The modulation of macrophage apoptosis during Streptococcus pneumoniae infection by HIV-1

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Investigators

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What is this study about?

We are investigating the molecular basis for the increased risk of developing invasive pneumococcal disease (IPD) among HIV seropositive individuals. By understanding this better we hope to develop a new approach to preventing this disease in those most at risk. To do this we would like to use cells from the lungs and blood of HIV seropositive patients that attend clinics in the South Yorkshire HIV Network.

The clinical problem

The definition of IPD includes the clinical syndromes of pneumococcal meningitis, bacteraemia and pneumonia. Data from cohorts of HIV seropositive individuals consistently show that the incidence of IPD among those on HAART is about 70/100,000, even with the use of pneumococcal vaccination. While lower than the incidence in those with HIV and not on HAART, it remains about 10 fold the incidence in the general population. The reason for this is not known.

IPD is a serious problem as it often requires intensive care management and is associated with a mortality rate of about 30%. In resource poor settings, principally Sub-Saharan Africa, rates of IPD in HIV are of the order of 4500/100,000.

The importance of innate immunity for defence against pneumococcal infection

In the context of pneumonia, the most common form of severe pneumococcal infection, a key immune cell is the alveolar macrophage. Pneumococci are carried in the nasopharynx by up to a quarter of the population. From time to time, pneumococci may be aspirated in to the lung alveolae where they are phagocytosed and killed by the alveolar macrophage.

A critical feature of the cell's response is to undergo cell death by apoptosis when the burden of ingested bacteria exceeds the capacity of the macrophage's killing machinery. By undergoing apoptosis, the macrophage both removes viable pneumococci from the alveolus and ceases its own (damaging) pro-inflammatory activity. A significant pneumococcal infection is avoided.

Macrophages, pneumococcal infection, HIV and apoptosis.

This critical apoptotic response appears to be prevented by HIV infection. Many research groups have found that HIV infected macrophages are resistant to apoptosis in general. In our laboratory in the University of Sheffield, we have demonstrated that HIV infection is associated with a reduced capacity for macrophages to undergo apoptosis in response to pneumococcal infection. We have also observed that this is associated with pneumococcal survival.

These are exciting findings. However, these experiments have used cells from healthy volunteers' blood which have then been infected with or exposed to HIV in the laboratory. To be sure of the validity of the findings from this somewhat artificial model the experiments need to be replicated in actual alveolar macrophages from the lungs of people with HIV infection.

What will my patients be asked to volunteer for?

Volunteers will be asked to have a bronchoscopy with bronchoalveolar lavage (BAL) and / or donate up to 200mL of blood.

Each volunteer will have a registration and screening appointment in either the infectious diseases or the GUM departments' HIV clinics at the RHH. Those that are eligible will then have spirometry and a date fixed for the BAL. Most patients will be eligible -the key criterion is that they have healthy lungs.

The BAL will be performed by consultant respiratory physicians in the endoscopy suite of the Royal Hallamshire hospital. It is performed as an outpatient. The whole appointment takes 2 to 3 hours, the procedure itself about 20 minutes. As sedation may be used volunteers will need to come with a friend or relative to take them home.

A separate appointment will be made for the blood donation, again in the department of infectious diseases or GUM at the RHH.

The blood and BAL samples will given a study number but otherwise anonymised, and then processed to isolate the macrophages and perform pneumococcal challenge experiments in the University of Sheffield medical school research laboratories. All the work will be done by Dr Collini.

When will the study be open?

The study will start recruiting in July 2012 and complete by July 2013. We aim to recruit 20 HIV seropositive individuals and 10 HIV seronegative 'matched control' subjects.

How do I and my patients find out more?

Please read the other information on this website or contact Dr Paul Collini directly by email: p.collini@sheffield.ac.uk