New research allows a better understanding of host response to infection

Pseudomonas aeruginosa bacteria can cause severe infections in people already suffering from other health conditions. In light of increasing antibiotic resistance in these bacteria, new treatment options are urgently needed. As a first step towards this goal, Professor Ruxana Sadikot and colleagues at Emory University School of Medicine, Atlanta, USA, investigated the role of one particular molecule produced by P. aeruginosa on the function of bronchial epithelial cells. The results are promising and have improved understanding of how P. aeruginosa causes disease, as well as suggesting a potential new treatment option for the future.

Most bacteria are harmless to humans. Some, like the commensal bacteria that live in our guts, are helpful – or even vital. Other bacteria are harmful, with the potential to cause serious infection. There are some, however, which pose no threat to healthy individuals but can be life-threatening to those already suffering from other conditions.

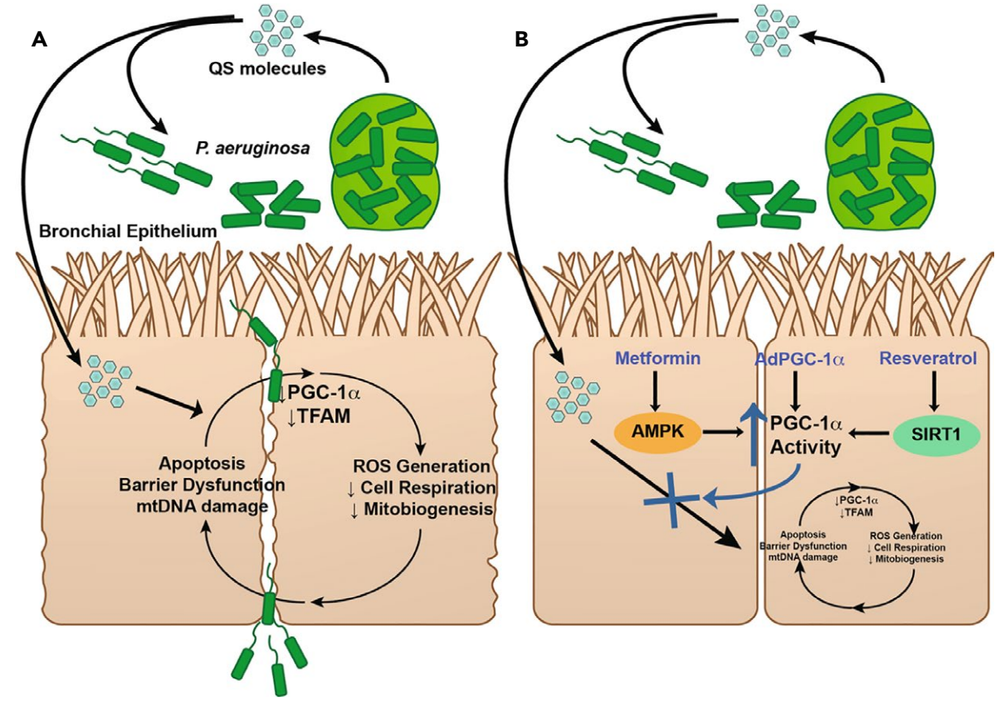
Pseudomonas aeruginosa is an extremely common bacteria, often found in soil and groundwater. For most people, coming into contact with these bacteria will have no effect. However, *P. aeruginosa* is an opportunistic pathogen; this means that it can cause serious problems in people who are already ill, or who have a suppressed immune system. *P. aeruginosa* often manifests itself as a respiratory tract infection and is responsible for many hospital-acquired infections. This causes a particular problem for patients who need to have equipment, such as a breathing tube, left inside their body for a period of time.

Unfortunately, *P. aeruginosa* is becoming increasingly resistant to antibiotic treatment, increasing the risk to patients who are already vulnerable. New ways to prevent and treat *P. aeruginosa* infection are urgently needed. These strategies may attempt to kill the bacteria or inhibit their growth, target their ability to infect a host, or even boost the patient's immune system so that they are better able to fight off the infection. However, before this can happen, researchers need to gain a more detailed understanding of exactly how *P. aeruginosa* causes disease.

HOW DOES *P. AERUGINOSA* INFECTION CAUSE DISEASE?

Some strains of *P. aeruginosa* are known to be able to boost their ability to infect a host by adapting to their environment. They do this by controlling which of their genes are expressed (used to produce proteins) at any time. This ability appears to be dependent on a system known as quorum sensing (QS), which both allows communication between bacteria and affects the biology of the host. The molecules that make up the QS system of *P. aeruginosa* have been identified in the lungs of patients who have been infected by the bacteria. Also, strains of *P. aeruginosa* that lack QS are less likely to cause disease. Taken together, this evidence suggests that QS plays an important role in the ability of *P. aeruginosa* to infect host cells.

In recent research, Prof Ruxana Sadikot of Emory University School of Medicine investigated the effect of one specific component of *P. aeruginosa*'s QS system, a molecule called 3-oxo-C12-HSL, on the function of bronchial epithelial cells. These cells, which line the upper airways, are susceptible to damage during *P. aeruginosa* infection. Previous research suggests that this might be due to the ability of the QS molecule to disrupt the number and function of mitochondria in the epithelial cells. Mitochondria are small structures that generate the chemical energy the cell needs; without them, the cell cannot function properly. In the lungs and airways, mitochondria help epithelial cells to create a physical barrier to pathogens like bacteria.



From: *Pseudomonas aeruginosa* Induced Host Epithelial Cell Mitochondrial Dysfunction

Effect of *P. aeruginosa* QS molecules on lung epithelial host response. (A) QS molecules disrupt mitochondrial bioenergetics, attenuate cellular respiration, induce ROS generation and the apoptosis pathway, repress the PGC-1α-TFAM mitochondrial biogenesis pathway, and trigger loss of barrier integrity. (B) Therapy targeting activation of the PGC-1α pathway via genetic or pharmacologic approaches partially rescues the impairments in mitochondrial respiration, mitochondrial biogenesis, and barrier integrity.

Normally, when mitochondria are damaged, they can be swiftly replaced in a process called biogenesis – the growth and division of other, pre-existing mitochondria. Key to this process is a protein called PGC-1α, which helps to maintain a sufficient number of functioning mitochondria within the cell.

In their recent work, Prof Sadikot and her colleagues looked at the effects of 3-oxo-C12-HSL on the mitochondrial functioning of bronchial epithelial cells. Specifically, the team aimed to understand whether activation of the PGC-1α protein could help to compensate for the damage done by *P. aeruginosa*'s QS system – and whether this could open up a new potential treatment option.

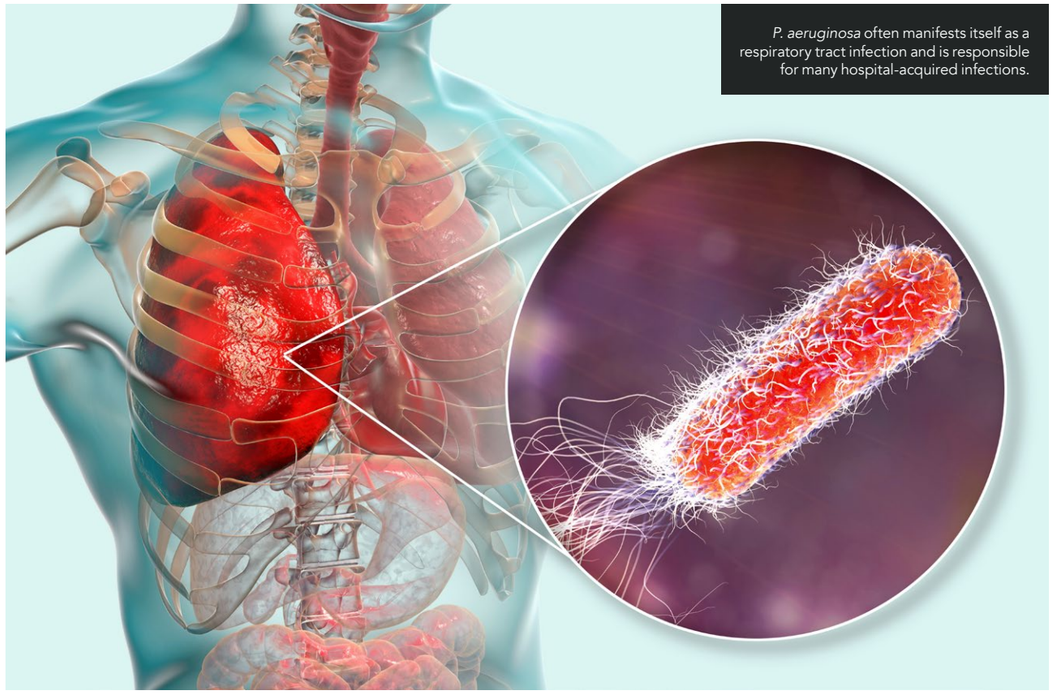
***P. aeruginosa* can effectively evade the normal defences of the lungs and airways by damaging the mitochondria of the bronchial epithelial cells.**

TRACKING THE DAMAGE CAUSED BY *P. AERUGINOSA*

Prof Sadikot and her colleagues used an *in vitro* method to examine the way that *P. aeruginosa* behaves when it infects bronchial epithelial cells. After the bacteria were added to the epithelial cells, the team used a variety of different techniques to observe the consequences.

The experiments produced a number of significant results. Firstly, the researchers were able to successfully demonstrate that *P. aeruginosa* does disrupt the mitochondria of bronchial epithelial cells. In particular, the team discovered that both infecting the cells with *P. aeruginosa* and treating them with 3-oxo-C12-HSL leads to a reduction in the number and size of mitochondria. Overall, the data suggested that *P. aeruginosa* can effectively evade the normal defences of the lungs and airways by damaging the mitochondria of the bronchial epithelial cells.

In order to better understand the likely consequences of the disruption of mitochondria by *P. aeruginosa*, the researchers looked more closely at



P. aeruginosa often manifests itself as a respiratory tract infection and is responsible for many hospital-acquired infections.

Kateryna Kon /Shutterstock.com

the activity of the mitochondria in the infected cells. This revealed that the *P. aeruginosa* QS system limits the ability of mitochondria to generate the chemical energy needed by the cell. In turn, this reduces the ability of the cell to fight disease. In a further blow to the cell, the team discovered that 3-oxo-C12-HSL does not just destroy and shrink mitochondria – it also suppresses the ability of the cell to replace the lost mitochondria.

As Prof Sadikot had suspected, activating the PGC-1α protein partially restored mitochondrial function in the infected cells. Activating this protein had two effects: the energy-producing abilities of the mitochondria were rejuvenated, and the cell was able to replace at least some of the lost or damaged mitochondria.

Finally, the researchers investigated the potential of two drugs in restoring the defences of bronchial epithelial cells. Both of these medications boost the activity of PGC-1α and are already used by doctors in the treatment of other conditions. Prof Sadikot and her colleagues were able to show that the drugs did, in fact, somewhat restore the barrier-like properties of epithelial cells, allowing them to better resist infection.

Activating PGC-1α protects bronchial epithelial cells to a certain extent, allowing the body to maintain its immune response.

TOWARDS A NEW TREATMENT?

Prof Sadikot and her colleagues are the first researchers to shed light on the precise impact of *P. aeruginosa* QS molecules on the process of generating new mitochondria. Along with the other results of this study, this finding has important clinical implications in suggesting new potential treatment opportunities.

When planning their research, the team hypothesised that activating the PGC-1α protein might improve the ability of mitochondria to produce energy, allow the cell to replace lost mitochondria, and support cellular defences against infection. The results showed that this does appear to happen: activating PGC-1α protects bronchial epithelial cells to a certain extent, allowing the body to maintain its immune response to *P. aeruginosa* infection. This finding is supported by previous research, in which researchers found that activation of the PGC-1α protein helps the body to repair various different types of damage. Overall, Prof Sadikot and her colleagues hope that their research so far represents the first step towards a potential new treatment to boost the host immune response to *P. aeruginosa* infection.

While the researchers acknowledge that more research is needed – on how exactly the investigated drugs restore the barrier function of epithelial cells, for example – before this new treatment becomes a reality, their findings have made a significant contribution to the understanding of the interactions between the invading *P. aeruginosa* and host cell mitochondria. In time, vulnerable patients with difficult-to-treat *P. aeruginosa* infections may be able to benefit from the work of the team at Emory University.

Behind the Research

Prof Ruxana Sadikot

E: Ruxana.sadikot@emory.edu **W:** http://www.ncbi.nlm.nih.gov/pubmed/?term=sadikot+r

Research Objectives

Prof Sadikot is developing new strategies to combat *P. aeruginosa* and other resistant pathogens.

Detail

Address
1017 Emory Parc Pl
Decatur, GA 30033
USA

Bio

Dr Ruxana Sadikot graduated from the Bombay University with a Medical Doctorate. She continued her medical training in the U.K. where she received the prestigious Membership of Royal College of Physicians (MRCP) in 1992. Dr Sadikot then trained in respiratory medicine at Yorkshire Health Authority following which she moved to the U.S. She completed a fellowship training in pulmonary and critical care medicine at the Vanderbilt University in Nashville TN in 2001 and was appointed as an Assistant Professor (tenure track) in the Division of Pulmonary and Critical Care. After four years, she was recruited to the University of Illinois in Chicago where she served as the associate program director for pulmonary and critical care fellowship and was tenured and promoted to the rank of Associate Professor. In September 2012 she joined the University of Florida where she served as the section chief of Pulmonary and Critical Care Medicine for the Malcom Randall VA Hospital and was promoted to the rank of Professor of Medicine with tenure. In 2014 Dr Sadikot was recruited to the Emory University as Professor of Medicine and currently serves as the section chief of Pulmonary and Critical Medicine at the Atlanta VAMC.

Funding
- National Institute of Health
- Department of Veterans Affairs
- Cystic Fibrosis Foundation

Collaborators
- Dr Mike Koval
- Dr Joanna Goldberg

References

Maurice, N.M., et al. (2019). *Pseudomonas aeruginosa* Induced Host Epithelial Cell Mitochondrial Dysfunction. *Nature Scientific Reports*, 9, 11929. Available at: https://doi.org/10.1038/s41598-019-47457-1

Janthiwa Sutthiboriban/Shutterstock.com