Protein involved in cystic fibrosis also plays role in emphysema, chronic lung disease

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This is principal investigator Neeraj Vij, Ph.D. Credit: Johns Hopkins Children's Center

A team of Johns Hopkins Children's Center researchers has discovered that a protein involved in cystic fibrosis (CF) also regulates inflammation and cell death in emphysema and may be responsible for other chronic lung diseases.

The findings, published online in the December issue of The *Journal of Immunology*, pave the way toward new treatments to prevent lung damage caused by infections or cigarette smoke in emphysema.

The protein, called CFTR (cystic fibrosis transmembrane conductance regulator), is already well known for its role in transporting chloride in and out of cells. In CF, the protein's chloride-carrying ability is absent due to genetic mutations, resulting in the buildup of thick sticky mucus in the lungs, which causes lung infections and breathing problems.

But the new Hopkins study indicates that CFTR is involved in immune regulation and immune response on a far wider scale. The research - conducted in mice and using lung tissue from people with and without emphysema - shows that those with lung damage from emphysema had less CFTR on the cell surface and that changes in the level of CFTR corresponded directly to disease severity. Decreases in CFTR also corresponded to increased buildup in the lung cells of a fatty molecule called ceramide, a well-known trigger of inflammation and cell death. Thus, the researchers say, by regulating ceramide's inflammation-causing activity, CFTR appears to be a watchdog for inflammation and cell death.

"Our findings suggest that CFTR is a multi-tasker protein that is not only involved in chloride transport but also in regulating cell death and inflammation by keeping in check the rampant and dangerous accumulation of ceramide," said principal investigator Neeraj Vij, Ph.D., a pulmonary researcher at Hopkins Children's and assistant professor at the Johns Hopkins University School of Medicine.

To elucidate the role played by cigarette smoking - the leading cause of emphysema - the researchers analyzed CFTR and ceramide levels in lung tissue obtained from non-smokers and from light and heavy former or current smokers. To further explore the link between cigarette smoke, CFTR and ceramide, the researchers compared lung tissue from mice with "virgin" lungs never exposed to smoke to tissue from the lungs of mice exposed to cigarette smoke for five hours a day over five days. The lungs of smoke-exposed mice had decreased CFTR expression and increased ceramide levels, thus confirming the role of cigarette smoke in lung damage. The heavier the smoking, the greater the lung damage, the lower the CFTR expression and the higher the ceramide accumulation, the researchers noted, clearly linking CFTR and ceramide levels to smoking history and disease

severity.

Beyond clarifying the link between CFTR, ceramide and lung damage, the Hopkins team explained just how CFTR causes ceramide to trigger lung-damaging inflammation. Analyzing lung cells from people and mice lacking CFTR in their cell membrane under a microscope and with a technique called flow cytometry that captures changes in inflammatory and protein markers, the scientists noticed increased clustering of ceramide molecules on sections of the cell membrane called lipid rafts, known to be hot spots where inflammatory signaling proteins congregate. This clustering, the researchers said, leads to increased inflammatory signaling, greater inflammation and cell damage, but cells with normal CFTR had no such clustering. Apparently, the researchers say, when functioning properly CFTR keeps a lid on the signaling activity of inflammatory receptors by preventing them from clustering, thus warding off inflammation and lung damage.

"We anticipate that membrane CFTR and ceramide may turn out to be useful predictors of susceptibility to lung damage from smoking and infections and may be tailored for drug therapy to alter disease course," Vij said.

To further test their hypothesis, the researchers used two types of ceramide inhibitors to treat mice with lung damage caused by a bacterial infection. One of the inhibitors, FB1, successfully decreased ceramide buildup in mice with intact CFTR but failed to stop ceramide accumulation in mice with absent CFTR, as is the case in CF. However, the other type of inhibitor, AMT, curbed ceramide activity in the mice with the absent CFTR, while failing to do so in those with decreased CFTR.

"Each inhibitor appeared to be effective based on the levels of membrane CFTR and ceramide, suggesting two different therapies tailored to treat lung damage stemming from two distinct lung disorders - emphysema and CF," said co-investigator Manish Bodas, Ph.D., a post-doctoral fellow in Vij's lab at Hopkins Children's.

More information:
www.ncbi.nlm.nih.gov/pubmed/21135173

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