Tuberculosis bacterium may undermine immune regulation to drive disease progression

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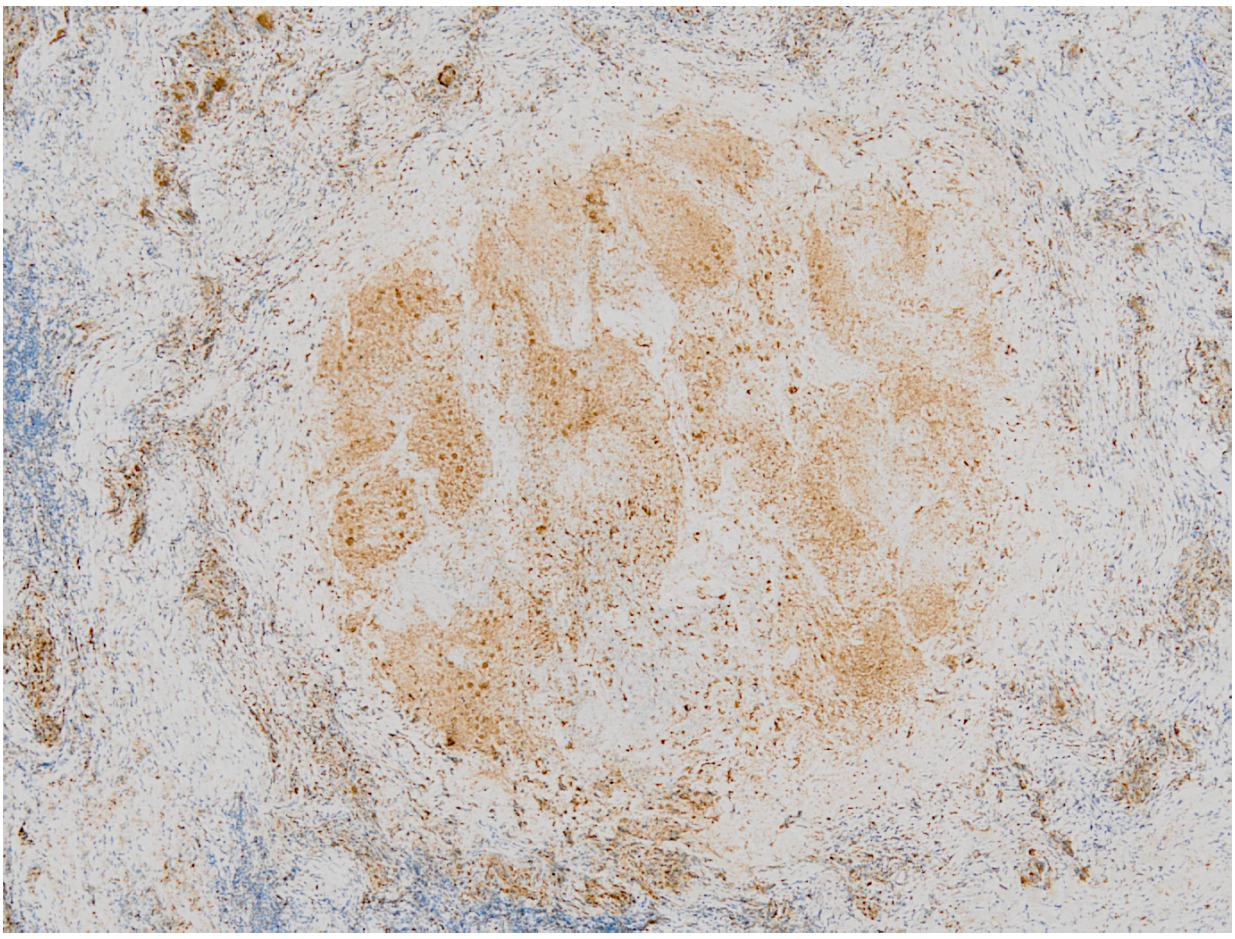

The bacterium that causes tuberculosis -- *Mycobacterium tuberculosis* (Mtb) -- may disrupt human immune system regulation processes to promote destruction of lung tissue, according to new research published in *PLOS Pathogens*. Credit: Brace PT, et al. (2017)

Mycobacterium tuberculosis (Mtb)—may disrupt human immune system regulation processes to promote destruction of lung tissue, according to new research published in *PLOS Pathogens*.

Previous research has explored how Mtb evades immune system attack, but less is known about its strategies for manipulating the immune system to drive pathogenesis. Patience Brace of the University of Southampton, U.K., and colleagues hypothesized that Mtb targets immune system pathways that normally prevent overreaction to infection.

To test this idea, the research team studied the molecular effects of Mtb on isolated human white blood cells—immune cells that help destroy unwanted invaders or unhealthy human cells. They found that Mtb inhibits an important signaling pathway known as PI3K/AKT/mTORC1, resulting in greater production of a protein called matrix metalloproteinase-1 (MMP-1) by white blood cells.

MMP-1 normally helps to remodel lung matrix, but it can also harm human tissue in excess. The PI3K/AKT/mTORC1 pathway usually keeps too much of it from being made, but in tuberculosis patients MMP-1 is known to attack and destroy lung tissue, making patients highly infectious.

To test whether Mtb suppresses the PI3K/AKT/mTORC1 pathway in humans, the scientists examined expression in white blood cells within infected lung tissue of tuberculosis patients. They found that a gene required for this pathway was not expressed in these cells, suggesting that Mtb may have suppressed the pathway in these patients, potentially increasing MMP-1 production.

In isolated white blood cells, Mtb also appeared to increase production of MMP-1 by disrupting a second signaling pathway known as the MAP kinase-interacting kinase (MNK) pathway. The link between the MNK pathway and MMP-1 production was previously unknown.

Based on their findings, the authors caution that new and existing drugs for tuberculosis should not inadvertently suppress the pathways explored in this study. Doing so could promote the spread of tuberculosis, which already kills more people worldwide than any other infectious disease.

"Tuberculosis has co-evolved with humans to become an ultimate pathogen, and we identify a mechanism whereby the bacteria disables the 'brakes' of the immune system to cause lung destruction and spread," says Brace.

More information: Brace PT, Tezera LB, Bielecka MK, Mellows T, Garay D, Tian S, et al. (2017) Mycobacterium tuberculosis subverts negative regulatory pathways in human macrophages to drive immunopathology. *PLoS Pathog* 13(6): e1006367. doi.org/10.1371/journal.ppat.1006367

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