

Cystic Fibrosis Research News

Title:

Citrullination of extracellular histone H3.1 reduces antibacterial activity and exacerbates its proteolytic degradation

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What was your research question?

The aim of this study was to investigate how changes to the protein structure of histones, particularly histone H3.1, affects their ability to kill bacteria that infect the lungs of people with cystic fibrosis (CF).

Why is this important?

People with CF often suffer from respiratory problems because their airways are more susceptible to chronic bacterial infections. To clear these infections, the body destroys the build-up of immune cells (mainly a type known as neutrophils). As a result, CF airways have a higher level of antibacterial histones and an accompanying enzyme named PADI4 compared to the airways in healthy people. This enzyme is also released from neutrophils and causes changes to the protein structure of antibacterial histones, a process called 'citrullination'. These changes may mean the immune system is less able to clear invading bacteria, which allows more bacterial growth in the lungs. Therefore, these histones need to balance bacteria levels, possibly with the help of medical interventions.

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What did you do?

We investigated four histones (H2A, H2B, H3.1, and H4) for their ability to kill a common CF airway bacterium, *Pseudomonas aeruginosa* (*P. aeruginosa*). We then looked at how this ability was altered following citrullination. Of particular interest was histone H3.1, as this histone was seen to be most affected by citrullination. Finally, we looked at lung samples from healthy people and people with CF (samples from lung transplants) to search for differences in the location and content of PADI4 and histone H3.1. These proteins were also measured in the sputum of healthy volunteers and people with CF for further confirmation of our findings.

What did you find?

We identified specific areas of histone H3.1 that showed antibacterial effects against the bacterium *P. aeruginosa*. In addition, we showed that citrullination of histone H3.1 reduced this antibacterial effect and made the histone more easily degraded by neutrophil enzymes. In the lung tissue obtained from people with CF, we saw high concentrations of histone H3.1 and PADI4 in comparison to healthy lungs. Furthermore, we found traces of degraded histone H3.1 in the sputum of people with CF but not in the sputum from the healthy volunteers.

What does this mean and reasons for caution?

The large quantity of neutrophils being destroyed in the airways of people with CF suggests that the released histones are very active against bacteria. However, this response can be hampered by neutrophil enzymes that cause histone degradation and citrullination. This study is limited by the specific nature of these interactions. Although important, we recognize that *P. aeruginosa* is not the only type of bacteria found in the lungs, PADI4 is not the only citrullinating enzyme, and histone H3.1 is not the only protein regulating bacterial clearance in CF. Our findings shed light on a small part of a much larger and complex biological interaction.

What's next?

It is important that novel treatments are developed to restore and maintain the balance between histone immune functions, such as antibacterial activity and resolution of inflammation. Using drugs to affect PADI4-activity may therefore be a future target for treating bacterial airway infection in CF.

Original manuscript citation and associated presentations:

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