Could the ability to expel worms lead to a future asthma treatment?

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Based on experiments with worms similar to those that infest millions of children in the tropics, researchers see potential for a new way to treat asthma. Parasitic infections and asthma may cause the human immune system to react in some of the same ways, and may one day be cured by manipulating some of the same proteins, according to research published today in the journal *Science*.

To be effective, the immune system must "decide" which cells and chemicals need to be ramped up to best destroy the invader at hand, be it bacterium, virus or worm. In 1986, Tim Mosmann, Ph.D., now director of the David H. Smith Center for Vaccine Biology and Immunology at the University of Rochester Medical Center, led a team that first described a new concept for how the immune system might make such choices: the Th1/Th2 Model. A landmark in immunology, it was a major step toward unraveling the system's complexities. Today's study results show how the model continues to define new players in the immune system and to suggest new treatment approaches.

"The point of the study is that each new detail in our understanding of the immune system creates opportunities to make changes that counter disease," said Mosmann. "These results, while early, suggest that helping the body make more of a newly defined immune chemical may prevent roundworm infection, and that shutting it down may reduce lung damage in asthma."

Part of the immune system is adaptive, pumping out vast numbers of

immune cells on the hope that one will be the right shape to link up with, and become activated by, any invader encountered. When one of those immune cells recognizes an invader, it expands into an army of clones specifically selected to attack that organism. One workhorse of the adaptive system is the helper T cell, a white blood cell that secretes protein messengers called cytokines to accelerate the immune response.

According to Mosmann's model, T cells differentiate into two major sets of helper T cells, Type 1 (Th1) and Type 2 (Th2), each defined by the cytokines they produce. Each profile is more effective at attacking certain invaders, with Th1 responses, for example, better against bacteria that live inside cells. Th2 cytokines include interleukin-4 (IL-4), interleukin-5 (IL-5) and interleukin-13 (IL-13), all of which are useful in immune responses against worms. In a clue to the worm/asthma link, IL-4, IL-5 and IL-13 also trigger mechanisms that cause irreversible damage to the lungs of asthmatic patients.

How the mouse immune system reacts to the worms is central to Mosmann's research because mice and humans share the Th1/Th2 immune system divide, because mouse and human roundworm parasites are relatives, and because roundworm infection remains a major threat in the developing world. His basic research on T cell subsets was funded by the National Institute of Allergy and Infectious Diseases.

More than 15,000 species of parasitic roundworms infect everything from grapes to wasps to cattle. In humans, infection is usually caused by eating undercooked pork or wild game, or by poor hygiene, and brings repeated episodes of diarrhea, anemia and malnutrition. Stranded soldiers were once advised by field manuals to eat a cigarette or drink a tablespoon of kerosene to stun the worms, but modern antihelminthic drugs (e.g. Albendazole, Ivermectin, Thiabendazole) are effective and much safer. Drug treatments, however, do not reach many living in the worst conditions nor do they prevent patients from becoming re-

infected. Mosmann's work could conceivably lead to a vaccine that would confer permanent immunity to worm infection, but such research remains in the future.

Having been exposed to bacteria and parasites since early in evolution, tissues lining the gut and lungs of mice and humans have developed ways to prevent invaders from entering the body. Tissues lining the gut, for example, shed their outer cell layers when exposed to worms. Helper T cells release chemicals that cause gut cells to rapidly divide and reproduce (grow). As new cells are created, older, outer, infested layers die, fall off (shed) and are expelled from the body with solid waste.

Using molecular biology techniques, Mosmann's team found that roundworm infection led Th2 helper T cells, more than other T cell types, to produce greater amounts of a growth factor, amphiregulin, which triggers cells to divide and grow. The current results define amphiregulin for the first time as an important new player in the immune system, in the Th2 immune profile and perhaps in the many disease processes touched by it.

In the current study, mice were infected with the nematode parasite, Trichuris muris, a relative of the worm that causes trichinosis in humans. After 14 days of infection, the study found increased expression of amphiregulin along with higher levels of Th2 cytokines IL-4 and IL-13.

Researchers confirmed the relevance of amphiregulin in immune responses to the parasites by comparing worm counts in normal mice against mice that had been genetically engineered not to produce amphiregulin. Similar numbers of worm larvae were detected after ten days in both groups, and all mice cleared the parasite by day 19. Worm clearance at day 14, however, was significantly delayed in amphiregulin-deficient mice, as was the shed rate in their gut cells.

More immediate than the potential for an anti-worm vaccine, authors said, is the study's finding for the first time that amphiregulin is a product of Th2 cells, which are known to play key roles in asthma, the chronic disorder that blocks and damages air passages in the lungs of 20 million Americans.

Researchers believe airborne irritants cause Th2 cells to release interleukins, which in turn leads to the release of toxic granules that cause direct tissue damage in the lungs. As the lung tries to heal the damage, growth factors cause the airway walls to thicken, by as much as 300 percent in severe cases. Could amphiregulin be the growth factor that causes permanent thickening of asthmatic airways, restricting airflow more and more as time goes by"

Mosmann's team has already begun experiments to determine if the production of amphiregulin by the Th2 response in mice also occurs in human helper T cells. After that, researchers are interested in comparing amphiregulin expression levels in the cells of healthy versus asthmatic lungs.

Source: University of Rochester Medical Center