Designer vaccines may tailor immune response

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(PhysOrg.com) -- In Margaret Atwood's futuristic The Year of the Flood, sex workers wear "Biofilm Bodygloves" to protect themselves from infection. It turns out, though, that a prototype bodyglove may have already been invented. We call it the skin. Living inside the dermis, alongside connective tissue, blood vessels and collagen, are immune system T cells, armed with the ability to fight off infection.

HMS researchers found that the old-fashioned skin-scratching smallpox vaccine generates these skin-resident T cells, creating an internal bodyglove of smallpox immunity inside the skin—an effect not seen with injected vaccines. This discovery runs counter to the longstanding assumption that vaccines trigger the same immune response no matter how they are delivered. The findings, led by Thomas Kupper, suggest that it may be possible to design vaccines that place the strongest immune defenses at the borders of the body, giving it the power to beat infections before they sneak in.

T cells provide immunity by memorizing a viral antigen during vaccination or infection, recognizing it during a later infection and killing the infected cell. This kind of immunity is different from humoral immunity, in which antibodies recognize antigens and recruit other immune cells to fight the infection. One additional key difference is location: antibodies circulate in the blood while T cells embed themselves in peripheral tissues.

MORE THAN SCRATCHING THE SURFACE

Kupper, the Thomas B. Fitzpatrick professor of dermatology at HMS and Brigham and Women's Hospital, first learned in 2006 that skin-scratching vaccines activate T cells in the skin. T cells triggered by a skin-scratching vaccine begin their travels in skin-draining lymph nodes. These lymph nodes generate three populations of armed T cells: the front lines that home back to skin, called effector memory T cells; the backup troops that flow through the circulatory system, called central memory T cells; and a small cadre of effector memory T cells that home to other peripheral tissues such as the lungs or the gut.

Kupper's latest work compared different modes of vaccination, including skin scratching, intramuscular injection, and injection into the gut, to find out if different vaccination modes stimulate distinctive types of immunity.

He and first authors Luzheng Liu, HMS assistant professor of dermatology, and Qiong Zhong, a former HMS research fellow, found that skin scratching provided the most effective protection. Mice vaccinated with this method eliminated the virus from infected skin within six days while mice immunized via injection destroyed some but not all viral copies.

CELLULAR IMMUNITY

To tease out which types of immunity provided this protection, Kupper systematically eliminated portions of the immune response. He eliminated the antibody response by running the same test in mice incapable of forming antibodies. The skinscratched mice cleared the virus in six days while others did not, showing that antibodies play a key role in injected, but not skin-scratching, vaccinations. He then eliminated central memory T cells by blocking the exits of lymph nodes. Again, the skin-scratched mice cleared the virus completely while the viral load for all other immunization types remained high. The work

appeared in the February *Nature Medicine*.

“This elegant experimental work shows that skin scarification is a potent way of activating cellular immunity,” said Wayne Marasco, HMS associate professor of medicine at Dana-Farber Cancer Institute, who is investigating novel approaches to the influenza vaccine. “This is an important biological observation that no one recognized before.”

It isn’t clear yet how these armed T cells learn to home to the skin, but in 2006 Kupper found that different lymph nodes tag T cells with different homing molecules. The skin-draining node creates T cells with skin-homing molecules after skin-scratching vaccination. Mesenteric lymph nodes, which drain the gut, create T cells with guthoming molecules after vaccine injection into the gut.

Taken as a whole, the research suggests that it might be possible to design vaccines with “anatomically flexible protection,” said Kupper. “If we could come up with the right cocktail of modifiers for getting T cells to the right peripheral tissue, we could vaccinate in a sort of physiologically and biologically relevant way.”

For instance, imagine a malaria vaccine that could stimulate skin-resident memory T cells that quash infection from a mosquito bite. Imagine an HIV vaccine that builds a protective barrier of T cells in genital mucosa. “The idea,” said Kupper, “is to pair the biology of how you get infected with the right immune response. It’s a new way of thinking about vaccination.”

“This work shows that the way we are vaccinating now is probably completely wrong,” said Rachael Clark, HMS assistant professor of dermatology at BWH, who, along with Kupper, first discovered protective, long-lived, skin-resident T cells in 2006. “By injecting antigens into muscle, we are ignoring millions of years of evolution that

have designed organisms to produce complex and multifaceted immunity to agents that come through epithelial surfaces such as the skin."

Kupper and colleagues are continuing research to validate their hypothesis that tissue-resident cells provide important protection against infectious diseases. "It's fun to hypothesize about this idea," said Kupper, "but we have to demonstrate it further in the laboratory."

Provided by Harvard University

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