

Relation of Parasitic Worm Infection and SARS-CoV-2 Explored

Prior research has shown that helminth infection induces both innate and adaptive immune responses.

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Early in the COVID-19 pandemic, parts of the world with high rates of parasitic worm infection reported lower than expected illness and death from SARS-CoV-2, the virus that causes COVID-19.

Now, investigators from NIAID's Laboratory of Parasitic Diseases have published research using mice that provides a possible immunological explanation for that observation. [The study appears in Science Immunology](#) and was co-led by Oyebola O. Oyesola, PhD, and Kerry Hilligan, PhD, who worked in the laboratories of P'ng Loke, PhD, and Alan Sher, PhD.

The idea that parasitic worms—specifically helminths—shape the immune response to subsequent infections by other pathogens is not itself new. Prior research has shown that helminth infection induces responses from both the first-acting part of the immune system (the innate response) and the adaptive arm, which comes into play later. Indeed, mouse studies have shown that prior helminth infection allows the mice to withstand challenge with influenza virus, which, like SARS-CoV-2, is a respiratory virus.

The new research experimentally investigated an observation from a small hospital-based study in Ethiopia in which COVID-19 patients who were co-infected with helminths had a lessened risk of developing severe disease.

The team used a mouse model of SARS-CoV-2 adapted by Dr Hilligan in Dr. Sher's lab. Animals were infected with a helminth worm, *N. brasiliensis*, that is a stand-in for human hookworm infection. *N. brasiliensis* larvae travel to the lung, where they cause damage that is rapidly repaired once the infection clears. When later exposed to lethal doses of SARS-CoV-2, 60% of mice with prior worm infection survived, compared to 20% of mice without *N. brasiliensis* infection.

Further experiments showed that a parasitic worm that is restricted to the gut did not confer the same benefit, suggesting that the lung-migrating aspect of *N. brasiliensis* played a critical role in boosting resistance to severe SARS-CoV-2 disease.

Next, the scientists sought to distinguish contributions of innate and adaptive components at

different points in the course of infection by measuring total viral load in the lung at three and seven days after SARS-CoV-2 exposure.

At three days after exposure, viral loads differed only slightly between control animals and those that had been previously infected with *N. brasiliensis*. However, by the seventh day, worm-experienced mice had much lower levels of SARS-CoV-2 virus in their lungs. This finding indicated that improved adaptive responses, rather than any difference in innate immune actions to thwart virus entry, gave the worm-exposed animals their edge.

The team further defined the specific immune cells involved in the enhanced ability of worm-experienced mice to rapidly control SARS-CoV-2. In *N. brasiliensis*-exposed mice, they found, the amount of an adaptive immune cell called a CD8 T cell, which can recognize and destroy infected cells, was much higher at seven days after infection than CD8 levels in mice without worm exposure. The importance of this specific type of T cell was confirmed when the investigators treated mice with a substance that depleted CD8 T cells; this led to a large increase in SARS-CoV-2 burden in the worm-experienced mice.

Turning their attention to the immune response step prior to CD8 T cell arrival, the scientists examined whether signals produced by key members of the innate system, macrophages, differed depending on whether mice had prior worm exposure. In the lungs of worm-exposed mice, the team detected significantly more of macrophage-produced signals known to draw CD8 T cells than were seen in control mice.

“The results show that *N. brasiliensis* in the lung primes macrophages there so that they can react quickly to recruit CD8 T cells and thus more rapidly control a later SARS-CoV-2 infection,” explained Dr. Oyesola.

It is not known whether these results can explain the observations from epidemiological studies such as the one in Ethiopia, noted Dr. Oyesola. That will require follow-up immunologic studies using clinical samples, she said. Dr. Oyesola, who was recently awarded an NIH Independent Research Scholar Award, will continue her research at NIAID into how parasitic worm infections remodel innate immune responses and influence subsequent responses to viral infection.

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