Research confirms novel strategy in fight against infectious diseases

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New research shows that infectious disease-fighting drugs could be designed to block a pathogen's entry into cells rather than to kill the bug itself.

Historically, medications for infectious diseases have been designed to kill the offending pathogen. This new strategy is important, researchers say, because many parasites and bacteria can eventually mutate their way around drugs that target them, resulting in drug resistance.

In this study, scientists showed that using an experimental agent to block one type of an enzyme in cell cultures and mice prevented a specific parasite from entering white blood cells, a step required for the parasite to cause infection. This method applies to pathogens that must enter a host cell to survive and do their damage. Some bugs can thrive in a host body outside cell walls.

The researchers tested the experimental drug against *Leishmania* parasites, which are transmitted by the bite of infected sand flies. The pathogen causes a parasitic skin infection common in tropical and subtropical regions of the world, with an estimated 1.5 million new cases diagnosed each year worldwide.

"This represents a new way of thinking about treatment for infectious diseases. This was a proof of concept to see whether this emerging strategy is viable," said Abhay Satoskar, professor of pathology at Ohio State University and senior author of the study. "We aren't claiming we

have a new drug for treatment. If we know this strategy works, then drugs can be developed that target different pathways in the host that could be important for pathogen invasion and survival."

The research appears online this week in the early edition of the Proceedings of the National Academy of Sciences.

Leishmania essentially hijacks a host's white blood cells to cause a skin infection called cutaneous leishmaniasis, characterized by sores of various sizes that may or may not be painful.

The standard compounds used to treat the skin disease must be injected and can cause damage to veins and a host of unpleasant symptoms. The side effects, combined with the need to receive daily shots for three weeks, lead to poor patient compliance – which can then allow the parasites to develop resistance to the drugs.

To work around pathogens' abilities to circumvent treatment, scientists have begun developing agents that target specific elements of the infection process inside the host body. One such experimental drug is called AS-605240, and it targets one type of an enzyme that is activated when white blood cells recognize an intruder and the host body initiates an immune response.

This enzyme, PI3K gamma, controls cell movement as well as changes to a cell membrane that enable a pathogen to penetrate the cell wall. AS-605240 blocks the activity of the gamma form of the enzyme, which in turn is expected to reduce the number of cells recruited to an infection site and allow few pathogens to enter into the cells that are recruited.

Satoskar and colleagues ran a series of experiments on animal cell cultures to demonstrate that the PI3K gamma enzyme does indeed control white blood cell activity in the immune response to *Leishmania*

mexicana infection and that the presence of the experimental agent significantly reduced the ability of the parasites to penetrate white blood cell walls. The agent also reduced the number of phagocytes – one type of white blood cell – that were recruited to the infection site, meaning the parasites had fewer chances to find cells that could host them.

Additionally, the researchers tested these same responses in mice, with the same results. They then compared AS-605240 treatment of *Leishmania* infection in mice with the current standard drug treatment, sodium stibogluconate. After two weeks of treatment of lesions on the mice, the effects of both the experimental agent and the standard treatment were very similar, and both treatments reduced the number of parasites within skin lesions when compared with untreated lesions. When the treatments were combined, the healing effects were stronger than they were in mice that received just one type of treatment.

From here, Satoskar wants to fine-tune the strategy and consider other host-based pathways that could be safely manipulated to prevent pathogens from causing infection. The findings in this work suggest that such a strategy could be used not just for treatment, but for prevention as well.

"There is no prevention for these kinds of diseases," Satoskar said. "If we had a drug that would reduce the amount of phagocytes coming to the site of infection after parasites enter the skin, that would lead to a less severe infection that the body could probably control on its own."

Some people can self-heal from a *Leishmania* infection, but the time it takes is unpredictable so infections are typically treated, he said.

Provided by The Ohio State University