

# Cancer gene plays key role in cystic fibrosis lung infections

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PTEN is best known as a tumor suppressor, a type of protein that protects cells from growing uncontrollably and becoming cancerous. But according to a new study from Columbia University Medical Center (CUMC), PTEN has a second, previously unknown talent: working with another protein, CFTR, it also keeps lung tissue free and clear of potentially dangerous infections.

The findings, published in *Immunity*, explain why people with cystic [fibrosis](#) are particularly prone to respiratory infections—and suggest a new approach to treatment.

A quarter-century ago, researchers discovered that cystic fibrosis is caused by mutations in the CFTR gene, which makes an eponymous protein that transports chloride ions in and out of the cell. Without ion transport, mucus in the lung becomes thicker and stickier and traps bacteria—especially *Pseudomonas*—in the lung. The trapped bacteria exacerbate the body's inflammatory response, leading to persistent, debilitating infections.

But newer research suggests CFTR mutations also encourage infections through a completely different manner.

"Recent findings suggested that [cells](#) with CFTR mutations have a weaker response to bacteria, reducing their ability to clear infections and augmenting inflammation," said lead author Sebastián A. Riquelme, PhD, a postdoctoral fellow at CUMC. "This was interesting because it

pointed to a parallel deregulated immune mechanism that contributes to airway destruction, beyond CFTR's effect on mucus."

That's where PTEN comes into play. "We had no idea that PTEN was involved in cystic fibrosis," said study leader Alice Prince, MD, professor of pediatrics (in pharmacology). "We were studying mice that lack a form of PTEN and noticed that they had a severe inflammatory response to *Pseudomonas* and diminished clearance that looked a lot like what we see in patients with cystic fibrosis."

Delving deeper, the CUMC team discovered that when PTEN is located on the surface of lung and immune cells, it helps clear *Pseudomonas* bacteria and keeps the inflammatory response in check. But PTEN can do this only when it's attached to CFTR.

And in most cases of cystic fibrosis, little CFTR finds its way to the cell surface. As a result, the duo fail to connect, and *Pseudomonas* run wild.

As it happens, the latest generation of cystic fibrosis drugs push mutated CFTR to the cell surface, with the aim of improving chloride channel function and reducing a buildup of mucus. The new findings suggest that it might be beneficial to coax nonfunctional CFTR to the surface as well, since even abnormal CFTR can work with PTEN to fight infections, according to the researchers.

"Another idea is to find drugs that improve PTEN membrane anti-inflammatory activity directly," said Dr. Riquelme. "There are several PTEN promoters under investigation as cancer treatments that might prove useful in cystic fibrosis."

The study also raises the possibility that PTEN might have something to do with the increased risk of gastrointestinal cancer in [cystic fibrosis patients](#). "With better clinical care, these patients are living much longer,

and we're seeing a rise in gastrointestinal cancers," said Dr. Prince. "Some studies suggest that CFTR may be a tumor suppressor. Our work offers an alternative hypothesis, where CFTR mutations and lack of its partner, PTEN, might be driving this cancer in patients with [cystic fibrosis](#)."

The paper is titled, "Cystic fibrosis transmembrane conductance regulator attaches tumor suppressor PTEN to the membrane and promotes anti *Pseudomonas aeruginosa* immunity."

Provided by Columbia University Medical Center

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