European Cystic Fibrosis Society

Journal of Cystic Fibrosis
The Official Journal of the European Cystic Fibrosis Society

Cystic Fibrosis Research News

Title:

Bacterial Proteases and Haemostasis Dysregulation in the CF Lung

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What was your research question?

Bacteria which are associated with chronic lung infections in cystic fibrosis (CF) produce a number of molecules, including protein-degrading enzymes called proteases, which can reduce how our immune system reacts to infection. In this study we wanted to assess if these enzymes could also affect the process of blood clotting.

Why is this important?

Our lungs are constantly threatened by debris and infectious material present in our breath with both airways tissue and the fine vessels (capillaries), which supply blood to the lung, susceptible to damage. If bleeding occurs, a blood clot quickly forms due to our own (host) proteases creating a mesh onto which tiny blood cells (platelets) can bind. Blood in sputum is a common occurrence during an acute exacerbation in CF but typically resolves following antibiotic therapy. We therefore wondered if bacterial proteases have the potential to disrupt the process of blood clotting in the CF lung.

What did you do?

A number of CF-associated bacteria (*Pseudomonas aeruginosa and Burkholderia cepacia* complex spp.) were grown on mucin-coated plastic wells which enabled them to adhere and form a community (biofilm). Growth media was then collected and analysed for the presence of enzyme activities capable of degrading a critical host protein called fibrinogen. In the event of a bleed, fibrinogen is normally rapidly processed by a host protease (thrombin) to form the fibrin mesh onto which the clot forms. We examined whether the bacterial enzymes could prevent the formation of the fibrin mesh or the binding together (aggregation) of platelets; alteration of either could have the potential to disrupt clotting in the CF lung.

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What did you find?

Results demonstrate that key CF bacteria growing as biofilms on mucin (similar to the lung surface) produce a considerable amount of enzyme activity capable of degrading fibrinogen. Indeed, the degradation patterns observed were very different to that observed when fibrinogen is broken down to fibrin by thrombin. In the clotting experiments, the bacterial enzymes produced fragments of fibrinogen which had a greatly reduced or no ability to form the fibrin mesh (required to stabilise the clot). This could not be reversed by the addition of thrombin. In addition, we showed that the binding of platelets was also significantly affected.

What does this mean and reasons for caution?

Bleeding in the lungs is not very well understood, but is attributed to infection and inflammation-driven changes in the pulmonary system, including weakened bronchial arteries and abnormal new vessel formation (angiogenesis) which are susceptible to bleeds into the airway lumen during periods of acute infection. Our results show that CF-relevant bacterial proteases negatively impact fibrin mesh formation and platelet aggregation, two critical clotting processes, and suggest that these enzymes may potentially contribute to episodes of bleeding (haemoptysis) within the CF lung.

What's next?

We have shown that bacterial proteases may contribute to blood clotting dysregulation in CF airways, however further work is required to fully understand their contribution to massive bleeding events which are associated with a significant deterioration in lung function and a higher rate of mortality in 4.1% of CF patients.

Original manuscript citation in PubMed

https://www.ncbi.nlm.nih.gov/pubmed/?term=Bacterial+Proteases+and+Haemostasis+Dysregulation+in+the+CF+Lung

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