Scientists identify gene that controls immune response to chronic viral infections

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For nearly 20 years, Tatyana Golovkina, PhD, a microbiologist, geneticist and immunologist at the University of Chicago, has been working on a particularly thorny problem: Why are some people and animals able to fend off persistent viral infections while others can't?

Mice from a strain called I/LnJ are especially good at this. They can control infection with retroviruses from very different families by

producing specific antibodies that coat viruses and render them innocuous.

Golovkina, a professor of microbiology, was interested in what makes these mice special, so she began searching for the genes responsible for their remarkable immune response. In a new study published this week in the journal *Immunity*, she and her colleagues identify this gene. They also began to uncover more clues how it might work to control anti-virus immune responses.

Using a process called positional cloning, in which researchers progressively narrow down the location of a gene on the chromosome, they pinpointed it within the major histocompatibility complex (MHC) locus. The MHC locus is a well-known region of the genome involved with the immune system so it makes sense that the gene was located there, but this was a disconcerting discovery.

"It was a bummer at first because there are tons of genes within the MHC locus all controlling immune response, not only against viruses, but also many other microbial pathogens and non-microbial disorders," she said. "Most of the time when people map a gene to the MHC they give up and stop there, with an assumption that the gene encodes for one of the two major MHC molecules, MHC class I or and MHC class II."

But with the help of a biochemist, Lisa Denzin from Rutgers University, and a computational biologist, Aly Khan from the Toyota Technological Institute at Chicago, Golovkina and her team identified a gene called H2-Ob that enables this resistance. Together with another gene called H2-Oa, it makes a molecule called H2-O in mice and HLA-DO in humans.

H2-O has been known for years as a negative regulator of the MHC class II immune response, meaning that it shuts down the immune response.

Most researchers thought it was there to prevent autoimmune responses, which attack the body's own tissues. But in this case, none of the I/LnJ mice showed signs of autoimmunity, so H2-O must have another purpose.

Golovkina and her team discovered another interesting thing when they crossed I/LnJ mice that were resistant to infections with ones that were more susceptible. The resultant F1 mice were susceptible to infection. This indicated that the I/LnJ H2-Ob gene was recessive; both parents had to have a copy of the mutated gene to pass it on their offspring, and the product of the gene should be a non-functional protein.

"That was really surprising," Golovkina said. "Almost all pathogen-resistant mechanisms discovered so far are dominant, meaning that something needs to be gained to resist."

The immune system response to a virus in susceptible mice lasts three to four weeks, then the H2-O molecule tells it to stop. But the I/LnJ mice, which respond vigorously to infections, have a mutation on H2-Ob that makes it inactive. So, after they launch an immune response, it never shuts off. This keeps persistent retroviruses in check.

Golovkina hypothesizes that while letting the immune response keep running may keep chronic infections in check, such as retroviruses or hepatitis B and C, other pathogens like tuberculosis can take advantage of a persistent immune response because they can get access to certain cells when they're coated with antibodies (and I/LnJ mice happen to be susceptible to TB and produced anti-TB antibodies).

At some point during the evolution of these genes, it was more advantageous to be able to switch off the immune response to some infections (such as intracellular bacterial pathogens), but it came at the cost of not being able to fight other long-term infections.

Now that her team has identified the gene underlying anti-retrovirus and potentially anti-hepatitis B and C responses, Golovkina says that further research should be done to create genetic therapies to manipulate the function of this gene, or develop molecules that could interfere with the function of H2-O to allow the virus-specific response in chronically infected people.

Until then, she'll continue working on this problem, just as she has for the past 20 years.

"I have a very persistent nature in the way I do research," she said. "If I sincerely believe there is a very interesting biological question, nothing will prevent me from uncovering it."

More information: "Neutralizing Antibody Responses to Viral Infections Are Linked to the Non-classical MHC Class II Gene H2-Ob," *Immunity* (2017).

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