Timing, duration of biochemical bugle call critical for fighting viruses

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Researchers have identified the primary player of the biochemical bugle call that musters the body's defenders against viral infection.

Scientists at Washington University School of Medicine in St. Louis have shown that a key molecule, MDA5, is essential for producing enough interferon (the bugle call) to rally virus-fighting cells during certain viral infections. In mice, the lack of MDA5 forces the immune system to rely on less effective defenders, which may give the virus opportunities to establish or expand a chronic infection.

Like the cavalry charge in classic movies, timing is critical in fighting a viral infection. If a surge of interferon comes early enough, the immune system can limit or clear a virus. If the boost is too late, though, the defenses may already be overwhelmed.

"If an injection of interferon is given within a certain time frame in the infectious process, we found that it was possible to decrease viral spread and bolster antiviral CD8 T cell responses in our mouse model ," says first author Yaming Wang, a predoctoral trainee in immunobiology. "Adding interferon may also boost the power of antiviral vaccines that are being designed to help the immune system recognize and attack chronic viral infections such as HIV."

The research appears June 14 in Cell Host and Microbe.

Viruses can cause both temporary and chronic infections. In chronic infections, the virus goes into periods of relative quiescence that limit its spread and diminish conflicts with the immune system. Those periods are often interrupted by flare-ups when the virus shifts gears and becomes more active again.

Interferon, which is made by the body in many forms, is named for its ability to interfere with viral replication. It is currently used with antiviral medications to treat patients with hepatitis C who are having flare-ups.

"Interferon puts cells into an antiviral state," says senior author Marco Colonna, MD, professor of medicine and of pathology and immunology. "This prevents viruses from infecting cells or reproducing in them."

Some forms of interferon also summon critical immune CD8 T cells to infection sites, where the T cells either fight the infection directly or store information about the virus to speed recognition if it returns.

Wang and his colleagues showed that MDA5 is the major source of interferon during a meningitis-type infection known as lymphocytic choriomeningitis virus.

Interferon production by a specialized immune cell, the plasmacytoid dendritic cell, dropped off rapidly within the first day of infection, but MDA5 continued to boost interferon production for three to four days.

Prolonging interferon production allows infection-fighting cells to stay in the battle longer, but also increases the risk that those same cells could cause autoimmune damage. The results suggest that timing and balance are critical, according to co-author Melissa Swiecki, PhD, a postdoctoral research associate.

"As we consider the implications of these results for expanding or refining our use of interferon in the clinic, timing and magnitude are going to be the key words. Can we find ways to get patients interferon when they need it and in just the right amount?" Swiecki says.

Colonna and his colleagues are planning follow-up studies in humans.

More information: Wang Y, Swiecki M, Cella M, Alber G, Schreiber RD, Gilfillan S, Colonna M. Timing and magnitude of type I interferon responses by distinct viral sensors impact CD8 T cell exhaustion and chronic infection. *Cell Host and Microbe*, June 14, 2012.

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