



Scientists Discover Potential New Target in Fight Against 'Superbug'



- Antibiotic-resistant bacteria thrive in the lungs of seriously ill patients
- Scientists discover 'switch' that turns on aggressive infection in the superbug
- Hope that discovery could lead to new treatments

University of Cambridge researchers have discovered how an antibiotic-resistant superbug exploits oxygen-limited conditions in the lungs of patients with severe respiratory disease to thrive.

It is hoped the discovery could lead to new ways to target the *Pseudomonas aeruginosa* bacterium, which is responsible for six per cent of healthcare associated infections in NHS patients and has a widespread resistance to many antibiotics.

Infection by *P. aeruginosa* is a major cause of death in patients with Cystic Fibrosis.

The research, funded by the Biotechnology and Biological Sciences Research Council (BBSRC) and published in *Open Biology*, shows that an infection pathway in *P. aeruginosa* is activated when the bug encounters low-oxygen conditions.

Lead investigator Dr Martin Welch, from the University of Cambridge Department of Biochemistry, said: "This is particularly important because the bug is strongly associated with infections in patients with severe respiratory disease; most famously patients with cystic fibrosis - many of whom eventually succumb to *P. aeruginosa* infections.

"Counter-intuitively, the lung tissue of such patients is oxygen-limited, so this could trigger the pathway."

P. aeruginosa infection in the lungs promotes an inflammatory response that destroys lung tissue.

When the bug encounters low oxygen conditions, a mechanism called the Type III Secretion System (T3SS) is triggered.

The T3SS resembles a molecular-scale 'hypodermic syringe' which is thought to inject toxins directly from the bacterium into the host cell, where they subvert its function and lead to cell death.

The team identified a metabolic 'switch' regulating T3SS activity, called the glyoxylate shunt, which is activated when oxygen is sparse.

When this 'switch' is turned on an enzyme called isocitrate lyase (ICL) is expressed, leading to activation of the T3SS. In the absence of ICL, the T3SS is not turned on in low-oxygen conditions.

Dr Welch added: "The mechanism by which ICL impacts on the T3SS involves a previously unrecognised regulatory pathway.

"Crucially we found that this regulatory pathway also affected the formation of antibiotic-resistant biofilms by *P. aeruginosa*. This is important because biofilm formation is known to play an important role in the pathology of cystic fibrosis-associated infections. Our study therefore opens up new potential avenues for the development of novel antibacterial therapeutic interventions."

Dr Janet Allen, Director of Research at the Cystic Fibrosis Trust said: "Many people with Cystic Fibrosis will develop *Pseudomonas aeruginosa* during their lives and it can cause chronic infection, which reduces lung function and therefore life expectancy. The Cystic Fibrosis Trust welcomes this research from the University of Cambridge which helps us to understand more about why this bacterium thrives in the lungs of those with cystic fibrosis, and could in the future lead to more treatments."

Professor Douglas Kell, BBSRC Chief Executive, said: "By understanding the intriguing mechanisms used by this bacterium during infections, this research could make a profound difference to for those with Cystic Fibrosis and may one day help to save lives."

Notes to editors

- The paper "Type III secretion system expression in oxygen-limited *Pseudomonas aeruginosa* cultures is stimulated by isocitrate lyase activity" by Chung et al. is available at <http://rsob.royalsocietypublishing.org/embargo?embargoed-uri=http%3A%2F%2Frsob.royalsocietypublishing.org%2Fcontent%2F3%2F1%2F120131>.
- *P. aeruginosa* is responsible for six per cent of healthcare associated infections in NHS patients: www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317134304594 (external PDF)

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