Evolutionary roots of ancient bacteria may open new line of attack on CF

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The redox-active pigments responsible for the blue-green stain of the mucus that clogs the lungs of children and adults with cystic fibrosis (CF) are primarily signaling molecules that allow large clusters of the opportunistic infection agent, *Pseudomonas aeruginosa*, to organize themselves into structured communities, report Massachusetts Institute of Technology geobiologists at American Society for Cell Biology (ASCB) 48th Annual Meeting, Dec. 13-17, 2008 in San Francisco.

For decades, these pigments, called phenazines, have been wrongly regarded as antibiotics, generated by *P. aeruginosa*, to kill off the microbe's bacterial competitors in the lungs.

This new insight about the leading cause of death of people with CF suggests that the phenazine-processing machinery could become a potential target for drugs to treat *P. aeruginosa* infections in CF patients, says Dianne K. Newman, who heads the MIT lab, and postdoctoral fellow Lars Dietrich.

P. aeruginosa appears as a classic opportunistic infection, easily shrugged off by healthy people but a grave threat to those with CF, which chokes the lungs of its victims with sticky mucus.

"We have a long way to go before being able to test this idea, but the hope is that if survival in the lung is influenced by phenazine -- or some other electron-shuttling molecule or molecules --tampering with phenazine trafficking might be a potential way to make antibiotics more

effective," explains Newman, whose lab investigates how ancestral bacteria on the early Earth evolved the ability to metabolize minerals.

Newman and Dietrich looked at phenazines from an evolutionary perspective, and using RNA arrays to probe all of the small molecules' actions, they discovered that phenazines are not mere redox-active weapons but are molecules that activate the transcription factor SoxR.

In Escherichia coli and other closely related bacteria, SoxR regulates the response to superoxide stress and appears to be utilized to regulate a handful of genes that might be involved in the transport and modification of redox-active signals.

By manipulating phenazine activity in colonies of *P. aeruginosa* grown in the lab, the MIT scientists learned that these molecules create a smooth biofilm surface under which the colony can prosper in anaerobic bliss.

The less phenazine available, the more wrinkled and less strong the colony surface becomes.

A thick biofilm also develops in the lungs of patients with CF infected with *P. aeruginosa*. Sealed under the biofilm are the pseudomonads that have adapted to the patients' lungs, developed antibiotic resistance and formed large anaerobic colonies.

Most people with CF die from a cascade of damaging lung infections. Pathogenic bacteria such as Staphylococcus aureus weaken the CF patient, but it is the onset of *P. aeruginosa* infection that signals a dangerous turn.

Source: American Society for Cell Biology

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