Re-programming innate immune cells to fight tuberculosis

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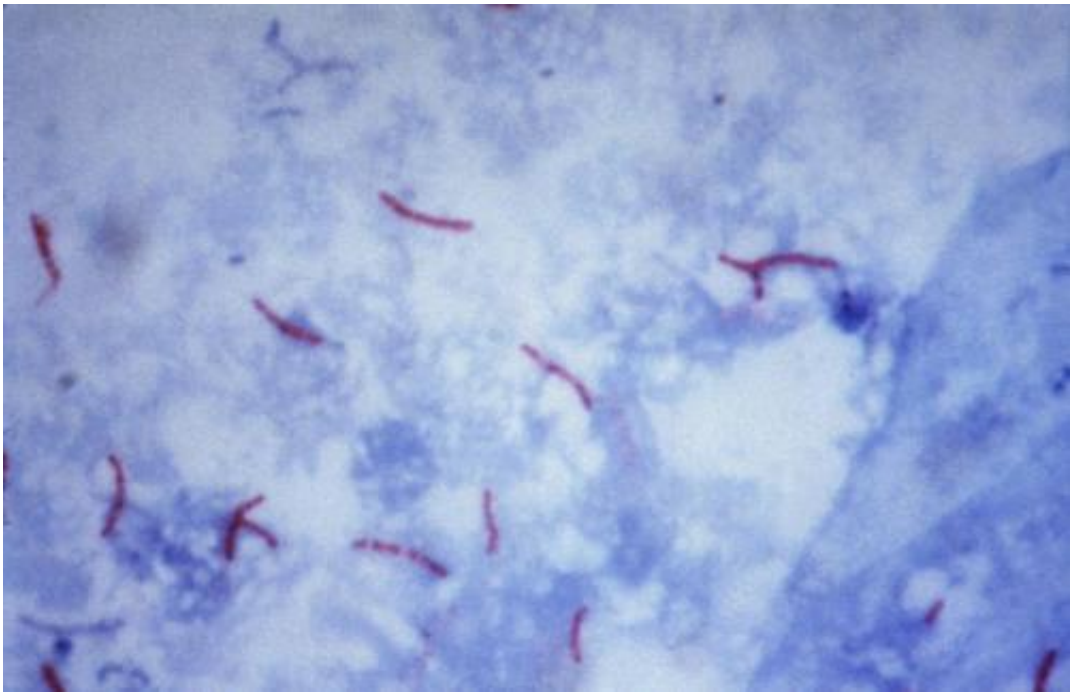

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains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

Tuberculosis (TB), an infectious disease which attacks the lungs, claims a life every 20 seconds and 1.5 million lives worldwide every year. A cure has eluded scientists for more than a century but, now, a Montreal

team of researchers may have discovered a new weapon to combat this global killer. The team is re-programing - or 'training' - immune cells to make them kill TB. These groundbreaking findings are published online today in the journal *Cell*.

"The current available BCG-vaccine is not effective. The current antibiotic treatments are toxic and have resulted in generating TB-resistance strains. The antibiotics era is approaching its end; we are in serious trouble with this bug if we don't investigate an alternative approach," says lead corresponding author Dr. Maziar Divangahi, a pulmonary immunologist and expert in immunity to TB at the Research Institute of the McGill University Health Centre (RI-MUHC).

Working with Université de Montréal geneticist Luis Barreiro and his team at the UdeM-affiliated CHU Sainte-Justine Research Centre, the researchers were able to dissect and identify the genomic pathways involved in triggering an enhanced innate immune response against TB.

Up until now, efforts in generating a vaccine against TB have been mainly focused on T cells (cells from the adaptive arm of our immune response with memory capacity), with very disappointing outcomes in both pre-clinical as well as clinical trials. Now, Dr. Divangahi's and Barreiro's teams have shown for the first time that when BCG is administered to mice in a way that enables access to the bone marrow, it can reprogram stem cells. These primitive cells are responsible for generating all immune cells including the innate arm of our immune response, the first line of defense in the war against TB.

Cells trained to eradicate TB

The innate system - via stem cells in the bone marrow - mobilizes macrophages, which are a type of white blood cell that swallows and kills invading bacteria like Mycobacterium tuberculosis (Mtb) that

causes TB. They are the immune system's first responders.

However, Mtb disarms the killing program of macrophages and uses them as a kind of "sanctuary" to replicate and grow. Dr. Divangahi's team looked at that process and aimed to find out how to boost the TB-killing efficiency of macrophages. With this goal in mind, Dr. Divangahi's team vaccinated mice with BCG and in a series of experiments observed that in the bone marrow BCG was able to reprogram or "educate" the stem cells to proliferate and generate TB slaying macrophages.

"Although we demonstrated that BCG educates stem cells to generate trained immunity, we had no idea about the molecular mechanisms that were involved in this protective pathway," says Dr. Divangahi, who is also an Associate Director of the Translational Research in Respiratory Diseases Program at the RI-MUHC and an Associate Professor of Medicine at McGill University.

To find out what those molecular mechanisms were, Dr. Divangahi initiated a collaboration with Dr. Barreiro and his team at Sainte-Justine. Their goal was to dissect the genomic pathways involved in triggering the enhanced innate immune response against TB.

Dr. Barreiro's team demonstrated how the protective programs were imprinted and transmitted from stem cells all the way to macrophages. In addition, they identified the genetic imprint of the protective pathways in educated macrophages that were "turned on" to kill the TB pathogen. "It's really about finding different ways to develop better vaccines, ones that will harness the power of macrophages and finally put the body's innate immune memory to use," says Dr. Barreiro.

"The current vaccine - BCG - was introduced in 1921 and has failed to control the tuberculosis epidemic. This work will completely re-orient

efforts to develop a new vaccine for TB," adds Dr. Marcel Behr, director of the McGill International TB Centre in Montreal.

Although researchers and colleagues are extremely hopeful that this novel approach will generate an effective vaccine against TB and potentially other infectious diseases, Dr. Divangahi added a word of caution. "This is only the tip of the iceberg and further research is clearly required to fully harness the power of stem cells in immunity against infectious diseases."

More information: "BCG educates hematopoietic stem cells to generate protective innate immunity against tuberculosis," by Eva Kaufmann, Joaquin Sanz, Jonathan L. Dunn, Nargis Khan, Laura E. Mendonça, Alain Pacis, Fanny Tzelepis, Erwan Pernet, Anne Dumaine, Jean-Christophe Grenier, Florence Mailhot-Léonard, Eisha Ahmed, Jad Belle, Rickvinder Besla, Bruce Mazer, Irah L. King, Anastasia Nijnik, Clinton S. Robbins, Luis B. Barreiro, and Maziar Divangahi, was published Jan. 11, 2018, in *Cell*.

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