Uncovering new strategies to reduce TB susceptibility in HIV-infected individuals

Dr Henry Mwandumba is a Clinician Scientist at the Malawi-Liverpool-Wellcome Trust Clinical Research Programme, and Consultant Physician at Queen Elizabeth Central Hospital, Blantyre, Malawi in Southeast Africa. He leads a group of researchers with two main goals; to understand how humans develop immunity to TB in the lungs, and why the risk of TB is greater during HIV infection.

**Infectious Diseases**

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**Tuberculosis (TB), caused by the bacterium Mycobacterium tuberculosis, is a serious cause of disease and mortality worldwide, especially in developing countries. Co-infection with the human immunodeficiency virus (HIV) aggravates this situation, and puts intense pressure on national healthcare services in sub-Saharan Africa, where up to 80% of TB patients are HIV-infected, and where TB is now the leading cause of death in HIV-infected individuals.**

Dr Mwandumba believes that a better understanding of the mechanisms underlying resistance and susceptibility to TB is essential to reduce the incidence of HIV-associated TB worldwide. HIV is still 5-10 times more prevalent in HIV-infected adults on ART than in HIV-uninfected individuals. The risk of developing active TB is increased in HIV-infected individuals, even before significant CD4+ T cell depletion occurs. These facts indicate that CD4+ T cells are not the only determinant of TB risk, and that increasing their numbers alone is not enough to maintain full protection against TB.

**ANTIRETROVIRAL THERAPY IS NOT ENOUGH**

Antiretroviral therapy (ART) is the standard treatment for HIV, and it usually involves a combination of drugs that work together to slow down viral replication. CD4+ T cells are a subset of white blood cells that are targeted by HIV. Successful ART therapy leads to an increase in this cell population, thus boosting the body’s immune defences. While ART has significantly reduced the rates of HIV and HIV-associated TB worldwide, TB is still 5-10 times more prevalent in HIV-infected adults on ART than in HIV-uninfected individuals. The risk of developing active TB is increased in HIV-infected individuals, even before significant CD4+ T cell depletion occurs. These facts indicate that CD4+ T cells are not the only determinant of TB risk, and that increasing their numbers alone is not enough to maintain full protection against TB.

The increased risk of TB in HIV sufferers also suggests that HIV infection alters the immune environment in the lung, since TB most often infects the lung. The important question of how HIV impacts lung immunity and susceptibility to TB has dominated Dr Mwandumba’s research for over a decade.

**ALVEOLAR MACROPHAGES – THE BIG EATERS**

Alveolar macrophages (AM) are highly differentiated immune cells that occupy the interface of the external environment and the alveolar tissue of the lungs. They are often the first professional phagocytes encountered during TB infection, and like all phagocytes, they are capable of phagocytosing (eating), internalising and delivering pathogen-derived material to acidic, pathogen-degrading lysosomes inside the cell.

The endosomal-lysosomal system is an extremely effective barrier against bacterial infection, comprising three major activities: phagocytosis, endocytosis, and endosomal acidification. During phagocytosis, AM engulf bacteria, which then become enclosed into intracellular organelles called phagosomes. During endocytosis, phagosomes are trafficked through the AM in compartments called endosomes, eventually fusing with lysosomes, which are specialised organelles containing degradative enzymes. Lysosomal enzymes function under acidic conditions, and progressive endosomal acidification is therefore a prerequisite for a fully functioning endosomal-lysosomal system.

**ANSWERS FROM HUMAN LUNGS**

As part of a long-standing research programme at Queen Elizabeth Central Hospital, Dr Mwandumba’s group has access to lung samples from HIV-infected, TB-infected, co-infected, and healthy human volunteers. The group employs a combination of microscopy, flow cytometry (cell staining and counting), and molecular biology techniques to visualise immune cells in these lung specimens, to assess their function, and to detect infection-induced changes in their behaviour.

**TB INFECTION ARRESTS AM PHAGOSOMES**

It is well documented that HIV and TB can synergise and provoke immune responses that exacerbate both infections. However, despite the importance of AM in lung immunity, very few researchers have investigated their physiology in TB patients. Dr Mwandumba’s research addressed this deficit in a study examining the properties of human AM obtained from the lungs of patients infected with TB.

The study revealed that the ability of AM to phagocytose synthetic beads was not affected by HIV or TB infection. Furthermore,
I believe that public health interventions, informed by relevant data on mechanisms underlying increased susceptibility to TB, are required for effective TB control.