How the tuberculosis vaccine may protect against other diseases

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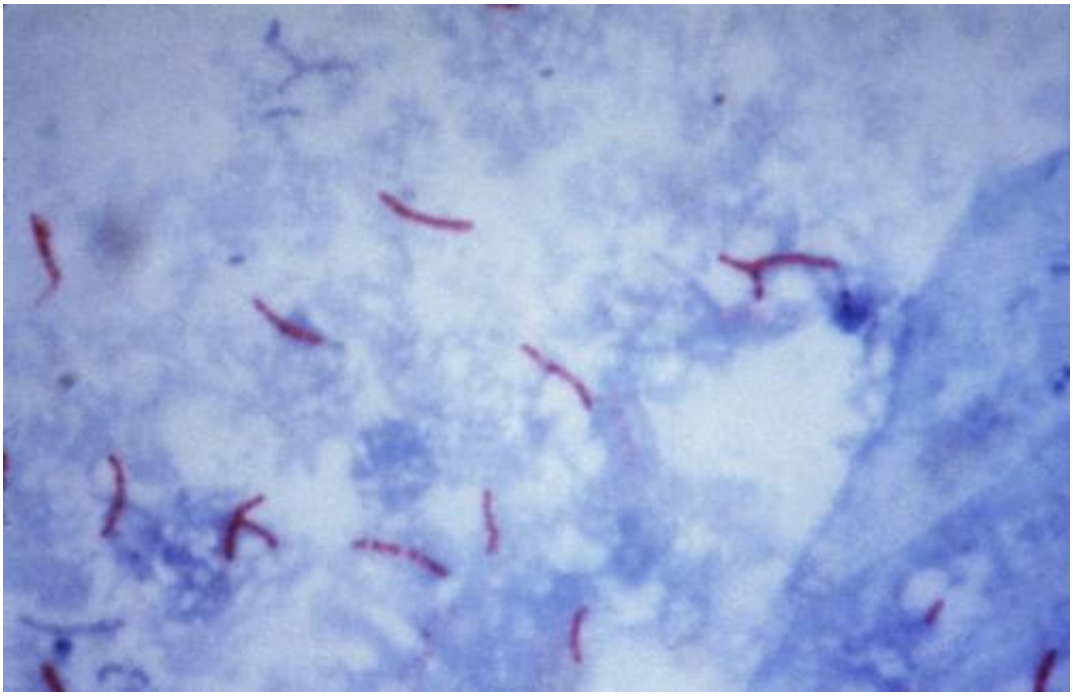

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

The tuberculosis vaccine is well known to help protect against other infectious diseases, as well as cancer, but the exact mechanisms have not been clear. A study published December 6 in *Cell Reports* now shows

that the broad-spectrum effects of the Bacillus Calmette-Guerin (BCG) vaccine—the most widely used vaccine in the world—could be mediated by metabolic and epigenetic changes in white blood cells called monocytes through a process called trained immunity. This discovery could pave the way for strategies that combine immunological and metabolic stimulation to boost the effectiveness of vaccines and anti-cancer therapies.

"The implications of these findings are double: On the one hand, we have uncovered new biological interactions that link cellular metabolism with immune responses, and on the other hand, we have opened the door for new therapeutic approaches in which metabolism modulators modulate innate immune responses and can serve as potential novel immunotherapies," says senior study author Mihai Netea of Radboud University Medical Center. "However, what it is important to realize is that this is the beginning of the process to bring this to clinical practice, and more studies are needed for that."

Many epidemiological studies have demonstrated BCG's capacity to protect against infections other than tuberculosis. For example, early administration of the BCG vaccine reduces child mortality, mainly due to a reduction in lower respiratory infections and harmful immune responses triggered by infections. BCG is also used to treat bladder cancer and appears to be beneficial in several other conditions, including asthma and parasitic diseases. However, it has not been clear exactly how BCG exerts its wide-ranging effects.

To address this question, Netea and his team examined BCG-induced metabolic changes in innate immune cells called monocytes. They found that vaccination induced a strong, long-lasting increase in glycolysis and, to a lesser extent, glutamine metabolism in mice and humans. This shift in glucose metabolism toward glycolysis was necessary to trigger trained immunity. This process relies on epigenetic changes, which affect gene

activity without altering the DNA sequence, to enhance the ability of innate immune cells to recognize and mount more effective responses against previously encountered pathogens.

Specifically, BCG-induced metabolic changes were required to induce modifications to proteins called histones, which act as scaffolds around which DNA wraps. In the human cohorts, single-nucleotide variations in genes encoding glycolysis enzymes affected the induction of trained immunity in monocytes. Taken together, the results show that cellular metabolism reprogramming is a central process involved in BCG-induced trained immunity.

"These findings change the concept that the innate immune system cannot adapt in the long-term after an infection or vaccination," Netea says. "The whole concept that the function of innate immune cells can change in a stable way, for example, being improved by certain vaccines such as BCG, is a paradigm shift in immunology, as until not too long ago it was assumed that only the adaptive immune system can adapt to previous infections or vaccinations."

Host immune responses are classically divided into innate immune responses, which react rapidly and nonspecifically upon encountering a pathogen, and adaptive immune responses, which are slower to develop but are specific and build up immunological memory, Netea explains. The discovery of trained immunity has challenged the dogma that only adaptive immunity can build immunological memory.

According to Netea, the next step is to conduct a bigger, broader analysis of circulating monocytes in BCG-vaccinated individuals at risk for infections. "In the future, bigger studies should assess inter-individual variation in these responses, in order to be able to identify which factors influence vaccination responses at the level of a person," Netea says. "In the end, a better understanding of BCG-induced trained immunity could

lead to the development of strategies that alter cellular metabolism pathways to improve human host defense mechanisms and boost the effectiveness of vaccines and immunotherapy in patients."

More information: *Cell Reports*, Arts et al.: "Immunometabolic pathways in BCG-induced trained immunity" www.cell.com/cell-reports/full … 2211-1247(16)31552-2 , DOI: 10.1016/j.celrep.2016.11.011

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