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Cystic Fibrosis Research News

Title:

Resolvin D1 regulates epithelial ion transport and inflammation in cystic fibrosis airways

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What was your research question?

Can a naturally produced regulator of inflammation in the body, Resolvin D1, correct the default of the salt transport defects and enhance killing of bacteria in the fluid lining the lungs in cystic fibrosis?

Why is this important?

Cystic fibrosis (CF) affects many organs but the progressive lung destruction is the main cause of disease symptoms and survival. In the lung, clearance of inhaled microbes (bacteria, viruses…) requires an adequate amount of water of the thin layer of water lining the airway and an effective reaction of the defense system by specialised bacterial killing cells called macrophages. Mutations of the CF gene (CFTR), result in salt transport defects that cause a lack of chloride secretion and an excessive absorption of sodium in the lung. These contribute to less water of the fluid lining the cells of the airways and favours growth of bacterial and sustained inflammation. One of the challenges of treating cystic fibrosis disease in the lung has been to design a therapy which will overcome the mucus plugging in the airways and the chronic infection and inflammation. Current therapies involve drugs which correct the function of CFTR but this strategy is expensive and so far limited to rarer CFTR mutations. Other strategies have been plagued by the side effects of responses of the defense system.

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The potential of using a molecule which is naturally produced in the body and which would target infection, inflammation and salt channels would be a great boon in CF therapy.

What did you do?

We carried out experiments on the possible positive effects of a naturally produced regulator of inflammation in the body called "Resolvin D1" on airway cells and defense cells called macrophages from people with cystic fibrosis. We measured the activity of chloride and sodium channels using sophisticated electrical measurements. We were also able to make the dynamic changes visible in the amount of water of the fluid lining the airway cells using a special type of laser microscope. We measured the ability of macrophages to kill the bacteria Pseudomonas aeruginosa. We also performed studies in a mouse model of cystic fibrosis to determine if Resolvin D1 corrected the salt transport defects in the upper airways.

What did you find?

We found that Resolvin D1 reversed key components of CF lung disease. Resolvin D1 corrected the abnormalities of salt transport in human CF lung cells and in CF mice. Resolvin D1 restored the volume of the airway surface liquid layer making it less thick and sticky while also decreasing reactions of the defense systems and stimulated the macrophages to kill the bacteria.

What does this mean and reasons for caution?

Our study demonstrates the unique ability of Resolvin D1 to restore normal salt transport function and the airway surface fluid as well as regulating the dense system of the CF airway. Resolvin D1 shows potential for treatment for some of the most difficult aspects of CF disease. Inflammation and bacterial infection are complex processes and caution is needed when interpreting the reasons for imbalances in the defense system in the CF lung.

What's next?

This study strongly suggests a potential therapeutic role for Resolvin D1 in treating the airway disease of patients with cystic fibrosis, for all CFTR mutations. A further step will be the design of a clinical trial in CF patients to assess safety, efficacy and restorative effects of Resolvin D1 under a wide range of CFTR mutations.

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