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A single protein helps the body keep watch over the Epstein-Barr virus

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Some 90 percent of people are exposed to the Epstein Barr virus (EBV) at some point in their life. Even though it is quickly cleared from the body, the virus can linger silently for years in small numbers of infected B cells. According to researchers at Children's Hospital Boston and the Immune Disease Institute (IDI), the immune system subdues the virus by watching for a single viral protein called LMP1, knowledge that has already helped suggest two new treatments for the EBV-fueled cancers seen in some immunosuppressed patients.

The study team, led by Klaus Rajewksy, MD, and Baochun Zhang, MD, PhD, of the Program in Cellular and Molecular Medicine at Children Hospital Boston and the IDI, reported their results online this week in the journal *Cell*.

While the immune system's T cells rapidly clear most EBV-infected B cells, about one in a million infected cells escapes destruction. Within these cells, the virus enters a latent phase, kept in check by the watchful eye of so-called memory T cells. This uneasy relationship usually holds steady the rest of a person's life, unless something – such as infection with HIV or use of anti-rejection drugs following a transplant – suppresses the immune system and breaks the surveillance. The virus can then reawaken and drive the development of B cell cancers like AIDS-associated B cell lymphoma and post-transplant lymphoproliferative disorder.

To better understand how the immune system maintains its watch and

how the virus turns cells cancerous, Rajewsky and his team had generated a model mimicking latent EBV infection by engineering mice whose B cells contained an inducible version of viral LMP1. Researchers have long known that EBV needs LMP1 to turn B cells cancerous, but modeling this relationship in vivo had proven challenging.

"We had previously attempted to develop an animal model of LMP1 transformation of B cells," said Rajewsky, who recently moved to the Max Delbrück Center for Molecular Medicine in Germany, "but we had never been able to get the mice in our models to actually produce any mature B cells. The immune response against the LMP1-producing B cells was so robust that the cells were eliminated very early on."

Their breakthrough came when Zhang and colleagues reengineered the model to lack T cells. "The mice were initially fine, but succumbed within two to three months to aggressive B cell lymphomas," Rajewsky said. "The profile mimicked very closely what we see in immunosuppressed lymphoma patients." In additional experiments with Rajewsky's original model, the team eliminated the mice's T cells before activating the viral protein in B cells, sparking a similar but even more rapid fatal disease.

The team also made several observations with possible clinical application. First, they noted that in the mouse model the LMP1 producing B cells were being attacked by a specific kind of T cell called a CD4+ T cell. "Transplant patients who develop B cell lymphomas because they are immunosuppressed by their anti-rejection drugs are often treated with T cells that carry the CD8 marker," Rajewsky noted. "These results would argue for also considering CD4+ T cells for treatment."

Second, they found that tumors in the LMP1 producing mice often displayed targets recognized by another kind of immune cell called a

natural killer (NK) cell. Seeing an opportunity, Rajewsky worked with cancer immunologist Glenn Dranoff, MD and colleagues at Dana-Farber Cancer Institute, to test a potential therapeutic agent that uses a portion of the NK cell activating receptor called NKG2D, fused to the stimulatory Fc portion of an antibody, a combination capable of activating and directing immune attack against tumor cells. In a transplantation model of LMP1-fueled lymphomas, the NKG2D-Fc fusion proved quite capable of reducing tumor growth and prolonging survival of the recipients.

"These preclinical results suggest administration of the NKG2D-Fc fusion protein, perhaps combined with treatment with CD4+ T cells, could benefit some patients with EBV-driven lymphomas," Rajewsky said. "What we can say with certainty, though, is that LMP1 is the immune system's primary surveillance trigger following EBV infection and clearance, knowledge that we think will open doors to additional treatment options."

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