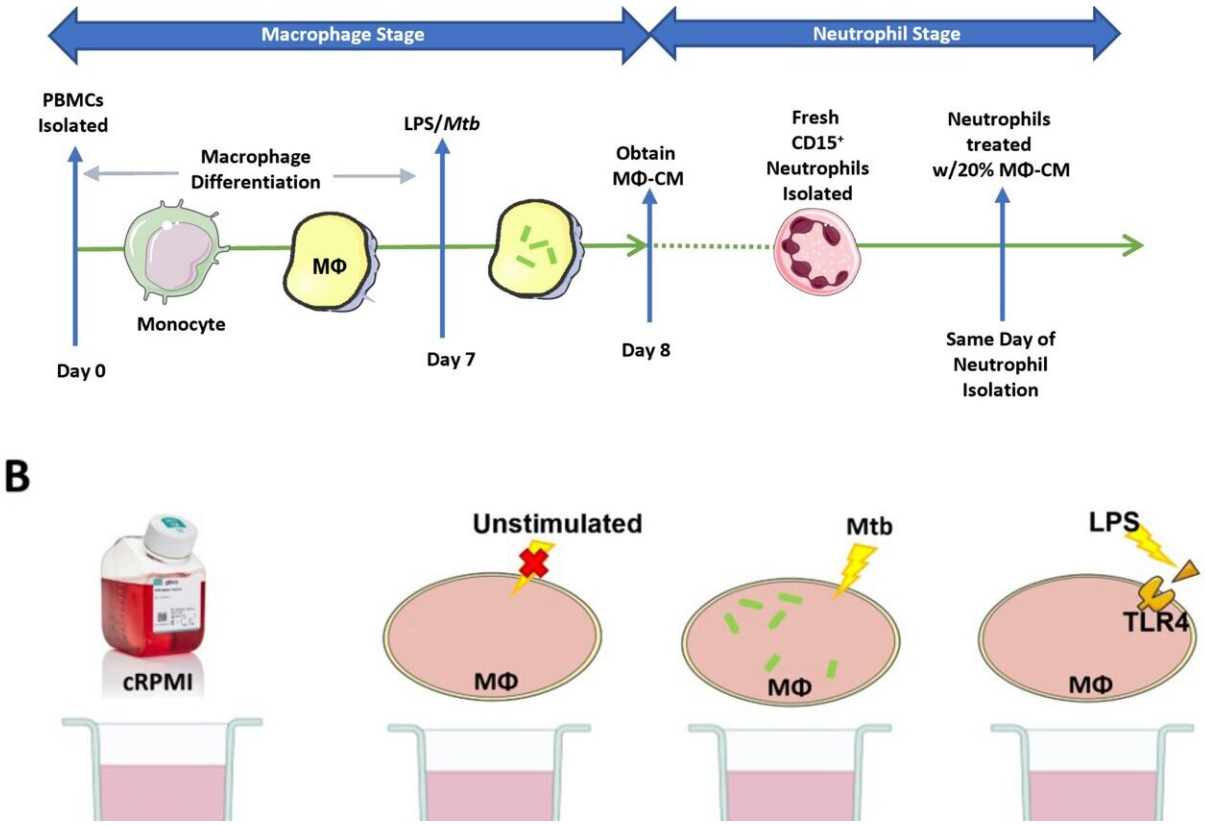
Research uncovers new reasons to target neutrophils for tuberculosis therapy

April 16 2024



Methods Summary. (A) Macrophage Stage and Neutrophil Stage. (B) All treatments with MΦ-CM consisted of freshly isolated neutrophils being exposed to 20% cRPMI, 20% MΦ-CM from unstimulated hMDMs, 20% MΦ-CM from Mtb-stimulated hMDMs, and 20% MΦ-CM from LPS-stimulated hMDMs. Credit: *International Journal of Molecular Sciences* (2024). DOI: 10.3390/ijms25052898

Tuberculosis is the biggest infectious killer in the world, causing 1.2 million deaths every year. In common with other pneumonia types, tuberculosis can destroy the human lung as a result of excessive inflammation.

One of the greatest drivers of this excessive inflammation is an immune cell called the neutrophil, which paradoxically plays an important protective role during early infection. However, like a double-edged sword, overactive neutrophils can cause lung tissue damage in established tuberculosis disease. Researchers wanted to know more about how tuberculosis infection drives this damage.

Using cell models of infection, the researchers from the Trinity team at St James's Hospital examined the cross-talk between two lung immune cells: the macrophage and the neutrophil. These cells contrive to cause lung disease in the setting of tuberculosis.

The group found that macrophages infected with Mycobacterium tuberculosis, the bacteria that causes tuberculosis, could directly activate neutrophils, heighten their metabolism, and lead to the production of Neutrophil Extracellular Traps (or NETs). NETs are known to drive type 1 interferons, the proteins that are harbingers of severe tuberculosis disease. These events also detain the damaging neutrophil cells in the lung where further insult can occur.

The paper, "Human macrophages activate bystander neutrophils' metabolism and effector functions when challenged with mycobacterium tuberculosis," is published in the *International Journal of Molecular Sciences*.

By dissecting out these pathways of human disease, the group has improved our understanding of how we might target inflammatory neutrophils in lung disease. Simple measures like administering steroids

to tuberculosis patients might diminish destructive neutrophil activity, and spare the lung.

This work provides scientific plausibility for using anti-neutrophil directed therapies in tuberculosis treatment alongside antibiotics. As the rate of antibiotic resistant tuberculosis infections are constantly increasing, finding alternative ways to treat patients is now vitally important.

Ph.D. student Dearbhla Murphy, lead author of the paper said, "We're really excited about this work as it shows the importance of investigating how macrophages and neutrophils interact and the significance of this interaction during tuberculosis infection. Studying how neutrophils are influenced by other cells can help us identify druggable targets to help develop new therapies for tuberculosis. This is especially important as the number of antibiotic-resistant tuberculosis cases are rising every year and novel therapies are desperately needed to overcome this."

Professor Joseph Keane, Clinical Medicine, Trinity College Dublin and St James's Hospital, said, "Targeting the neutrophil is one of the hottest topics in tuberculosis research. This mechanistic research encourages the development of therapies that will limit lung damage in this important infection."

More information: Dearbhla M. Murphy et al, Human Macrophages Activate Bystander Neutrophils' Metabolism and Effector Functions When Challenged with Mycobacterium tuberculosis, *International Journal of Molecular Sciences* (2024). DOI: 10.3390/ijms25052898

Provided by Trinity College Dublin