Study finds interferon, one of the body's proteins, induces persistent viral infection

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Scientists at The Scripps Research Institute (TSRI) have made a counterintuitive finding that may lead to new ways to clear persistent infection that is the hallmark of such diseases as AIDS, hepatitis B and hepatitis C.

The study, reported in the April 12, 2013 issue of the journal *Science*, focused on the activity of the body's type 1 interferon (IFN-I) proteins. Since its discovery over 50 years ago, IFN-I has been believed to be an especially powerful antiviral agent that marshals the immune system's response against the body's foreign invaders. But in the new study, the TSRI scientists document in mice that IFN-I initiates persistent infection and limits the generation of an effective antiviral immune response.

"Our findings illuminate an unexpected role for IFN-I protein(s) in persistent infections, which has major implications for how we treat these infections," said Michael B. A. Oldstone, a professor in the Department of Immunology and Microbial Science at TSRI and senior investigator for the study.

Mystery of Immune Suppression

For decades, Oldstone and other virologists around the world have been trying to understand how some viruses manage to persist in their hosts.

One big clue, discovered only in recent years, is that some of these viruses are especially effective at getting into cells of the immune system known as dendritic cells. These cells serve as key detectors of infection and normally respond to viral infection by producing IFN-I proteins. They also produce both immune-enhancing proteins (cytokines/chemokines) to drive forward a vigorous immune response, as well as immune-suppressing proteins including interleukin-10 (IL-10) and PD-1, which act as a braking system that balances the immune response to keep within healthy (non-autoimmune) limits.

Persistent viruses can use this immune-suppressing effect for their own purposes. In several experimental models of persistent infections and in humans with persistent infections, a rise in IL-10 and PD-L1 is followed by declines in the function and numbers of antiviral T-cells. Many of the surviving T cells are rendered ineffectual—a phenomenon called "T-cell exhaustion" or "hyporesponsiveness."

A Surprising Observation

To better understand how this immune-suppressing response develops, Oldstone and his team, including first authors John R. Teijaro and Cherie Ng, along with Brian Sullivan, looked in detail at the early events in a persistent viral infection. The team used a now-standard animal model that Oldstone developed almost 30 years ago: laboratory mice infected with lymphocytic choriomeningitis virus (LCMV) Clone (Cl) 13 strain.

One initial observation surprised them. "A day after infection, bloodstream levels of IFN-I were at least several times higher in the persistent infection, compared to a non-persistent LCMV infection," said Teijaro.

The persistent LCMV Cl 13 strain also turned out to be much better at infecting plasmacytoid dendritic cells—which are considered the principal source of IFN-I proteins during viral infections. By contrast, the LCMV Armstrong (ARM) 53b strain, from which Cl 13 was derived, generated significantly less IFN-I and did not induce a persistent infection but rather generated antiviral effector CD8 T cells; this infection was terminated within 7 to 10 days. Cl 13 differs from ARM by only three amino acids (protein building blocks) of which just two are important; one in the glycoprotein for binding and entry into dendritic cells and the other in the viral polymerase that enhances viral replication.

Earlier Clearance and Fewer Malfunctions

The production of IFN-Is by plasmacytoid dendritic cells has been considered a normal and beneficial part of the immune reaction to a viral infection. "We usually think of IFN-I proteins as antiviral proteins, so that more IFN is better," said Ng. Indeed, when she and Teijaro used a monoclonal antibody to block IFN-I-alpha-beta (-?-?) receptor, activity just prior to or after infection with Cl 13, they observed a sharp drop in the production of IL-10 and PD-L1, loss of excessive cytokine/chemokine expression (cytokine storm) and maintenance of normal secondary lymphoid tissue architecture.

But the scientists found over the longer term a sharp drop in levels of immune-suppressing IL-10, as well as PD-L1, both inducers of T-cell exhaustion, was associated with restoration of antiviral immune response and virus clearance. And although blocking the IFN-I-?-? receptor led to higher bloodstream levels of virus in the first days after infection, it soon brought about a stronger, infection-clearing response.

"Even when we blocked IFN-I-?-? receptor after a persistent infection had been established and T-cell exhaustion had set in, we still saw a significantly earlier clearance of the virus," Ng said.

Blocking IFN-I-?-? receptor also prevented or reversed other immune malfunctions caused by the persistent LCMV strain, including a disruption of the structure of the spleen tissue and diminished T cell entry and maintenance within lymphoid structures in the spleen that contain dendritic cells. The interaction of dendritic cells with T cells is necessary to generate antiviral effector CD8 and CD4 T cells. "We saw a restoration of this lymphoid architecture, as well as an increase in a subset of antiviral T cells, natural killer cells and dendritic cells, and restoration of antiviral CD4 T cell function," said Teijaro.

Potentially Broad Applications

Oldstone and his team now plan to study IFN-I signaling pathways in further detail. In particular, they hope to determine whether the IFN-I-?-? receptor blocking strategy can work against chronic viral infections in humans. The scientists will also seek small pharmacologic molecules with the same function.

"Most of our findings in the LCMV model mirror what has been observed in human persistent infections, namely the upregulation of IL-10 and PD-L1, and the disruption of lymphoid architecture," said Oldstone.

Conceivably, the IFN-I-?-? receptor-blocking strategy could have broad clinical applications. In terms of viruses alone, chronic HIV, hepatitis B and hepatitis C infections collectively are found in hundreds of millions of people worldwide. Other common persistent viruses include Epstein-Barr virus, cytomegalovirus and cancer-causing human papilloma virus. Researchers have estimated that the average person at any one time carries at least several persistent, often silent viral infections.

More information: "Persistent LCMV infection is controlled by blockade of type 1 interferon signaling," *Science*, 2013.

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