CHIEF SCIENTIST OFFICE

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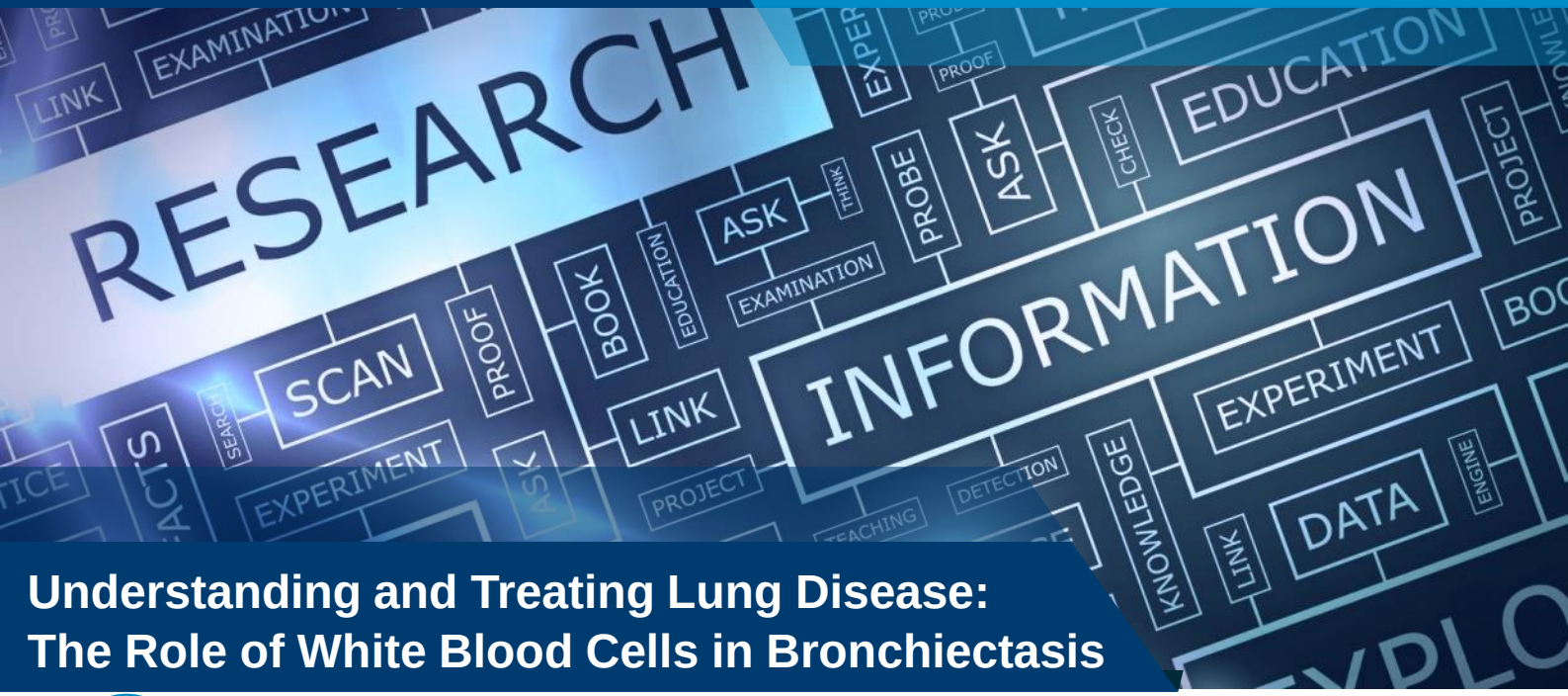
RESEARCH PROJECT BRIEFING



Understanding and Treating Lung Disease: The Role of White Blood Cells in Bronchiectasis

AIMS

1) To understand how neutrophils, a type of white blood cell, work in patients with bronchiectasis, a lung condition where the airways become damaged and widened, leading to mucus build-up and infections

2) To explore whether the metabolism of white blood cells changes in people with bronchiectasis

3) To investigate if common drug treatments could improve neutrophil function in people with bronchiectasis

KEY FINDINGS

1) We found that severe bronchiectasis increases the formation of neutrophil extracellular traps (NETs), where neutrophils "explode", causing significant tissue damage, instead of killing bacteria.

2) We found that a protein called resistin, which is known to affect the metabolism of cells and therefore their function, was increased in the airways of people with bronchiectasis.

3) Treatment of cells with resistin causes increased formation of neutrophil extracellular traps suggesting it was potentially causing changes in neutrophil behaviour in the lungs of people with bronchiectasis

4) We studied the metabolism of neutrophil cells from people with bronchiectasis and found that they are altered in severe bronchiectasis. Treatment of cells with resistin could induce similar changes to these cells.

WHAT DID THE STUDY INVOLVE?

1) We enrolled more than 400 patients into two cohort studies where we measured the levels of neutrophil extracellular traps and resistin in sputum (phlegm) samples and gathered extensive clinical information about the patients.
2) We isolated neutrophils (the most common type of white blood cell) from the blood of people with bronchiectasis and studied the metabolism of the cells.
3) In the laboratory we added resistin and other inflammatory mediators to the cells from bronchiectasis patients and healthy people to study how the metabolism of these cells were changed.
4) We tested whether drugs that affect metabolism such as AMPK activators or NRF2 activators changed the metabolism and function of these cells

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

Neutrophil extracellular traps (NETs) are a feature of severe bronchiectasis

We studied 450 people with bronchiectasis from across Europe. We first used a highly detailed technique for studying all the proteins in sputum (phlegm) samples from people with bronchiectasis. We compared patients with severe and mild disease based on their doctor's assessment and found 70 proteins that were different between the groups. These markers included resistin, a protein previously shown to affect the metabolism of cells. There was more resistin in people with severe bronchiectasis. We developed a method to measure NETs and found that high levels of NETs identified patients at higher risk of worsening the condition and becoming admitted to hospital.

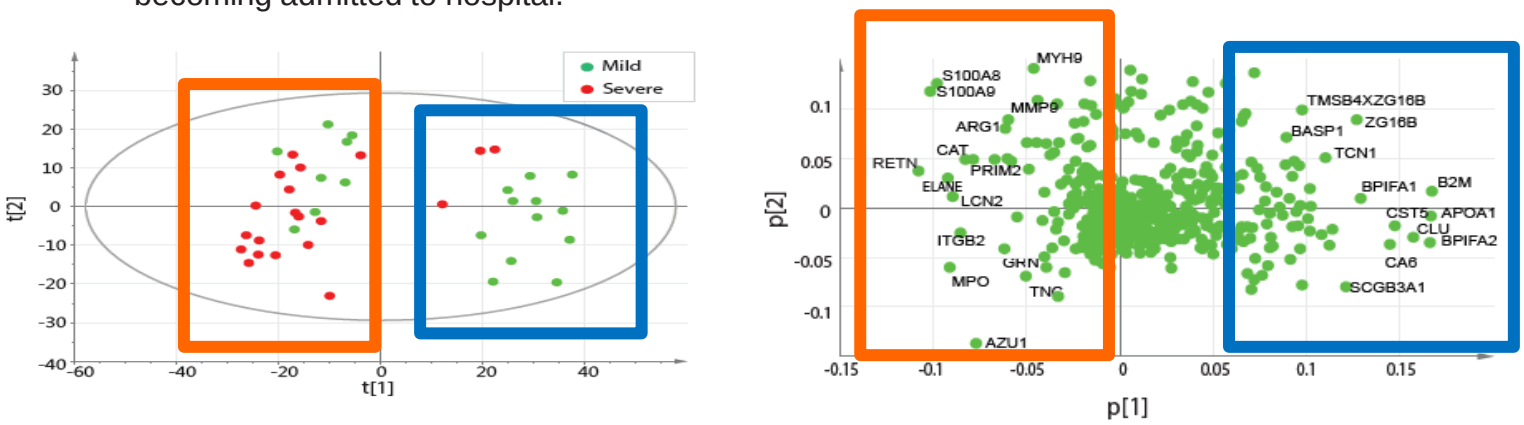
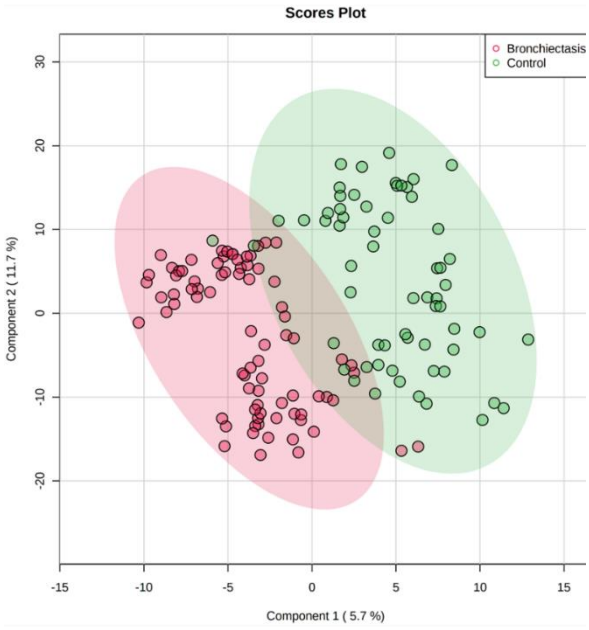


Image 1: proteomic study showing markers associated with severe bronchiectasis (orange squares) and mild bronchiectasis (blue squares). RETN=resistin

To test whether the metabolism of blood cells are altered in people with bronchiectasis

Based on the high levels of resistin and other proteins which affect the metabolism of cells we hypothesised that the metabolism of cells would be altered in people with bronchiectasis. We obtained pure neutrophils from the blood of these patients and from people without lung disease as controls. We added resistin to these cells to study what effect resistin had on neutrophils. Finally, we added drugs which block or enhance metabolic function such as AMPK inhibitors and activators, to test whether changing the metabolism of cells could improve their function.

Image 2: neutrophil metabolomics

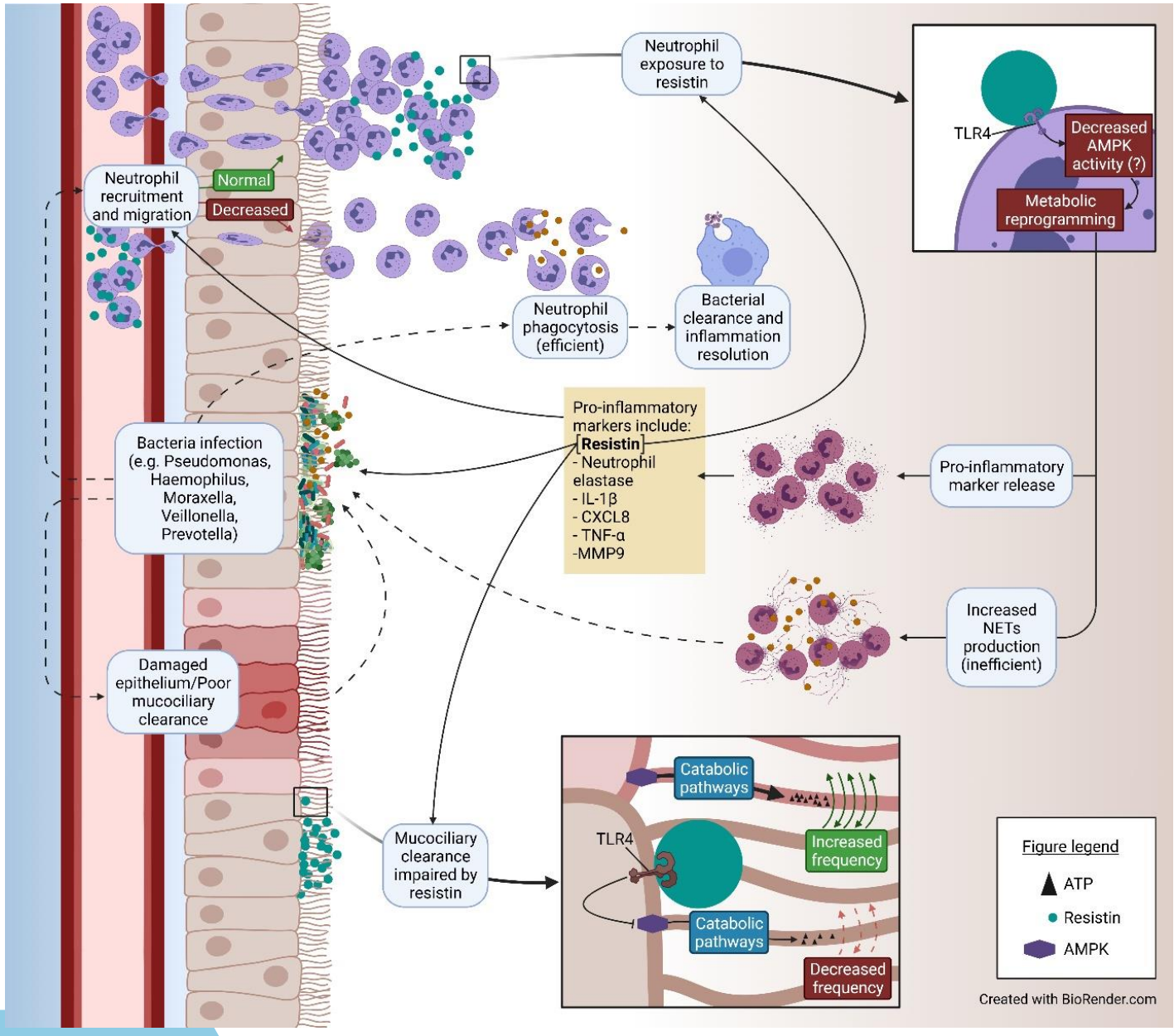


We found that the metabolism of neutrophils in bronchiectasis patients was different to controls (image 2) and that changes in metabolism were also seen when neutrophils were exposed to resistin, similar to those seen when cells were exposed to bacteria.

Adding resistin to neutrophils from healthy people without bronchiectasis led to an increase the formation of NETs.

We also found that resistin and other proteins released during inflammation affected the clearance of mucus from the lungs by slowing down cilia, small hairlike structures found in the lungs which are critical to defending the lungs against infection. This may lead to more infections, which we observed in people with high levels of resistin.

The image below summarises the findings of our study, showing how in the diseased state we see a reduction in clearance of bacteria by neutrophils, increased inflammation and increased NETs, and a failure to remove bacteria and mucus from the lungs. Resistin and NETs are shown to play an important role in these processes.



WHAT IMPACT COULD THE FINDINGS HAVE?

- We believe these findings could lead to the development of new treatments for bronchiectasis. The results have been important in the development of drugs called Dipeptidyl peptidase-1 inhibitors which are now in clinical trials to reduce neutrophil-related inflammation in bronchiectasis patients.

- We have identified NETs as a key target for treating bronchiectasis. This has directly led to the development of a new project called AIR-NET (Anti-inflammatory repurposing Network) which was funded by a charity called Lifearc to develop new therapies against NETs.

- After some experiments using a specific type of antibody to target *pseudomonas bacteria*, we have launched a clinical trial called “GREAT-2” which is testing whether we can enhance the function of neutrophils to kill *Pseudomonas aeruginosa* by boosting healthy neutrophil function.

HOW WILL THE RESULTS BE SHARED?

This project has led to a number of publications in peer reviewed scientific journals eg PMID: 33609487, PMID: 35436182, PMID: 35050830 among others. Results have been disseminated to the professional community through presentations at the World Bronchiectasis Conference and European Respiratory Society conferences.
Results have been disseminated to patient groups through the annual European Lung Foundation patient conference which I have organised https://europeanlung.org/en/get-involved/events/bronchiectasis-patient-conference-2023/ . Further publications are planned.

CONCLUSION

- Neutrophil extracellular traps and associated proteins such as resistin are linked to the severity of bronchiectasis and are identified as a key therapeutic target

- Neutrophils in bronchiectasis are “metabolically reprogrammed” leading to altered function

RESEARCH TEAM & CONTACT

Professor James D Chalmers

jchalmers@dundee.ac.uk

Address. Ninewells Hospital and Medical School, Dundee, DD1 9SY

01382383642