most serious clinical manifestations of the disease result from a decrease in fluid and salt secretion; these include blockage of exocrine outflow from the pancreas and accumulation of heavy dehydrated mucus in the airways (in the sweat gland, salt reabsorption is defective, hence the ancient diagnostic test). Work from the laboratories of Paul Quinton at the University of California at Riverside and Richard Boucher at the University of North Carolina first suggested that the primary defect might be in chloride transport (*5, 6*), and it soon became evident that a cyclic AMP–dependent transepithelial chloride current is present in normal but not CF epithelia (*7*). Later the laboratories of Raymond Frizzell at the University of Alabama and Michael Welsh at the University of Iowa identified an apical membrane chloride channel, the activity of which can be increased by cyclic AMP–dependent protein kinase in normal but not in CF cells (*8, 9*). These elegant studies focused attention on the modulation of the chloride channel by this kinase as the locus of the CF defect.

Now another protein kinase has entered the picture. In last week's *Science* William Guggino, Richard Huganir, and their colleagues at Johns Hopkins University (*1*), and independently Michael Welsh, Paul Greengard, and co-workers (*2*), reported that protein kinase C (PKC) can also activate the chloride channel and that this activation is defective in CF. One of these groups also found (*2*) that under certain conditions PKC can inactivate rather than activate the chloride channel, and this down-regulation is not defective in CF cells. Although the physiological significance of these findings remains to be determined (there is no information about physiological stimuli that might activate PKC in epithelial cells, and the inactivation by PKC occurs only in the presence of high and perhaps nonphysiological concentrations of calcium), these two papers make it clear that regulation of the apical membrane chloride channel is more complex than was previously thought.

The story continues with a report in this week's *Science* by Qais Al-Awqati and his colleagues at Columbia University (*3*). Using a blocker of epithelial chloride flux as an affinity ligand, they have purified several proteins from kidney and trachea that exhibit chloride channel activity when they are reconstituted into artificial phospholipid bilayer membranes. If one or more of these proteins turns out to be all or part of the secretory chloride channel which is defective in CF, it may be possible to compare the detailed molecular structure of the chloride channel from normal and CF epithelia. Finally, in another report in this issue, Boucher's group describes a stable human airway epithelial cell line, produced by retroviral transformation of CF airway epithelia, which maintains the defect in the secretory chloride channel (*4*). This is very important, because there is no animal model for CF, and human airway cells are in limited supply and are often contaminated by the chronic bacterial infections in CF airway mucus. Another potential benefit of this cell line is that it can be used to screen candidate genes in the search for the genetic defect in CF.

What then for the future? Certainly our understanding of the regulatory defect in CF is far from complete, as the two papers on channel phosphorylation make clear. What is most encouraging is the diversity of approaches that are being used to attack the problem of CF, and the possibilities for interaction among them. It is often at the interfaces between disciplines where the most exciting discoveries are made, and the constellation of concepts, tissues, and techniques may now be in place to allow an all-out assault on CF.

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