CAF/22/10 – Regulation of Lung Inflammation and Infection by Neutrophil Subsets in Bronchiectasis.

Bronchiectasis is a lung disease affecting millions of people globally. In bronchiectasis, the lungs are damaged and struggle to clear infections. This leads to a vicious cycle where cells of the immune system called neutrophils over-react and cause inflammation that damages the lungs. Patients suffer a persistent cough, breathlessness and are more susceptible to chest infections.

Patients receive repeated courses of antibiotics but this causes side effects and antibiotic resistance. There is an urgent need to find alternative treatments.

Studying the immune system could hold the key to finding treatments to halt this vicious cycle. Neutrophils have historically been believed to be a homogeneous population of cells but recent research has shown there to be different type of cells (called subsets), some of which promote more inflammation and some of which try to control the inflammation. Changes in the subsets of neutrophils in the body have been observed in chronic diseases such as asthma and acute conditions such as COVID-19 and contribute to disease. Whether there is a change in circulating subsets in bronchiectasis is not known.

There are currently no licensed therapies targeting the inflammatory aspect of bronchiectasis but a trial has shown that taking drugs called DPP-1 inhibitors reduces inflammation in the lungs caused by neutrophils, and leads to a reduced need for antibiotics. These are a promising new therapy but do have some side effects, meaning we need to target them towards people who are most likely to benefit.

In this study, we hypothesise that circulating neutrophil subsets are altered in patients with bronchiectasis. We will perform an observational study recruiting 30 people with severe bronchiectasis, 30 people with mild bronchiectasis, and 30 people without bronchiectasis. We will ask them to provide blood samples and samples from the lungs. We will test for neutrophil subsets by staining the neutrophils for markers on the surface of the cells that indicate their function. We will also test levels of inflammation, how well neutrophils work to fight bacteria, and what types of bacteria are growing in the lungs. We specifically hypothesise that severe patients will have increased expression of a subset marked by CD177 and proteinase-3. This subset accounts for 45-65% of healthy peoples' neutrophils but this proportion is increased in inflammatory conditions. We further believe that bronchiectasis patients will have reduced levels of OLFM4+ neutrophils, which have an anti-inflammatory function.

Our initial studies show that patients with more severe bronchiectasis have increased levels proteinase-3 and reduced levels of OLFM-4, meaning they have more pro-inflammation signals and a reduction in anti-inflammatory signals. OLFM-4 is a natural inhibitor of DPP-1 and proteinase-3 is activated by DPP-1. Therefore, measuring neutrophil subsets may identify patients more likely to benefit from DPP-1 inhibition.

Our initial studies also showed that adding OLFM-4 to lung cells could help them clear infections more easily. Other studies have shown that OLFM-4 may also reduce inflammation, and may help prevent infection with some viruses and bacteria. We want to investigate this further to see if we can identify other targets for future bronchiectasis treatments. Using lung cells in the laboratory we will investigate how inflammation caused by different neutrophil subsets affects the lungs natural defences.

Finally, we have recently completed a large trial of DPP-1 inhibition in patients with bronchiectasis. We will use samples from this trial to test whether biomarkers developed through our experiments predict which patients will respond best to treatment.

This research will increase our understand of bronchiectasis and may open the door for new diagnostic tests and treatments for this common and devastating disease.