Toward an effective TB vaccine: Analysis of the immune response to a promising candidate

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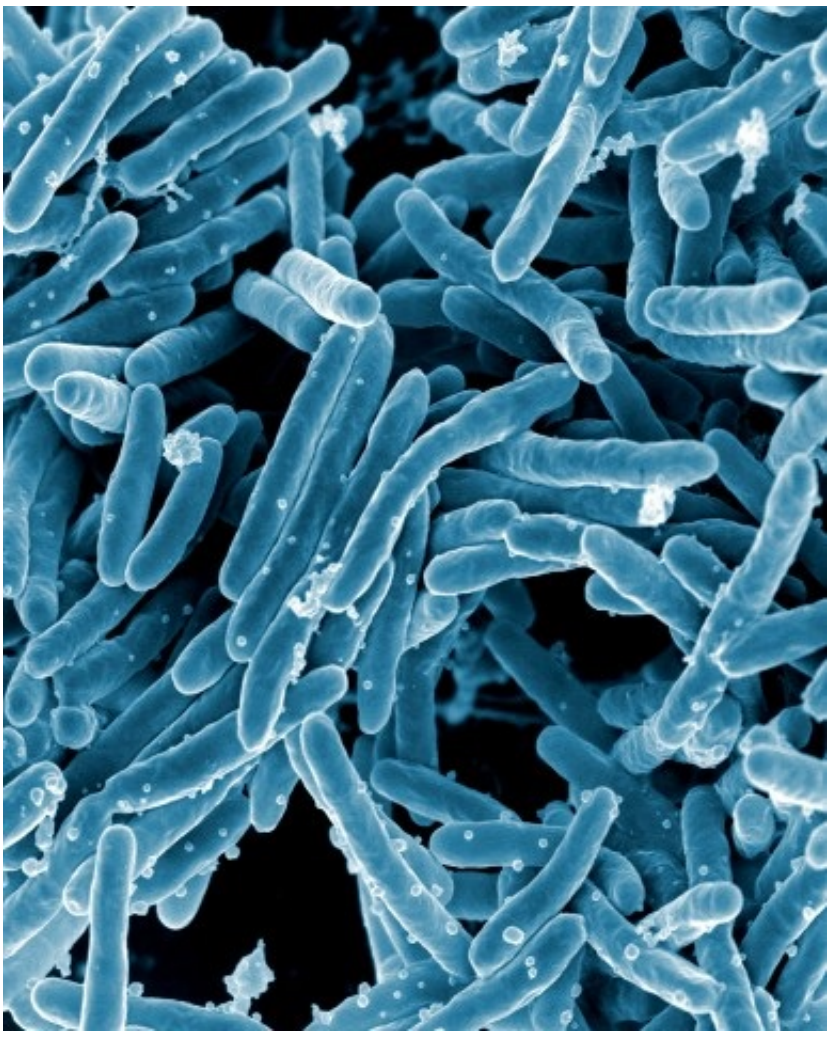

Scanning electron micrograph of *Mycobacterium tuberculosis* bacteria, which cause tuberculosis. Credit: NIAID

BCG, the only currently approved TB vaccine, has been around for almost a century and is only partially effective. When given to children, BCG is estimated to prevent 20% of infections and to protect half of the infected individuals from developing active TB, and protection fades over time. Given the complicated TB treatment, the rise of adult TB cases in conjunction with the HIV epidemic, and increasing multidrug resistant TB strains, a new and better vaccine is a global health priority. A study published on July 28th in *PLOS Pathogens* dissects the immune response in mice to an experimental vaccine and shows why it is highly effective.

Mycobacteria have a complex cell envelope and use sophisticated transport systems to shuttle proteins across this barrier. *Mycobacterium tuberculosis* has at least three such systems, called ESX-1, ESX-3, and ESX-5, which are involved in interactions with the human host and contribute to the pathogen's ability to cause disease. Strains that are missing these systems are attenuated (i.e., weakened and unable to cause disease). The BCG strain, for example, (which is actually an attenuated version of the closely related *Mycobacterium bovis*), is missing a functional ESX-1 system.

Laleh Majlessi, from the team of Roland Brosch at Institut Pasteur in Paris, France, Daria Bottai from the University of Pisa, Italy, and colleagues had previously reported a new attenuated *M. tuberculosis* strain as a promising vaccine candidate. The strain, called Mtb Δppe25-pe19, is missing a stretch of DNA in the ESX-5 locus that codes for five so-called PE/PPE proteins. PE/PPE proteins are unique to mycobacteria, contribute to their ability to cause disease, and are highly immunogenic (that is, they can provoke specific and strong immune responses).

There are over 160 PE/PPE proteins in *M. tuberculosis*, which are shuttled by the ESX-5 transporter. The Mtb Δppe25-pe19 strain lacks

five of the proteins, but because the transporter itself is intact, it is able to export the other PE/PPE proteins. As a result, immunized mice show specific T-cell responses against a many PE/PPE proteins. Because the deleted ESX-5-locus PE/PPE proteins are similar to others, T cells in immunized mice recognize the former as well.

In this study, the researchers characterized in detail the immune response in mice injected with the Mtb Δppe25-pe19 vaccine candidate. When they compared the Mtb Δppe25-pe19 strain with a virulent (i.e., disease-causing) Mtb strain that contains the full complement of all PE/PPE proteins, they found that both were equally able to induce a strong and diverse immune response to all mycobacterial PE/PPE proteins. Together with results that an Mtb strain with a defective ESX-5 transporter is less able to protect immunized mice against subsequent Mtb challenge, this suggests that T cell responses against PE/PPE proteins correlate with immune protection.

Unlike the BCG strain, Mtb Δppe25-pe19 has an intact ESX-1 transport system. Consistent with this, the researchers show that immunization with Mtb Δppe25-pe19 induces specific immune responses to several substrates of the ESX-1 system. Besides specific responses, ESX1-proficient mycobacteria induce so-called 'phagosomal rupture', a process that overcomes containment of the mycobacteria within a specific host cell compartment, which then triggers numerous pathways of innate (non-specific) immune responses. Like wild-type (fully virulent) Mtb and in contrast to attenuated BCG, Mtb Δppe25-pe19 is able to induce phagosomal rupture and provoke the resulting innate immune response.

Their results, the researchers conclude, "offer detailed insights into the immune mechanisms underlying the remarkable protective efficacy of the live attenuated Mtb Δppe25-pe19 vaccine candidate, as well as the specific potential of PE/PPE proteins as protective immunogens". They

go on to say, "our results pave the way for further development of candidates in preclinical models of anti-tuberculosis vaccination".

More information: *PLOS Pathogens*, DOI: 10.1371/journal.ppat.1005770