Penn Vet study shows immune cells in the skin remember and defend against parasites (Update)

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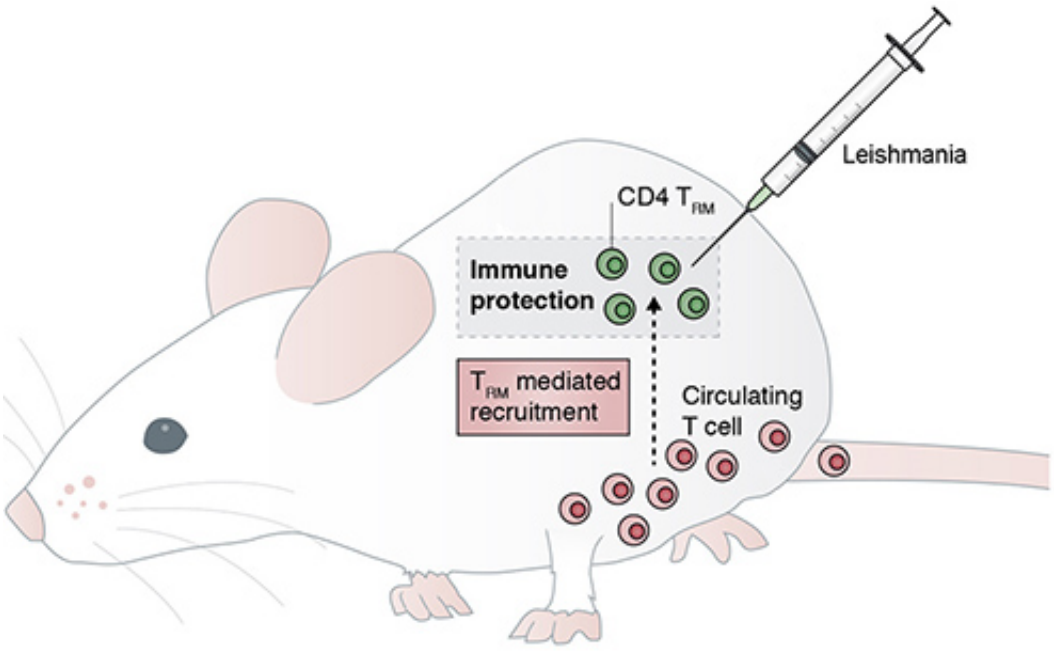

Glennie et al. show that memory $CD4^+$ T cells (green) in the skin reduce the number of parasites after secondary Leishmania infection by recruiting parasite-fighting memory $CD4^+$ T cells (red) circulating in the blood. Credit: The Rockefeller University Press

Just as the brain forms memories of familiar faces, the immune system remembers pathogens it has encountered in the past. T cells with these memories circulate in the blood stream looking for sites of new

infection.

Recently, however, researchers have shown that memory T cells specific to viral infections can also set up residence in particular tissues. There, they stand guard, ready to respond quickly to the first sign of reinfection.

Now, research led by a team from the University of Pennsylvania School of Veterinary Medicine shows that these resident memory T cells also form in response to parasite infection. The new study found that, after infection with the parasitic disease leishmaniasis, a population of T cells with a memory for the parasite remained in the skin.

This is the first time that a group of T cells has been found to be resident in a tissue in response to a parasite infection, and the finding could help inform efforts to develop an effective vaccine for leishmaniasis, as well as other diseases such as tuberculosis and leprosy.

Penn Vet's Phillip Scott, vice dean for research and academic resources and professor of immunology, was the senior author on the study, which graduate student Nelson D. Glennie led. Penn Vet's Venkata A. Yeramilli, Daniel P. Beiting and Susan W. Volk contributed, along with Casey T. Weaver of the University of Alabama at Birmingham.

The researchers reported their findings in the *Journal of Experimental Medicine*.

Affecting 12 million people in the tropics, as well as dogs and other mammals, leishmaniasis is transmitted by sand flies. The cutaneous form of the disease causes skin ulcers that can sometimes lead to disfiguring tissue damage.

For more than three decades, Scott's work has focused on the immune system's response to Leishmania infection and more specifically the role

of T cells. T cells detect invaders in the body and can kill infected cells either directly, in the case of CD8 T cells, or indirectly, in the case of CD4 T cells, by enlisting the help of other immune cells. Scott's lab has found that CD4 cells are particularly important in controlling leishmaniasis.

After an infection, a population of memory T cells remains in the body to respond quickly if reinfection occurs. Yet findings from Scott's lab supported the idea that circulating T cells weren't the only way the immune system protected against reinfection.

Studies in the lab showed that transferring circulating CD4 T cells from a mouse that had contracted and then recovered from leishmania infection into a mouse that had never had the infection, known as a "naïve" animal, offered partial but not complete protection from subsequent infection.

"Transferring the cells to a naïve animal would not provide the same level of protection as we would see in the animals they came from," Scott said. "So there was always a sense something was missing."

Perhaps, the researchers thought, the missing element was a type of resident memory CD4 T cell.

Taking mice that had had and then recovered from leishmaniasis, Scott's team looked for Leishmania parasite-specific T cells in areas of the skin, both from the site of infection and other sites. They found Leishmania-responsive cells throughout the skin of these mice, even in sites distant from the initial infection, as long as a year after infection.

"It was a little surprising that there were so many Leishmania-reacting cells in the skin," Scott said, "but it still left us with, Well, maybe they're just circulating cells that happen to have been found in the skin."

To determine whether the memory cells were indeed resident in the skin and not just replenished from the circulatory system, the researchers transferred skin grafts from mice that had had leishmaniasis to mice that had not. The parasite-responsive CD4 cells persisted in the grafts for at least four weeks, confirming that the cells were resident and not circulating.

Further experiments showed that, in the skin, leishmaniasis infection prompts genes involved in immune response to increase in production. The researchers also found that the Leishmania-specific resident CD4 memory cells could recruit other T cells to the site of infection, a necessary step for killing invading parasites.

Finally, the researchers wanted to see if these tissue-resident CD4 cells could fight off infection alone, or whether they also needed circulating CD4 cells to mount an immune response. They found that naïve mice that had a skin graft from a previously infected mouse couldn't effectively control an infection. However, if an uninfected mouse also received an injection of Leishmania-responsive T cells, they were able to respond to a subsequent infection as well as a mouse that had developed natural immunity.

The findings not only show that resident CD4 T memory cells play a key role in protecting against reinfection, they also hold crucial clues for how to produce an effective vaccine for leishmaniasis and possibly other infections. Currently no vaccine exists for leishmaniasis.

"Now that we know the important role that these resident cells play, we want to design vaccines that generate these tissue-homing cells," Scott said.

The technique that was once used to give smallpox vaccines, scratching the skin in a process known as scarification, has been shown to

effectively generate tissue-resident memory cells.

While this enhanced understanding of resident memory T cells could have lifesaving consequences, there could also be a dark side to these cells, Scott cautioned.

"Now that we know that these cells exist, it makes sense to ask whether they could they be involved in autoimmune conditions," Scott said.

More information: Glennie, N.D., et al. 2015. J. Exp. Med. DOI: 10.1084/jem.20142101

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