

How lung energetics helps immunity battle TB

New advance explains how cigarette smoking causes lung immune cell exhaustion, leading to tuberculosis.

The tuberculosis immunology research group at Trinity College Dublin and St James's Hospital Dublin have discovered how crucial immune cells in the lung, called macrophages, affect a change in metabolism, to respond to the bacteria that causes tuberculosis (*Mycobacterium tuberculosis*). In 2017, 321 TB cases were notified in Ireland. This included 2 multi-drug resistant cases and 3 extensively drug resistant cases –which are very difficult to treat. Researchers at St James's are trying to design ways to support the human immune system to prevent this infectious disease arising in marginalised members of society. Many of the TB patients attending St James's Hospital are smokers, although little is known how smoking causes tuberculosis susceptibility.

Now the team of scientists at St James's Hospital have shown that immune cells in the lungs, called macrophages, can turn on helpful pathways of energy production after infection with the tuberculosis bacteria. Using lung cells, kindly donated by volunteers who attend St James's Hospital, they have now demonstrated that these energetic pathways can be recruited in the lung after bacterial infection. This can effectively control the bacteria after it has been inhaled from an infectious person with TB. This ability to switch metabolism appears to be a central process in host defence. This is because when they looked at lung macrophages taken from volunteers who smoke, they noticed that these smokers cells had markedly reduced metabolic activity - and had no metabolic reserves to respond to the infection. This is a first description of smoker's lung cells as an **exhausted macrophage**, and the investigators are now looking at ways to restore these helpful pathways to fortify immunity in smokers – to prevent infectious diseases.

Commenting on the significance of the finding, Dr Laura Gleeson, who is a recipient of the HRB health professional fellowship, said *“because volunteers attend St James's and partake in medical research, we were able to tightly compare smokers to non-smokers - to understand better how lung immunity against tuberculosis works. Our new description of macrophage exhaustion in the lung might also lead to treatments that could be applied to other TB susceptible groups. These include persons who suffer from immunosuppressive conditions such as diabetes, HIV, and those taking immunosuppressive drugs”*. Dr Fred Sheedy, co-senior author of the paper said, *“by better understanding the immunological processes which are damaged in the lungs of the smoker, we might also uncover ways to support the health of people who smoke to avoid not just infections but also lung cancer”*.

Professor Joseph Keane, who is a recipient of the HRB clinician scientist award, is co-senior author on this paper. This research was funded by the Health Research Board, the Royal City

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