Experimental immune-boosting drug worsens TB in mice

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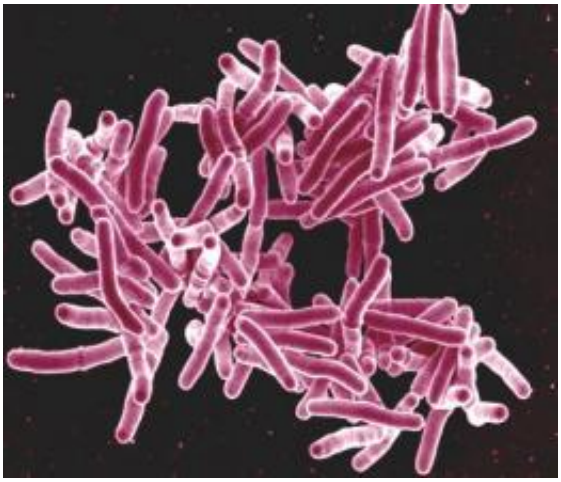

This is a colorized scanning electron micrograph of *Mycobaterium tuberculosis*, the bacteria that cause TB. Credit: NIAID

An experimental drug that boosts production of the immune system protein interferon worsens tuberculosis (TB) in mice, according to scientists from the National Institutes of Health. The drug acts indirectly by drawing certain immune cells, in which Mycobacterium tuberculosis (M.tb) bacteria thrive, to the lungs. The findings may have potential implications for the care of people infected with TB, the authors note. The research is reported in the May 3 issue of *Journal of Clinical Investigation,* now available online.

"Although our research was conducted in mice, our combined findings

suggest that reactivation of TB should be considered as a potential side effect if compounds that boost type I interferon production, like the one used in this study, are tested in people who may be infected with M.tb," says Alan Sher, Ph.D., of the National Institute of Allergy and Infectious Diseases (NIAID), NIH, who led the team of scientists.

Most people infected with M.tb do not develop active TB. Instead, the infection remains dormant, often for decades. Eventually, about 10 percent of people with latent infection do go on to develop active disease. Common triggers for reactivation include aging or other conditions that lower immunity.

Dr. Sher and his colleagues studied the effects of an experimental drug called poly-ICLC on immune responses to TB infection. Poly-ICLC stimulates the body to produce a potent immune system protein called type I interferon (type I IFN). Interferon was named for its ability to interfere with viral infections. Synthetic IFN is used to treat hepatitis B and C virus infections, as well as certain kinds of cancers.

In mouse studies, poly-ICLC protected the animals from viruses that can cause lethal infections, including pandemic influenza and SARS. It has also been shown to enhance the effects of several experimental vaccines when tested in animals. Poly-ICLC also is being tested in multiple human clinical trials as a possible cancer treatment when combined with cancer vaccines.

Earlier research into the effects of type I IFN on bacterial infections produced mixed results, notes Dr. Sher. Some studies showed that giving IFN to mice with non-tuberculous mycobacterial infections (Mycobacterium avium) lowered the amount of bacteria in their bodies. But in other studies, naturally occurring IFN appeared to promote rather than limit the growth of bacteria in mice infected with M.tb.

To sort out the mixed findings, NIAID investigator Lis R.V. Antonelli, Ph.D., dropped poly-ICLC into the noses of mice that had been infected with M.tb. The mice were infected either one day earlier to mimic an acute TB infection, or four months earlier to simulate a chronic TB infection. They were then compared with TB-infected, untreated mice. All the mice treated with poly-ICLC developed severe lung tissue damage. Moreover, levels of M.tb in their lungs were 100 times greater than in M.tb-infected mice that did not receive poly-ICLC.

Next, Dr. Antonelli performed a series of experiments to determine what kind of immune system cell was involved in hastening the disease in poly-ICLC-treated mice. Again, they compared poly-ICLC treated and untreated, M.tb-infected mice. In the treated group, the scientists found a fourfold increase in a specific subpopulation of immune cells called macrophages. In most infectious diseases, macrophages are drawn to the site of infection and help defend the host against disease. But when type I IFN production was elevated by poly-ICLC treatment, the surge in macrophages to the M.tb-infected lung actually harmed the host, notes Dr. Sher. TB bacteria live inside macrophages, and the specific subset detected in these experiments appears especially hospitable to M.tb.

Dr. Sher and his colleagues are currently testing the relevance of these findings to humans by determining whether under certain conditions type I IFN promotes the growth of M.tb in human macrophages. Such research could also provide important clues to exactly how and under what conditions latent TB is reactivated.

More information: LRV Antonelli et al. Intranasal poly-IC treatment exacerbates tuberculosis in mice through the pulmonary recruitment of a pathogen-permissive monocyte/macrophage population. Journal of Clinical Investigation, DOI:10.1172/JCI40817