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Cystic Fibrosis Research News

Title:

Depletion of BAFF cytokine exacerbates infection *in Pseudomonas aeruginosa* infected mice

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What was your research question?

Research performed in other laboratories demonstrated that people with cystic fibrosis (CF) have a higher level of a growth factor called BAFF, which is important for the development of a subtype of white blood cells called B cells, than people who don't have this condition.

Why is this important?

These discoveries hinted at the possibility that lowering the level of BAFF in the blood might decrease the constant inflammation in the lungs of people with CF and therefore improve their ability to fight bacterial infection. However, since inflammation is an essential component of a person's immune response against infection, this approach could be a double-edged sword. Therefore, we decided to test the effect of lowering levels of BAFF on lung function in mice infected with *Pseudomonas aeruginosa*, the most common bacteria infecting the lungs of people with CF.

What did you do?

We developed a mouse model with CF, that did not express any alternative chloride transporters and whose lungs depend on the expression of cystic fibrosis transmembrane regulator (*CFTR*) to function. We used this mouse model to the test the role of BAFF in controlling lung infection. We showed that B6 mice (known as the C57BI/6 strain of mice)

without the *CFTR* gene are more susceptible to bacterial lung infections and have more problems with digestion compared to their controls, a symptom which is also seen in people with CF. Our results clearly demonstrated that as in humans, the lungs of these mice are inflamed even without infection and their lungs do not function correctly even at the fairly young age. We measured the levels of different types of immune cells and *P. aeruginosa* and lung function in our mouse model as well as mice with a normal level of CFTR before and after treatment with anti-BAFF treatment.

What did you find?

We discovered that decreasing the level of BAFF using anti-BAFF antibodies in the mice without the *CFTR* gene weakened their ability to fight lung infection with *P. aeruginosa*. Even in mice expressing a normal level of *CFTR*, decreasing levels of BAFF also decreased their ability to fight infections. Indeed, mice that were treated with antibodies that neutralise BAFF had a significantly higher number of bacteria in their lungs than mice treated with saline (salty water). Furthermore, decreasing BAFF in mice which do not express *CFTR* gene, led to more constriction in the lungs, which indicated that the overall lung function was being compromised.

What does this mean and reasons for caution?

In order to study lung disease triggered by the mutation in the *CFTR* gene and to develop new treatments, scientists need an animal model that will successfully recapitulate most of the symptoms of the disease found in humans so they are able to test their theories and then the treatment they are proposing. Our study showed that decreasing the level of BAFF would not be an effective treatment for controlling inflammation in people with CF. Moreover, decreasing the level of BAFF in people with lupus with the current anti-BAFF treatments raises concerns for the lupus patients who are treated with anti-BAFF therapies when they happen to get lung infection.

What's next?

Our data clearly show that our mouse model of CF lung disease can be used to evaluate both safety and efficacy of any promising interventions in the future. These results demonstrate that BAFF is an important regulatory molecule helping to maintain the immune response to infection and should not be maintained at CF patients and call for attention the physicians who are using currently approved anti-BAFF therapies (ie. Belimumab®) to treat patients with lupus who may want to consider discontinuation of the treatment during the course lung infections.

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