New Perspective on Cystic Fibrosis

Molecular biologists have overturned a fundamental assumption about the mechanism behind cystic fibrosis, pointing the way to new strategies for diagnosis and treatment.

Until now, scientists believed that most cases of the disease stemmed from defective activity of a mutant protein at the surfaces of cells in respiratory passages and certain organs. But the latest evidence indicates that the key to cystic fibrosis may be the protein's *absence* in the cell membrane.

The discovery offers "a new perspective on the disease" and may "explain a lot of what we see [in cystic fibrosis]," comments Douglas M. Jefferson of Tufts University School of Medicine in Boston.

At the heart of cystic fibrosis lies a protein called CFTR, which normally helps pump chloride ions across cell membranes. Without CFTR, an imbalance in ion and fluid transport ensues, leading to the thick mucus buildup and frequent respiratory infections that characterize the disease. Earlier this fall, scientists demonstrated that inserting the normal CFTR gene into cultured airway cells from cystic fibrosis patients corrected the chloride transport defect *in vitro* (SN: 9/22/90, p.181). Scientists at Tufts University, Genzyme Corp. in Framingham, Mass., and the University of Iowa in Iowa City carried out the research.

Now, some of the Genzyme scientists involved in that work have found that an error in the processing of CFTR appears to be a primary cause of the disease. The slip-up prevents the protein from maturing and reaching its cell-surface destination, the researchers report in the Nov. 16 CELL.

Normally, newly synthesized CFTR undergoes final adjustments in two cellular compartments – the endoplasmic reticulum and the Golgi apparatus – where carbohydrates get tacked onto the protein. The fully processed CFTR then moves from the Golgi to the cell surface.

But in cystic fibrosis, "the [mutated] protein never makes it to the cell surface," says study leader Alan E. Smith. He and his colleagues chemically synthesized a DNA sequence coding for CFTR but missing a specific amino acid, creating a mutation known as delta F508. After inserting the altered gene into monkey kidney cells *in vitro,* the scientists observed that the CFTR made by these cells was only partially processed.

"The protein doesn't mature," Smith says. "It gets stuck, we think, in the endoplasmic reticulum." Other cystic-fibrosis-causing mutations in the same region yielded similarly incomplete CFTR, the researchers found.

Since the delta F508 defect shows up in 70 percent of cystic fibrosis patients, the investigators conclude that this and other mutations interfering with CFTR maturation probably underlie most cases of the disorder. They suggest that the mutant CFTR may have an abnormal shape, which the endoplasmic reticulum detects through a "quality control system" that prevents fine-tuning and transport of defective proteins. This system could rely on a "molecular chaperone" that must bind the CFTR in order for processing to occur, Smith speculates. If misshapen CFTR goes unrecognized by the chaperone, it may never exit the endoplasmic reticulum and may instead undergo degradation.

Jefferson says the new findings may explain why parents of affected children remain healthy even though each carries one defective copy of the CFTR gene in addition to one "good" copy. If the mutant CFTR is absent from the cell surface, it can't interfere with the functional activity of CFTR encoded by the normal gene, and thus cannot induce the disease, he says.

The Genzyme team speculates that measuring children's levels of mature CFTR might offer a simpler diagnostic test than the current searches for chromosomal mutations. And if studies show that mutant CFTR becomes at least partially functional when mature, drugs that complete its processing and transport may provide a new treatment approach, they say. Smith told SCIENCE NEWS his group is attempting to develop a protein-replacement aerosol that, when inhaled, would deliver normal CFTR to cell surfaces. *– I. Chen*

'Big dig' unearths clues to garbage decay

Begun in 1948 atop a swamp on Staten Island, N.Y., the Fresh Kills landfill – the world's largest – covers 4,950 acres and holds 2.3 billion cubic feet of refuse. A year ago, this massive monument to a throwaway society hosted the first multidisciplinary excavation aimed at understanding why some landfill wastes decay more slowly than expected.

Five participating research teams unveiled their preliminary findings last week in Arlington, Va., at a meeting of the Society of Environmental Toxicology and Chemistry. Though most of their reports confirmed the suspected importance of moisture in fostering decay, several teams dug up surprises.

William L. Rathje and his archaeological team from the University of Arizona's Garbage Project joined in last year's "big dig" after unearthing wastes from six other landfills (SN: 10/6/90, p.218). At Fresh Kills, they used a bucket auger to chew out 47 boreholes, extracting 5,184 pounds of samples.

Near the surface, the Tucson researchers found that dry wastes showed little decay. But the deeper they dug, the wetter their finds. At 20 to 25 feet, they encountered heavily decayed gray slime. Because Fresh Kills has no clay barrier to separate initially interred wastes from the underground stream running another 5 to 10 feet down, the lower wastes suck up stream water "almost like a sponge," Rathje says.

Sampling revealed that paper accounts for 40 to 50 percent of the landfill's volume, plastics for up to 12 percent and metals for about 7 percent, he says. Construction and demolition debris held the only big surprise, representing 12 percent of Fresh Kills' volume. Because neither trade associations nor municipalities record contributions of such debris to the national waste stream, there were no formal data on its magnitude, Rathje says.

Yet construction debris may alter decay processes, asserts Joseph M. Suflita of the University of Oklahoma in Norman. Researchers have assumed that methane-producing bacteria complete the breakdown of cellulose-based wastes, such as paper, wood and yard clippings. However, the Oklahoma team discovered that when sulfates are present, competing "sulfate-reducing" bacteria may usurp that role.

Suflita's group detected sulfates, sometimes at extremely high levels, in most of the buried paper, textiles and other cellulosic materials at Fresh Kills. They also determined that fresh paper and textiles contain little or no sulfates. Suflita now suspects that gypsum board used in construction may be the sulfates' primary source.

While his findings point to a potential mechanism in cellulose decay, another team uncovered a potential obstacle to cellulose decay: the unexpected scarcity of microbes that initiate breakdown of this large polymeric molecule. Anna C. Palmisano of Procter & Gamble Co. in Cincinnati reports that only two of 28 soil samples tested by her group contained bacteria that can produce the enzymes needed to cleave cellulose into smaller units. *– J. Raloff*