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In the kitchen, a way to treat cystic fibrosis?

A spice may protect a mutant, but functional, protein from the cell's quality control system.

A possible compound for the treatment of cystic fibrosis may be as close as the kitchen spice rack. Researchers at Yale and the University of Toronto reported recently in *Science* that curcumin, an element of the spice turmeric, helps correct a protein defect associated with this genetic disease.

Through a mechanism that is not completely understood, curcumin protects a mutant, yet functional, protein from the cell's quality control machinery. Cystic fibrosis stems from a defect in this protein, the cystic fibrosis transmembrane conductance regulator (CFTR), which moves chloride across cellular membranes to maintain a balance of ions and water. When that balance is disrupted, mucous becomes a sludge that clogs respiratory and digestive pathways, ultimately causing infections. Most people with cystic fibrosis do not live past the age of 30.

The most common form of cystic fibrosis is called delta F508, and is due to the deletion of a single amino acid from the sequence of CFTR. Although the protein is still able to mitigate most cystic fibrosis symptoms, cellular quality control machinery tags it for degradation, because without the amino acid it cannot fold properly. "Even though [it] works, it gets thrown out," said Michael J. Caplan, M.D. '87, Ph.D. '87, professor of cellular and molecular physiology and cell biology and the principal investigator of the study. Working with Marie E. Egan, M.D., associate professor of pediatrics and cellular and molecular physiology, and others, he may have found a way to subvert quality control.

As part of the quality control process, some chaperone proteins bind to calcium, commonly found in the endoplasmic reticulum (ER). To help CFTR evade quality control, Caplan and Egan sought compounds that would disable the chaperones by depleting calcium stores in the ER. Previously identified compounds blocked calcium pump action in the ER, but proved to be toxic. A search through the literature turned up curcumin, a weak inhibitor of ER calcium pumps.

Remarkably, it worked—and well, at least in tissue culture and mouse models. The researchers noted a restoration of ion transport in mice that received curcumin, and in cell lines bathed in curcumin, a fraction of the mutated protein migrated to the cell membrane and restored a significant level of ion transport function.

Given these findings, Egan and Caplan plan to collaborate with the Cystic Fibrosis Foundation and Seer Pharmaceuticals in a clinical trial to assess curcumin's potency in patients with cystic fibrosis. However, Egan stresses that more research is needed: "What it does to people versus what it does in mice may be very different. We first need to get a better handle on the mechanism," Egan said. To that end, Egan and Caplan are trying to determine whether curcumin blocks calcium pump action or whether it binds to CFTR to help stabilize it. They are also investigating whether the active compound is curcumin or a metabolite of curcumin. If the data from both the clinical and basic research investigations

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prove its efficacy, curcumin may be the first cystic fibrosis drug that treats the cause of the disease rather than just the symptoms.

—*Kara Nyberg*