Scientists discover how tuberculosis hijacks the immune system

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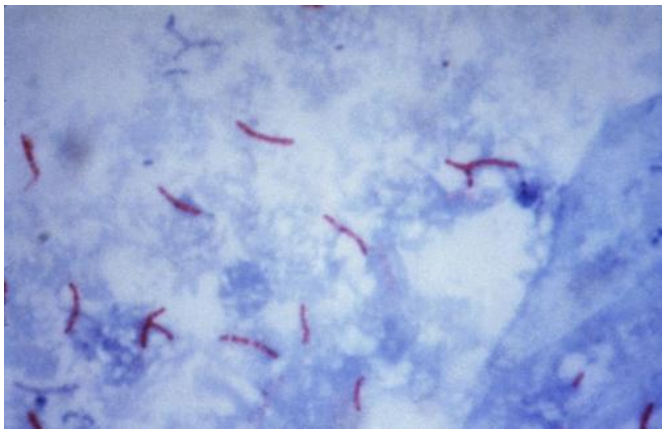

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

Scientists have unlocked a key element in understanding how human lungs fight tuberculosis (TB). They hope their research findings, which were published today in the international peer reviewed journal *Immunity*, will help pave the way towards new treatment approaches for TB, particularly in an era of increasing antibiotic resistance to TB.

Multi drug resistant TB is a global problem. These strains are resistant to several or most of the antibiotics used to treat TB. The need to find new strategies for treating TB, beyond antibiotics, is therefore critical and urgent.

Scientists at Trinity College Dublin and St James's Hospital in Ireland, working in a team with the University of Cambridge and University of Seattle, have identified a way that TB hijacks our immune cells in the early stages of infection to allow it to establish an infection in the lung.

Tuberculosis is the world's number one infectious killer, but half of infected persons clear the invading TB bacteria (known as mycobacteria) after inhaling it into their lungs. To date, it has not been understood how the immune system in the lungs manages to do this.

The lung contains a population of specialised immune cells, known as alveolar macrophages, which are the first responders to bacterial infections. These alveolar macrophages patrol the lung engulfing and destroying any bacteria they encounter along the way.

Using transparent zebra fish, the University of Cambridge and University of Seattle researchers tracked the mycobacteria in real time and identified which cells they infected at different stages of the disease. They found that the more virulent strains of mycobacteria are able to hijack the macrophage immune cells in the lung causing them to produce a protein that attracts white blood cells from the circulation. These white blood cells fuse with the macrophages and in turn become infected.

The Trinity team of Dr Seónadh O'Leary, Senior Research Fellow, Professor Joseph Keane, Professor in Medicine at Trinity and Consultant Respiratory Physician at St James's Hospital, and Dr Mary O'Sullivan, Associate Research Lecturer, used donated lung macrophage samples from patients in St James's Hospital to study the response of the human immune system to TB in the early stages of infection. They found that human alveolar macrophages behave similarly to zebrafish macrophages producing the same protein that attracts white blood cells to the lung. Unlike the resident alveolar macrophages these white blood cells lack the ability to curb the growth of mycobacteria which results in uncontrolled bacterial growth and inflammation and in the spread of the

infection.

Dr Seónadh O' Leary said: "We are fascinated how TB bacteria virulence factors can corrupt this human lung immune cell which is ordinarily exceptionally good at clearing infection. It's very exciting to work with our Cambridge colleagues on this research which improves our understanding of how TB infection compromises immunity. We are in a unique position to address the important challenges for TB treatment as we work with the human lung model. This allows us to continue in our research to design novel ways to support the effective lung cell and prevent infections in exposed people."

The Trinity/St. James's team is funded by the Health Research Board and the Royal City of Dublin Hospital Trust, and are now hoping to identify drugs that will enable these immune cells to stop the infection in its tracks—by killing the mycobacteria before they attract white blood cells to the lung.

Mairead O Driscoll, Interim Chief Executive at the Health Research Board congratulated the team: "Antidrug resistant TB is a global problem. We're delighted to be able to facilitate international collaboration to tackle this challenge. These findings represent a significant breakthrough in our understanding of how the bacteria avoids our immune system."

"Ireland is lucky to have such brilliant researchers, who are genuine world leaders in their fields. The Health Research Board is determined to continue to develop Ireland's health research capacity, so that we have the people, the facilities, and the support structures to produce more results like this."

Provided by Trinity College Dublin