

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Can Curcumin Cure Cystic Fibrosis?

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Cystic fibrosis, a progressive and ultimately fatal inherited disorder caused by a mutant cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, has mobilized the government, charitable foundations, the biotechnology industry, and academia to work together to accelerate the development of drugs to combat the disease. The tools of molecular biology have facilitated the entry of about two dozen drugs in the developmental pipeline, any one of which, if successful, could halt the progression of the disease. As recently reported by Egan and colleagues,¹ the newest therapeutic candidate is curcumin, a so-called nutraceutical agent or dietary supplement that is a mixture of compounds derived from the curry spice turmeric. Curcumin has been on the shelves of health food stores for some time and has been touted as an antioxidant, antiviral, antiinflammatory, anticancer, and cholesterol-lowering herbal supplement.

What led Egan et al. to study curcumin as a treatment for cystic fibrosis? They recognized that the most common cause of cystic fibrosis — the $\Delta F508$ mutation — results in a *CFTR* protein that is misprocessed in the endoplasmic reticulum; it is snagged by a chaperone protein and targeted for degradation, instead of making its way to the plasma membrane and forming a chloride channel. The absence of *CFTR* from the luminal-cell surface that lines the respiratory tract is associated with a deficit in chloride conductance regulated by cyclic AMP (cAMP) and a compensatory influx of sodium ions into the cell, with a consequent high sodium potential across the plasma membrane (Fig. 1). This promotes dehydration of the luminal environment and allows bacterial invasion and inflammation.

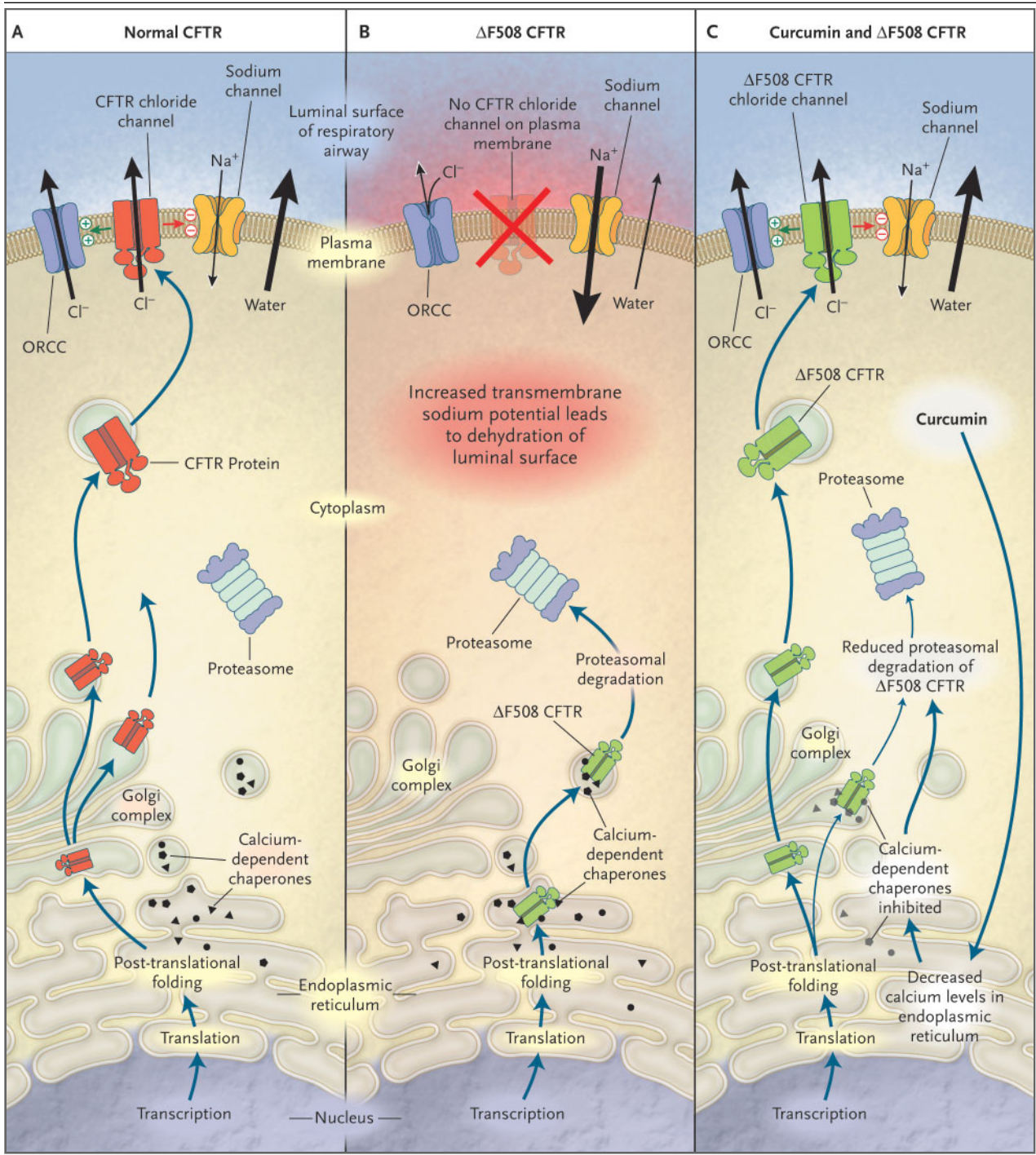
Because some chaperone proteins are dependent on high calcium levels, the authors reasoned that reducing the calcium levels in the endoplasmic reticulum might liberate the mutant *CFTR*, increasing the odds of its reaching the cell surface (Fig. 1). They had previously shown that curcumin inhibits a calcium pump (called sarcoplasmic reticulum Ca-ATPase) in the endoplasmic reticulum and that,

unlike some other inhibitors of this pump, curcumin has a low level of toxicity.

Egan et al. administered curcumin by oral gavage to mice engineered to express only the $\Delta F508$ allele.¹ This mutant mouse expresses the cystic fibrosis defect primarily in the gastrointestinal tract and rarely lives beyond four weeks. Treated mice had dramatically increased rates of survival and normal cAMP-mediated chloride transport across the nasal and gastrointestinal epithelia. In addition, the trans-epithelial sodium potential was reduced, suggesting that sufficient $\Delta F508$ protein reached the plasma membrane. Although the authors hypothesized that reduced calcium levels in the endoplasmic reticulum would ameliorate the effects of the $\Delta F508$ mutation by interfering with the function of the chaperone protein, the mechanism through which

Figure 1 (facing page). Curcumin, Calcium, and Cystic Fibrosis.

An important chloride channel in the plasma membrane is composed of cystic fibrosis transmembrane conductance regulator (*CFTR*) protein — the protein that is mutant in those with cystic fibrosis. The efflux of chloride ions into the lumen of the respiratory airway is coupled with the influx of sodium ions through the epithelial sodium channel, resulting in an ionic gradient across the plasma membrane and the movement of water from the cell into the lumen (Panel A). Wider black arrows indicate greater volume. Because the channels are coordinated, the activity of one affects the other. In patients with cystic fibrosis caused by the common $\Delta F508$ *CFTR* mutation, the mutant, misfolded *CFTR* protein is snagged by a chaperone protein and undergoes proteasomal degradation before it can reach the chloride channel. This results in higher sodium absorption from the lumen and dehydration of the luminal surface (Panel B). When Egan et al. administered the nutraceutical agent curcumin to mice that were homozygous for the mutant $\Delta F508$ allele, *CFTR* escaped degradation and appeared on the cell surface, the function of the chloride channel was restored, and the symptoms of cystic fibrosis were ameliorated (Panel C). Curcumin lowers calcium levels in the endoplasmic reticulum. These findings indicate a strategy to circumvent a proteasomal fate for $\Delta F508$ *CFTR*. ORCC denotes outwardly rectifying chloride channel.



curcumin counters these effects has yet to be determined.

Has anything like this effect of curcumin been seen before? The butyrate class of compounds effects a similar restoration of $\Delta F508$ processing, transport, and function in vitro and in vivo,² although 4-phenylbutyrate did not lower the sodium potential in humans (or in the mutant mice studied by Egan et al.¹). Neither curcumin nor 4-phenylbutyrate is expected to alter the chloride conductance of $\Delta F508$ CFTR. The isoflavonoid class of molecules, including genistein, directly stimulates cAMP-mediated chloride transport in the $\Delta F508$ mouse model and in another mouse model of cystic fibrosis.³ Genistein, a phytoestrogen, is found in high levels in soy products such as tofu and is marketed as a nutraceutical agent for the chemoprevention of breast and prostate cancers, cardiovascular disease, and postmenopausal symptoms. The repressive effect of some CFTR premature stop mutations on the expression of functional CFTR channels in the nasal epithelium of patients can be countered by exposure to certain aminoglycosides.⁴ This mechanism seems to work by interfering with the synthesis of the CFTR protein; the ribosome is thought to skip over the unexpected stop codon to produce a full-length, normal CFTR protein. Agonists of non-CFTR chloride channels can effect transmembrane transport of chloride into the lumen in vitro and in vivo.⁵ Whether any of these approaches will be sufficient to halt or reverse the decline in lung function in patients with cystic fibrosis has yet to be determined.

The next step is to test the nutraceutical curcumin in a phase 1, dose-escalation and safety trial in patients with cystic fibrosis. Such studies should

identify the active molecules and assess the absorption of the agent by the gastrointestinal tract, as well as the metabolism, safety, and duration of effect of curcumin. Physicians should counsel patients with cystic fibrosis to refrain from rushing to the health food store to buy curcumin, because inadequate or excessive doses of the agent could do more harm than good and could discourage the study of a potentially useful class of therapeutic agents. Instead, eligible patients should consider participating in placebo-controlled clinical trials of curcumin and thus speed up the movement of this compound through the developmental pipeline. On a more philosophical note, the study by Egan et al.¹ is another testament to the pharmacogenetic approach: small-molecule pharmacotherapy tailored to a specific genotype (in this case, the $\Delta F508$ mutation) is rapidly becoming a reality for patients with cystic fibrosis and other inherited disorders of protein function.

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