

Cystic Fibrosis Research News

Title:

Sputum trypsin-like protease activity relates to clinical outcome in cystic fibrosis.

Authors:

James A. Reihill¹, Kelly L. Moffitt¹, Lisa E.J. Douglas¹, J. Stuart Elborn², Andrew M. Jones³ & *S. Lorraine Martin¹.

Affiliations:

¹School of Pharmacy, ²Wellcome-Wolfson Institute for Experimental Medicine, Queen's University Belfast, Northern Ireland, BT9 7BL, UK. ³Wythenshawe Hospital, Manchester Adult Cystic Fibrosis Centre, South Moor Road, Manchester, M23 9LT, UK.

What was your research question?

The overactivation of a sodium ion channel (ENaC) by specific enzymes (trypsin-like proteases; TLPs) causes two of the main characteristics of cystic fibrosis (CF), dry airways and thickened mucus. In this study we wanted to determine whether TLP activity measured in CF sputum might have any relationship to lung function and ultimately patient outcomes.

Why is this important?

To date, research on proteases in CF has focused on an enzyme called neutrophil elastase (NE), which is an important marker of infection and inflammation. A number of researchers have highlighted an opportunity to regulate ENaC and possibly restore effective mucus clearance processes through inhibition of TLPs. However, despite the relationship of TLP activity to ENaC, resulting in airway dehydration and poor mucus clearance, there have been no studies to investigate levels of TLPs and whether any relationship to disease severity or disease progression exists.

What did you do?

We analysed a liquid sample (sol) prepared from CF sputum obtained from two separate populations of people with CF (29 and 33 adults in each population, respectively). Protease activities were determined by measuring the release of a fluorescent product or by a novel antibody-based detection method. Lung function was assessed by spirometry. Time in months until death or lung transplantation was obtained after collection of the sputum and used for an analysis of survival following sample procurement.

Cystic Fibrosis Research News

What did you find?

Results demonstrate that TLP activity was higher in individuals that had more severe lung disease and was also greater in individuals who did not survive beyond 5 years from the time of sample collection. Further statistical analysis demonstrated significantly reduced survival for individuals with high TLP activity. In contrast, neutrophil elastase displayed no significant associations with lung function or patient survival. The findings were similar across the two study populations.

What does this mean and reasons for caution?

Increased TLP activity may contribute to the impaired ion transport that is a key feature of CF airway cells. In addition to loss of CFTR function (due to CF mutations), overactive ENaC leads to dry, sticky mucus secretions that are difficult to clear and can lead to lung infections that are hard to treat. Sputum TLP activity may represent a novel non-invasive biomarker and/or therapeutic target for CF lung disease. This is important as the identification of biomarkers predictive of future outcome may aid our understanding of mechanisms of disease and may assist the assessment of new therapies.

What's next?

Detailed cell-based studies are ongoing, which may aid us in understanding more about the possible effects of high levels of airways TLP activity in CF. Future clinical studies investigating disease progression and outcomes may also help determine the usefulness of TLP activity as a potential biomarker and/or therapeutic target.

Original manuscript citation in PubMed

https://pubmed.ncbi.nlm.nih.gov/31932105-sputum-trypsin-like-protease-activity-relates-to-clinical-outcome-in-cystic-fibrosis/?from_single_result=Sputum+trypsin-like+protease+activity+relates+to+clinical+outcome+in+cystic+fibrosis.