Exposure to routine viruses makes mice better test subjects

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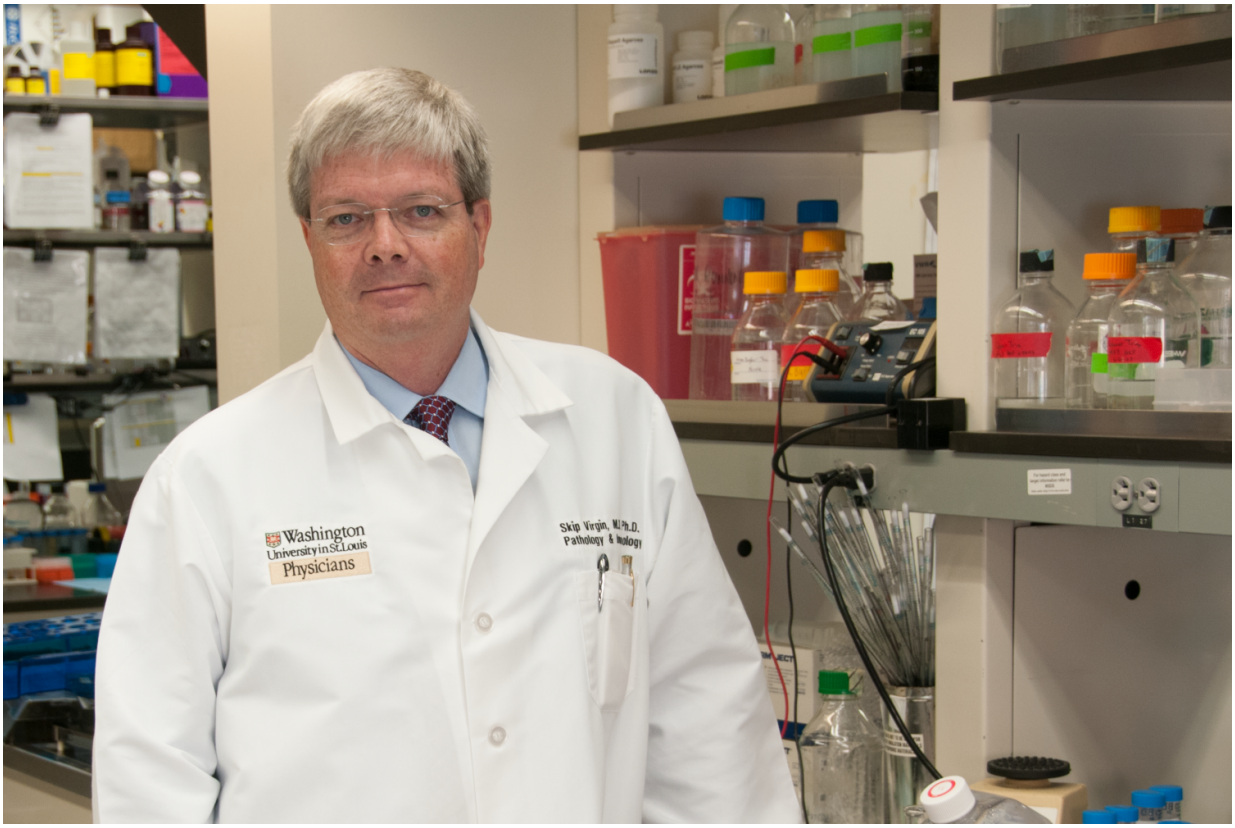

Skip Virgin, M.D., Ph.D., professor of microbiology, medicine, and pathology and immunology, has shown that infecting laboratory mice with the mouse equivalent of common human pathogens may make them better models for vaccine studies. Credit: Robert Boston/Washington University School of Medicine

Vaccines and therapeutics developed using mice often don't work as expected in humans. New research at Washington University School of Medicine in St. Louis points to the near-sterile surroundings of laboratory mice as a key reason.

When the researchers infected laboratory mice with the mouse equivalent of microbes that cause common infections in humans, the infections changed the animals' immune systems. The immune systems of uninfected mice resembled those of newborn humans, but the immune systems of the infected mice behaved like those of adult humans.

The paper is published April 20 in *Cell Host & Microbe*.

"If mice aren't perfect models, maybe part of the reason is that we've cleaned them up so much," said senior author Herbert "Skip" Virgin, IV, MD, PhD, the Mallinckrodt Professor of Pathology and Immunology and professor of microbiology and medicine. "Maybe we could make them better models for human diseases by giving them back some of the infections that would be normal to us as humans and every other mammal on the planet."

Animal studies do not always accurately predict how a vaccine or treatment will fare in humans. This is partially due to genetic differences - obviously mice are not just tiny, furry humans - but it also may be due to environmental differences between lab mice, which live in almost-sterile, well-controlled environments, and people, who are exposed to countless microbes starting at birth.

As part of the study, researchers infected mice raised in a clean research facility with two kinds of herpes viruses and an intestinal parasite that cause chronic infections, as well as the influenza virus, which causes a short-lived infection. Worldwide, all are related to common infections in

humans, although in the United States intestinal worms are uncommon.

Once the mice had recovered from the acute infections and the chronic infections had been established, the researchers extracted immune cells from their blood and studied which genes were active.

"There is almost no overlap between the genes that were active in the immune cells of the uninfected mice and in the infected mice," said Virgin. "These differences in which genes were turned on means that the activity of the whole immune system really fundamentally changed."

The same pattern of gene activity changes was found when the researchers and their collaborators compared immune cells from human umbilical cords with those from adult humans. Like research mice, newborn humans have experienced few, if any, infections.

"By giving the mice infections, we altered their gene expression in a way that made them more like adult humans and less like newborns," said Virgin. "This really suggests that lack of infection may be part of the reason that research mice are different than humans."

To test what effect these changes in the immune system had on the ability of the mice to respond to vaccination, the infected and control mice were given the yellow fever vaccine. Both groups produced effective, but somewhat different, responses.

"Something about the history of infections changed the quality of the antibody response," said Virgin.

People nearly always produce a strong immune response to the yellow fever vaccine, but that is not true of all vaccines. Some are more effective in one population than another. The vaccine for tuberculosis, for example, has been reported to work better in European than African

populations, and the reasons may have as much to do with the environment as with genetics.

"We all are chronically infected with multiple things, and that's normal," said Virgin. "It doesn't make us sick, but it may make us different from one part of the world to another, because of changes to those chronic infections or the commensal organisms that live on us."

To make a mouse model that accurately predicts how vaccines will work in people, scientists need to understand both the variation in human immune responses around the world, and the effect of different infections on the mouse immune system.

"We've established the principle that you can substantially change the nature of the immune response, but what we can't yet do is make the mouse make a human response," said first author Tiffany Reese, PhD, who led the project while a postdoctoral researcher in Virgin's lab and who is now an assistant professor of immunology and microbiology at the University of Texas Southwestern Medical Center. "We don't know which organisms change the immune system in which way. That's what we're working on now."

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