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Cystic Fibrosis Research News

Title:

Evidence of early increased sialylation of airway mucins and defective mucociliary clearance in CFTR$^{-/-}$ deficient piglets

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What was your research question?

Cystic fibrosis (CF) is notably characterised by changes in the sugar composition of mucins, which are the main organic components of mucus. Altered mucus is thought to promote long term infections by bacteria like *Pseudomonas aeruginosa*. We asked whether the sugar composition of mucins is already altered at birth and does the sugar composition make *P. aeruginosa* colonisation more likely?

Why is this important?

Pseudomonas aeruginosa is a bug that commonly infects the lungs of people with CF, making a faster decline in lung function more likely. For colonisation with *P. aeruginosa*, the bacteria need to firstly combine with the mucus in the airways and this mainly happens through a mucin-linked sugar called sialic acid. It is important to understand the processes that lead to the higher levels of sialic acid and how fast these happen so as to have a chance of controlling its detrimental effects quickly. In other words, it is crucial to know what comes first, the bacteria and the resulting inflammation or the sugar modification itself, to know what has to be fought first.

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What did you do?

We compared, the sugar composition of the mucins at birth between healthy piglets and CF piglets, a model that reliably reproduces the human disease. We looked at whether the changes that we had found were directly linked to the genetic mutation of CF and whether the changes were specific to mucins. Study the pig model from birth meant that we could rule out that these changes to mucins were the result of inflammation or bacterial infections. It also allowed us to carefully examine the influence of mucin sugars on *P. aeruginosa* adhesion and growth in the mucus. Finally, we examined the capacity of the CF piglet lungs to get rid of the bacteria which were bound to the mucus compared to that of healthy piglet lungs.

What did you find?

We found that the level of sialic acid in mucins from CF piglets at birth is significantly much higher than in healthy piglets. We realised that this difference was directly linked to the genetic mutation of CFTR because when we used drugs to inhibit CFTR in the healthy piglets, we caused a higher level of sialic acids. This phenomenon was specific to mucins and did not affect other proteins. It was also not due to pre-existing inflammation or bacterial infection. We also found that the CF lung was less able to efficiently transport mucus-bound bacteria out of the airway that healthy lungs.

What does this mean and reasons for caution?

Abnormally high levels of sialic acid in mucins are present at birth in CF piglets and therefore likely to be present in babies with CF. Increased levels might be beneficial to people which do not have CF in increasing the capture and expulsion of inhaled bacteria. However, the sticky mucus in the CF lung is not easily expelled, resulting in bacterial colonisation and contributing to the development of CF lung inflammation. Although we used an animal model, these findings cannot be replicated in humans as it would be traumatic for the babies. Nevertheless, the CF piglet model does reliably reproduce human CF lung disease.

What's next?

We need to better understand the processes in the cells that lead to changes in sugar levels in CF mucus that we have described. There are also two treatment approaches that might be explored: first, decreasing the level of sugars in mucin in the CF lung or two, design molecules to reduce *P. aeruginosa* colonisation.

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