Newly-discovered TB blood signal provides early warning for at-risk patients

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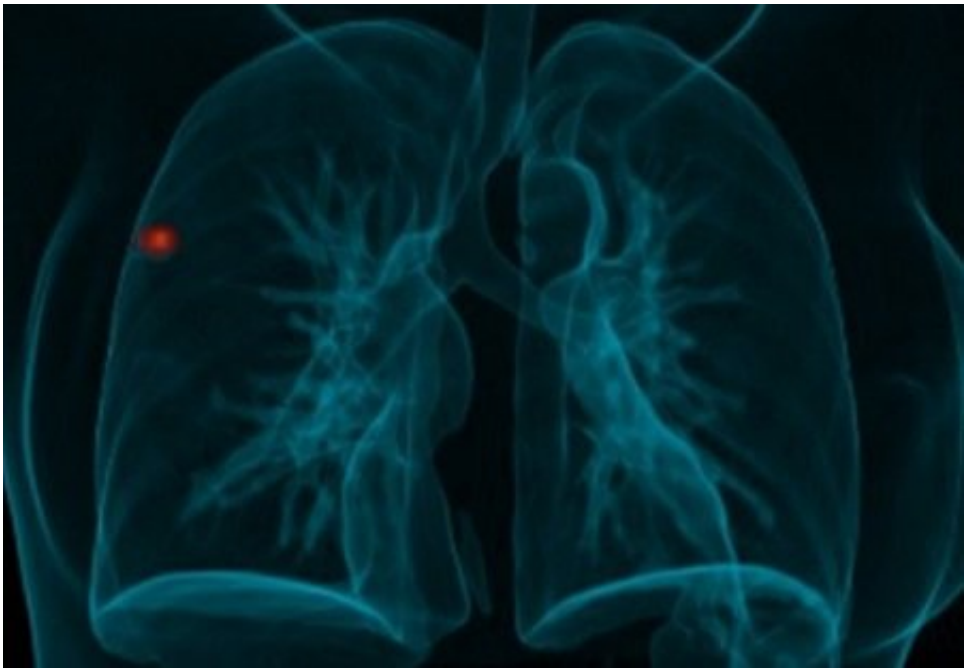

Credit: Hanif Esmail

Tuberculosis can be detected in people with HIV infection via a unique blood signal before symptoms appear, according to a new study by researchers from the Crick, Imperial College London and the University of Cape Town.

By providing new insights into how the body responds during the early stages of the disease, the findings could enable researchers to develop

tests to predict and prevent the worsening of symptoms in the most vulnerable patients.

Tuberculosis (TB) is typically classified as being either 'latent' or 'active.' Latent TB occurs when a person has been infected with the bacteria, but their immune system manages to control any further spread. They may develop active TB at a later stage, at which point the disease's symptoms will become apparent.

However, the study, published in *Proceedings of the National Academy of Sciences*, offers new evidence of a more nuanced transition from latent to active TB.

This is particularly significant for HIV-infected patients, who are 26 to 31 times more likely to develop active TB.

"We now know that TB can be detectable in the early stages of disease by transcript signals in blood, even in those with HIV co-infection," says the paper's first author Dr. Hanif Esmail, who worked on the project during his Ph.D. at the Crick and Imperial College London and is now based at Oxford University. "This gives hope that a test to identify people in the earliest stages of disease (before they develop symptoms or are picked up by current available tests) might be possible."

Senior author Professor Robert Wilkinson, Group Leader at the Crick and Professor in Infectious Diseases at Imperial, says: "This work reflects a significant increase in understanding that has arisen from longstanding collaboration with colleagues at the National Institutes of Health, the Francis Crick Institute—especially Professor Anne O'Garra—and the University of Cape Town.

"On hearing of our findings, researchers at the latter were able to re-examine their own data and confirmed our finding in a different

population. This increases hope that a test to predict those at greatest risk of progression of tuberculosis can indeed be derived."

In a previous investigation, the research team used high-resolution scans to reveal TB-related lung damage in ten out of 35 HIV-1-infected patients, who had no other symptoms. These patients were also found to be significantly more likely to develop active TB at a later date.

In this study, the team built on these findings by using an approach known as 'transcriptomics' to investigate which parts of active TB could be found in the blood of patients who were ostensibly symptomless.

One way the body reacts to changes and threats is to switch genes on and off, in order to allow them to adapt. In patients affected by TB, this happens with several different sets of genes.

'Transcriptomics' is where researchers use gene transcripts—which act as records of which genes are being switched, or "read—to put together a picture of what the body does to fight off a particular disease. The transcriptomic work was done in Professor Anne O'Garra's lab at the Crick, using patient samples recruited by Hanif and Robert.

Professor Anne O'Garra, Group Leader at the Crick and Chair in Infection Immunology at Imperial, says: "This is a very exciting new progression on the use of blood transcriptomics to detect early stages of TB in patients coinfected with HIV, following on from our original study published in *Nature* in 2010 where we demonstrated a TB signature in full blown TB. The detection of early disease in patients who do not have symptoms will guide early drug treatment and will help prevent further transmission."

In this study, researchers were able to take snapshots of which genes were being read in unwell people with active TB, subclinical TB (only

detectable through high-resolution scans) and latent TB. By comparing them, the team found that certain genes were switched on during the earliest subclinical stages of the disease. Significantly, this TB "signal" was detectable in the blood of a separate group of HIV uninfected people up to a year before they developed symptoms of the disease.

On the limitations of the research, Hanif says: "This was a small study of only 50 patients (10 of which had subclinical TB, 25 latent TB and 15 active TB). Larger studies will be needed for validation of findings. We have almost completed recruitment of a much larger study along similar lines which we hope will confirm and take forward these findings."

More information: Hanif Esmail et al. Complement pathway gene activation and rising circulating immune complexes characterize early disease in HIV-associated tuberculosis, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1711853115

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