

Cystic fibrosis patients may breathe easier, thanks to bioengineered antimicrobials

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By better understanding how antimicrobials bind and thereby get inactivated in the mucus of air passages, researchers at the University of Illinois may have found a way to help cystic fibrosis patients fight off deadly infections.

"While not a cure, this work has potential as a therapeutic strategy against bacterial infections in cystic fibrosis," said Gerard Wong a professor of materials science and engineering, of physics, and of bioengineering at the U. of I., and a corresponding author of a paper accepted for publication in the *Proceedings of the National Academy of Sciences.* The paper is to be posted this week on the journal's Web site.

Ordinarily, pulmonary passages are lined with a thin layer of mucus that traps bacteria and other pathogens. Moved along by the motions of countless cilia, the mucus also acts as a conveyor belt that disposes of the debris. In patients with cystic fibrosis, however, the mucus is more like molasses – thick and viscous. Because the cilia can no longer move the mucus, the layer becomes stuck, and the bacteria grow, multiply and colonize. Long-term bacterial infections are the primary cause of death in cystic fibrosis.

Using synchrotron X-ray scattering and molecular dynamics simulations, the researchers took a closer look at the mucous mess.

Debris in the infected mucus includes negatively charged, long-chained molecules such as mucin, DNA and actin (from dead white blood cells).



It turns out most of the body's antimicrobials, such as lysozyme, are positively charged.

"We found that actin and lysozyme – two of the most common components in infected mucus – form ordered bundles of aligned molecules, which is something you don't expect in something as messy as mucus," said Wong, who also is a researcher at the university's Beckman Institute. "Held together tightly by the attraction of opposite charge, these bundles basically lock up the antimicrobials so that they are unable to kill bacteria."

The researchers then developed a computational model to mimic the biological system. "The model accurately predicted the structure of the actin-lysozyme bundles, and agreed quantitatively with the small-angle X-ray scattering experiments," said Erik Luijten, a professor of materials science and engineering, and of physics, as well as a researcher at the Beckman Institute and the other corresponding author of the PNAS paper.

The next step was to find a way to liberate the lysozyme, or prevent it from binding in the first place. Using their model, the researchers explored the consequences of varying the positive charge on the lysozyme.

"When we reduced the charge, we found a huge effect in our model," Luijten said. "The lysozyme would not bind to the actin. It floated around independently in the mucus."

Then, through genetic engineering, the researchers made lysozyme with roughly half the normal charge. Experiments confirmed the simulations; the reduced charge prevented lysozyme from sticking to actin, without significantly reducing the all-important antimicrobial activity.



Although much work remains, future cystic fibrosis patients might use an inhaler to deliver genetically modified charge-reduced antimicrobials to upper airways. There, these 'non-stick' antimicrobials would go to work killing bacteria, and mitigate against long-term infection.

The implications of this research extend into other areas as well. In water purification, for example, one of the steps involves putting positively charged molecules in the water to grab negatively charged pollutants. The resulting aggregates settle to the bottom of holding tanks and are removed from the water supply.

"A better understanding of how oppositely charged molecules bind in aqueous environments could lead to ways of removing emerging pathogens in water purification," Wong said.

Source: University of Illinois at Urbana-Champaign

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