Study sheds light on why parasite makes TB infections worse

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Scientists at Washington University School of Medicine in St. Louis have shown how a parasitic worm infection common in the developing world increases susceptibility to tuberculosis. The study demonstrated that treating the parasite reduces lung damage seen in mice that also are infected with tuberculosis, thereby eliminating the vulnerability to tuberculosis (TB) that the parasite is known to cause. Credit: Wikimedia Commons/David Williams

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developing world increases susceptibility to tuberculosis. The study demonstrated that treating the parasite reduces lung damage seen in mice that also are infected with tuberculosis, thereby eliminating the vulnerability to tuberculosis (TB) that the parasite is known to cause.

The study raises the possibility of using inexpensive and widely available anti-parasitic drugs as a preventive measure in places where the parasite and TB are common—stopping infection with the parasite and reducing susceptibility to TB and the risk of a latent TB infection progressing to disease.

The research, from Washington University School of Medicine in St. Louis, appears online Nov. 16 in *The Journal of Clinical Investigation*.

"Scientists and doctors have known that having both infections—this parasitic worm and tuberculosis—results in increased susceptibility to severe lung disease than having TB alone," said Shabaana A. Khader, PhD, associate professor of molecular microbiology. "But if we don't understand why co-infection increases the susceptibility to TB, it is difficult to know how to deal with the situation."

Public health experts estimate that one-third of the world's population is infected with TB. Most of these infections are not active and cause no symptoms because individuals' immune systems are effective at containing it. According to the researchers, people with latent tuberculosis infections have a 10 percent lifetime risk of developing active TB. And that risk may go up when people are infected with a type of parasitic worm called helminths, which are common in parts of the world where TB is also prevalent.

Khader said that scientists have suspected that the parasitic infection has some way of blocking the protective immune response needed to keep TB in check. But Khader and her colleagues found that something else is

going on.

"We showed that the parasite activates a type of immune cell that drives inflammation rather than inhibiting the immune response that protects against active TB," Khader said. "If you treat the parasite alone in these mice that also have TB, you go back to having the good immunity against TB."

In the new study, the researchers showed that a molecule made by the parasite's eggs, rather than the parasite itself, drives inflammation. In response to a signal produced by the eggs, the inflammatory immune cells in the mice produced a molecule called arginase-1, which turned out to be important in further driving the inflammatory response. Khader said that when they studied mice that were co-infected with parasites and TB but that were engineered to have immune cells that could not produce arginase-1, the inflammatory response was absent.

"When you knock out this immune cell's ability to make arginase-1, you change the whole dynamic of the disease," Khader said. "Without the arginase, the inflammatory immune cells don't come into the lungs. In other words, you can make the immune system behave like the parasite is not there."

To assess whether the results in laboratory mice might be meaningful to TB patients, Khader worked with colleagues in India and Mexico to study blood samples and radiographic images of lungs from patients with both infections and with TB alone.

"We found a correlation between the amount of arginase activity in the blood and the severity of lung disease measured on chest X-rays," Khader said. "If they had more arginase activity, the TB patients had more lung damage."

Importantly, in co-infected mice, this increased lung damage did not correlate as strongly with the amount of TB bacteria measured. Such data are further evidence that the parasite is not lowering defenses against TB, but independently driving its own inflammatory response and increasing TB susceptibility.

Khader and her colleagues also found evidence that individual genetics play a role in the type of immune response—protective or inflammatory—the body mounts against TB, even in the absence of the parasite. This study and related work in her lab are informing efforts to produce a TB vaccine.

"If we're making vaccines, we need to ask whether the new vaccines will work if someone is having one type of immune response versus another," she said. "We plan to test vaccines in co-infections with both parasites and TB to see if such a vaccine could be effective even when the body mounts an immune response that is inflammatory rather than protective."

More information: Monin L, Griffiths KL, Lam WY, Gopal R, Kang DD, Ahmed M, Rajamanickam A, Cruz-Lagunas A, Zuniga J, Babu S, Kolls JK, Mitreva M, Rosa BA, Ramos-Payan R, Morrison TE, Murray PJ, Rangel-Moreno J, Pearce EJ, Khader SA. Helminth-induced arginase-1 exacerbates lung inflammation and disease severity in tuberculosis. The *Journal of Clinical Investigation*. Nov. 16, 2015.

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