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Breakthrough could give new hope to sufferers of Cystic Fibrosis

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Cystic Fibrosis is a devastating genetic disease which afflicts over 10,000 children across the country. The disease results in a declining lung function, which in turn leads to a higher likelihood of developing lung infections. These chronic lung infections have a severe impact on the quality of life and eventually lead to premature death.

Research highlighting the way in which lung-damaging bacteria use the body's own immune response to worsen the effect has brought new hope to sufferers of this disease and a related disease called bronchiectasis that afflicts over 100,000 adults in the UK.

The authors of the study, published in The *Journal of Experimental Medicine*, hope that their work will alter the way in which new vaccines and treatments are developed for Cystic Fibrosis and other variations of bronchiectasis.

Dr Ian Henderson, of the University of Birmingham, explained, "The impact of bronchiectasis is absolutely massive. In more severe cases patients can be bed-ridden for months and are constantly suffering from breathlessness, coughing and chest pain. The simplest everyday tasks that we take for granted can prove to be exhausting to the point of becoming impossible."

The pathogenic bacteria that cause such infections are usually destroyed by antibodies, the immune proteins that coat the outer surface of the intrusive bug and instigate the process by which other proteins can tackle

and destroy the bacteria. Despite the presence of such antibodies, some people are not able to fight off infections of the respiratory bacterium Pseudomonas aeruginosa.

The new research has found that in many patients the bacterium induces an abnormal antibody response, which has a negative consequence for fighting the infection in bronchiectasis patients and results in particularly poor lung function.

In this patient subset, there was an abundance of IgG2, an antibody that reacted to the bacteria but actually served to strip the blood of its normal bug-killing capacity. IgG2 bound itself onto extra-long sugars (LPS molecules) on the bacterial surface in a manner that was unique to the bugs that infected the bronchiectasis patients. When the team removed the sugar-specific IgG2 antibodies, the blood was once again able to combat infection with a fully restored antibacterial prowess.

It is not yet clear exactly how the IgG2 molecules protect the bug from being destroyed – but the discovery of their role in working against the body has implications for therapies already in development.

Dr Henderson added, "What this means, fundamentally, is that we have to proceed with real caution in developing treatments. Three attempts have been made to develop vaccines targeting the LPS molecule – this extra-long sugar – and each time it has failed. The children receiving the vaccine actually developed a more severe disease than those who didn't."

"Our results reveal why this would be the case. These vaccines would cause the immune system to provide so many antibodies that end up working alongside the LPS and prevent the bacteria from being killed."

The team are using their findings to inform a new line of research for treatment of patients and the development of vaccines to protect against

infections which afflict bronchiectasis patients. This research may also go some way to explaining why people may suffer with other chronic bacterial infections.

More information: Timothy J. Wells, Deborah Whitters, Yanina R. Sevastsyanovich, Jennifer N. Heath, John Pravin, Margaret Goodall, Douglas F. Browning, Matthew K. O'Shea, Amy Cranston, Anthony De Soyza, Adam F. Cunningham, Calman A. MacLennan, Ian R. Henderson and Robert A. Stockley (2014) Increased severity of respiratory infections associated with elevated anti-LPS IgG2 which inhibits serum bactericidal killing. The *Journal of Experimental Medicine*, DOI: 10.1084/jem.20132444

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