Two distinct tuberculosis subtypes identified, with implications for personalized therapy

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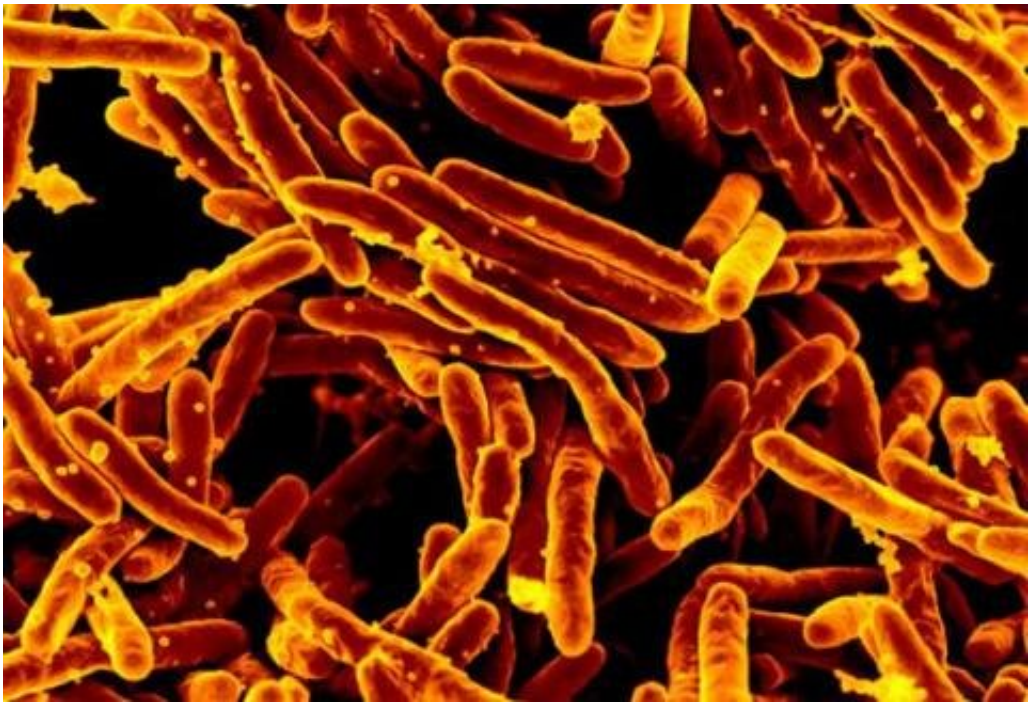

Scanning electron micrograph of Mycobacterium tuberculosis bacteria, which cause tuberculosis. Credit: NIAID

A recent study published by researchers at Baylor College of Medicine and Texas Children's Hospital, in collaboration with the German Center for Infection Research, identified two main subtypes or endotypes of tuberculosis according to the person's immune response to the infection. They found that one subtype had a better prognosis for curing tuberculosis than the other. Their findings, published in the *European*

Respiratory Journal, could improve personalized treatment options for the disease in the future.

"We conducted this research under the assumption that tuberculosis is not a uniform disease, that there are many pathways by which a person could develop the condition and that the outcome depends on the immune response produced by the infected person," said Dr. Andrew DiNardo, assistant professor of medicine-infectious diseases at Baylor and Texas Children's.

For people who contract tuberculosis, the course of the disease can vary significantly. Most people do not become ill after infection with Mycobacterium tuberculosis, the bacterium that causes the disease. However, people can develop chronic pneumonia and some also have disease in the lymph nodes, bones or the central nervous system. Some TB patients have suppressed and exhausted immune responses, while others have an overacting response that makes the condition worse.

"Endotype discovery based on gene expression profiles has revolutionized our understanding of cancer and tailored patient therapy. We hypothesized that a similar approach could identify distinct and clinically relevant TB endotypes, and the results exceeded our expectations," said senior author Dr. Cristian Coarfa, associate professor of molecular and cellular biology at Baylor and member of Baylor's Dan L Duncan Comprehensive Cancer Center.

DiNardo said that researchers in the field are looking for new therapies for the disease, as current therapies require six months of antibiotics. To identify new treatments, researchers have been studying the human immune response to tuberculosis bacteria to better understand what it takes to build protective immunity against this disease. This approach can lead to the development of personalized precision medicine therapies.

Led by Coarfa, the team applied cutting-edge unbiased bioinformatic techniques to analyze large patient datasets to look at immune responses to tuberculosis and identified two main clusters or endotypes of the disease. They then looked at these specific endotypes in two different patient cohorts and found that one endotype had a higher risk of treatment failure and death than the other. Using computer models, they then predicted what types of drugs could be used to treat each tuberculosis endotype.

"When we compared different drugs as potential personalized therapy, we found that one therapy could be inconsequential or detrimental to one TB subtype, but beneficial to the other," DiNardo said.

"The results of this study will pave the way for personalized therapies, with great potential to improve treatment outcomes for the deadliest of all bacterial infectious diseases," adds Professor Jan Heyckendorf, a DZIF tuberculosis researcher from Borstel and Kiel and one of the study's lead authors.

"Whereas gene expression or transcriptomic-based TB endotypes are already informative, future work will incorporate other informative 'omics,' such as metabolomics (metabolites present) and epigenomics or the regulation of gene expression via DNA methylation, leading to further refinement of endotypes and personalized therapy," said Coarfa.

Researchers will now implement clinical trials to treat tuberculosis in a stratified personalized therapy approach, similar to the approach that oncologists take when treating different subsets of cancers.

More information: Andrew R. DiNardo et al, Gene expression signatures identify biologically and clinically distinct tuberculosis endotypes, *European Respiratory Journal* (2022). DOI: 10.1183/13993003.02263-2021

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