Scientists identify interferon beta as likely culprit in persistent viral infections

May 13 2015

Michael B. A. Oldstone is a professor at The Scripps Research Institute. Credit:

Photo courtesy of The Scripps Research Institute.

Interferon proteins are normally considered virus-fighters, but scientists at The Scripps Research Institute (TSRI) have found evidence that one of them, interferon beta (IFNβ), has an immune-suppressing effect that can help some viruses establish persistent infections.

The results suggest that drugs blocking IFNβ might one day be used to treat persistent viral infections, which include HIV and hepatitis B and C infections.

"We found that IFNβ is important for the immunosuppressive effect seen in persistent infection, even though it signals through the same receptor used by IFNα proteins, which have very different effects," said TSRI Professor Michael B. A. Oldstone, senior investigator of the study, which appears in the May 13, 2015 issue of *Cell Host & Microbe*.

Brake or Gas Pedal?

Interferons, discovered nearly 60 years ago, are among the proteins secreted by cells in response to viral invasion. Their known functions include activating T cells, interfering with viral replication and enhancing the presentation of viral proteins to the immune system. They have long been considered essentially antiviral and immune-boosting, and lab-grown IFN type I proteins are used to treat hepatitis C infections and some cancers.

Yet, it is becoming clear that interferons don't simply boost the immune system. In a study reported in *Science* in 2013, for example, Oldstone and his laboratory found evidence that type I interferon signaling has a strong braking effect on the immune response—a braking effect that

may be co-opted by infecting viruses to enhance their survival. Oldstone notes blockade of type I interferon receptor signaling corrected virus-induced disorganization of secondary lymphoid tissue, allowed migration of T cells in the lymphoid tissue and diminished molecules responsible for aborting virus-specific T cell activity—all leading to restoration of T cell function and control of the viral infection.

For the new study, Oldstone and his team sought to identify whether IFNα or IFNβ was responsible for that braking effect. IFNβ was the prime suspect. In the mouse model of persistent infection, which uses a variant ("clone 13") of the mouse-infecting LCMV virus, IFNβ is produced in the mice at much higher levels than those seen with a non-persistent LCMV variant (ARM 53b). Of the 3,356 amino acids that comprise either LCMV Cl-13 or ARM, these viruses differ only by three amino acids. One of these is in the LCMV GP-1 spike responsible for binding to the host cell's receptor and entry, while a second is located in the polymerase protein and is associated with enhanced replication of LCMV Cl 13 1.5 to 2 logs more than LCMV ARM in dendritic cells. Moreover, IFNβ has been reported to have anti-inflammatory effects and is used to treat the autoimmune disease multiple sclerosis, although its precise mechanisms of action have been unknown.

Co-Opting the System

The team, including first author Cherie Ng, at the time a research associate in the Oldstone lab, examined mice raised without the gene for IFNβ and normal mice in which IFNβ activity was blocked with a monoclonal antibody.

This experiment showed the LCMV Cl-13-infected mice devoid of IFNβ signaling restored lymphoid architecture and enhanced T-cells primed for attacking LCMV. By day 30 of the infection, the mice also showed a significantly lower viral load in the spleen, liver, lung and bloodstream,

compared to mice with intact IFNβ signaling.

By contrast, blocking IFNα with an antibody that neutralizes six subtypes had none of these beneficial effects. Moreover, blocking IFNα activity led to greater viral spread early in the infection. These results implied that, although IFNα and IFNβ signal through the same cellular receptor, IFNα proteins are important in limiting early virus spread, whereas IFNβ is an immunosuppressive molecule.

"Researchers have long hypothesized that interferons evolved many different subtypes not just for the sake of redundancy, but because those subtypes have different biologic roles," said Oldstone. "In the case of IFNβ, that role may be to curb the immune response, thereby preventing excessive damage and autoimmunity due to that immune response."

"LCMV Cl-13 and likely other viruses that persist—and possibly cancers—have learned to co-opt that immunosuppressive function to abort T cell functions required to eliminate them," Oldstone said.

Next steps for Oldstone and his team include determining precisely how the binding of IFNα and IFNβ proteins to the IFN-I receptor differ, how those bindings alter the expression of immune-related genes and what points on the IFNβ pathway could best be targeted with drugs to treat persistent infections and perhaps some cancers.

Provided by The Scripps Research Institute