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# Scientists show lack of single protein results in persistent viral infection

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Scientists from The Scripps Research Institute have shown a single protein can make the difference between an infection clearing out of the body or persisting for life. The results also show where the defects occur in the immune system without the protein and offer the possibility that targeting this signaling pathway could be beneficial for treatment of persistent viral infections in humans. Currently hundreds of millions of people around the world are afflicted with persistent viral infections such as HIV, HCV, and HBV.

The new study is published in the June 14, 2012 issue of the journal *Cell Host & Microbe*.

In the new study, a team led by Scripps Research Professor Michael Oldstone showed what happened when a mouse engineered without the protein TLR7 was infected with lymphocytic choriomeningitis virus (LCMV), a virus employed to study the response of the immune system to microbes. While normal mice infected with a LCMV variant called Cl 13 could clear a persistent infection in 60 to 90 days, TLR7-deficient mice were unable to purge the infection throughout their lives.

"It is well known that RNA from many viruses, including influenza, HIV, and hepatitis C, induce signaling through TLR7," said Kevin Walsh, a research associate in Oldstone's lab and the first author of the study. "We demonstrated that TLR7 plays a significant role in the generation of immune responses required to clear persistent LCMV infection."

## 'Biological Warfare'

In terms of the constant biological warfare between host and microbes, the body is not so much a temple as it is a medieval city. An infectious agent can invade through the skin or mucosa, essentially scaling the walls. Once it's inside it has to deal with the body's first responders, called Toll-like receptors (TLR). These receptors are a pattern-recognition system to alert the immune system. TLRs form the first line of defense specifically by recognizing molecules of the invading pathogen.

Ten TLRs have been identified in humans. One of these, TLR7, is located inside the cell within endosomes and the RNA of viruses are detected after they have entered the cell. "TLR7 is a very important receptor in terms of viruses," noted Oldstone.

In the current study, the researchers chose to use LCMV to understand the role of TLR7. LCMV is, according to Oldstone, "has been, and continues to be a Rosetta Stone to explain basic concepts in immunology and virology."

Once it was clear that the absence of TLR7 compromised the immune system's ability to clear LCMV infection, Oldstone, Walsh, and their colleagues explored what was happening downstream of the receptor.

Interestingly, the research demonstrated that even when immune memory cells, which "learn" to fight an infection and impart long-term immunity, were transferred from TLR7-sufficient mice to TLR7-deficient mice, those deficient mice still couldn't clear the infection.

"The environment within TLR7-deficient mice suppressed the ability of these memory cells to clear the infection," said Walsh.

## Surprisingly Tired Cells

The team noticed several unexpected things. First, in the TLR7-deficient mice, there was a profusion of tired T cells. "You see more T cells in TLR7-deficient mice early after infection, but they don't actually clear the infection," said Walsh. "Even though there were more of them, they were less functional." Second, immune system B cells were severely hampered; specifically, the differentiation and maturation of B cells to plasma cells, cells responsible for generating antiviral antibody, was aborted. Thus, both essential arms of the immune system, cellular and humoral, required to clear viral infection were compromised.

Exhausted T cells produce fewer molecules to attack and destroy infected cells. Exhaustion occurs in TLR7-sufficient environments, too—but in those cases there is a resurrection of the T cells 60 to 90 days following infection with LCMV Cl 13, which allows the body to purge the virus. In the TLR7-deficient environment, this resurrection never happens. The exhausted T cells linger, as does the infection. T cell exhaustion is also found in HIV and hepatitis B and C infection.

"A number of phenomena that LCMV uses to cause a persistent infection is the same that HIV, hepatitis C and B use," said Oldstone. "That's what makes our observation important. It means that if you understood what is in the environment with loss of TLR7 signaling and how to correct that, you'd have a better chance of treating those persistent human infections. We know how to treat it in the mouse, and people are working very hard to do the treatments in humans."

**More information:** "Toll-like receptor 7 is required for effective adaptive immune responses that prevent persistent virus infection," *Cell Host & Microbe*.

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