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Cystic Fibrosis Research News

Title:

Systemic levels of anti-PAD4 autoantibodies correlate with airway obstruction in cystic fibrosis

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What was your research question?

Lung disease remains the main complication in cystic fibrosis (CF). CF lung disease is partially driven by immune cells called neutrophils. While neutrophils are unable to kill the main bacteria infecting CF patients, they have been associated with lung disease progression. The exact mechanism by which neutrophils damage lung tissue in CF remains undetermined. An antimicrobial mechanism of neutrophils, called neutrophil extracellular traps (NET) formation, has been proposed as a potential explanation. NETs trap and kill microbes under normal conditions, while in CF the role of NETs remains debated. Long-term presence of NETs in CF airways could lead to an autoimmune response. Therefore, our goal was to explore whether autoantibodies targeting NETs are present in CF patients.

Why is this important?

To address the potential presence of autoantibodies targeting NETs in CF is relevant because it would indicate that the immune system attacks host molecules in CF and there is an underappreciated autoimmune component of the disease. Autoantibodies could drive or contribute to disease symptoms in several, so far undiscovered, ways. Novel knowledge

gained on CF autoimmunity could also enable us to explore potential, new therapeutic options to treat CF.

What did you do?

We measured autoantibody levels in the blood of 37 people with CF, 20 with rheumatoid arthritis, 21 with systemic lupus erythematosus and 23 healthy individuals. Rheumatoid arthritis and lupus patients served as control groups since both are well-characterized autoimmune diseases with an important role for neutrophils and NETs in their disease symptoms. Within the blood collected we measured levels of anti-nucleosome, anti-citrullinated protein and anti-peptidylarginine deiminase 4 autoantibodies that all target NET components. Peptidylarginine deiminase 4 is an enzyme highly expressed in neutrophils that mediates histone citrullination and NET formation. Nucleosomes are present in NETs. We also assessed blood levels of NET components: cell-free DNA, NETs and neutrophil granule proteins.

What did you find?

Our most important finding is that blood concentrations of anti-peptidylarginine deiminase 4 autoantibodies were elevated in CF patients compared to healthy controls. The amount of this autoantibody related to the extent of CF lung disease. This autoantibody was also raised in the blood of rheumatoid arthritis patients similar to CF patients, while its circulating levels in lupus patients are not different from that of healthy subjects. We did not detect any differences in blood levels of anti-nucleosome or anti-citrullinated protein autoantibodies between CF patients and control individuals. No difference was observed in cell-free DNA or NET levels between CF patients and healthy subjects, either.

What does this mean and reasons for caution?

These results identified a new autoantibody, anti-peptidylarginine deiminase 4, that has elevated levels in CF and is linked to lung disease. Our data indicate that peptidylarginine deiminase 4 is targeted by the host immune system in CF. Although our results originate from a single CF patient cohort of limited size, they further strengthen that CF has an autoimmune component that has not been widely appreciated until recently.

What's next?

Future research will focus on expanding our observation described here to larger patient cohorts at multiple CF centres and on addressing whether anti-peptidylarginine deiminase 4 antibodies contribute to CF disease symptoms. Understanding what drives the inflammatory

process in CF airways will enable us to explore potential therapies to stop or stall this happening.

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