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Combination therapy boosts antiviral response to chronic infection

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A Yale-led team has identified a promising new combination immunotherapy to enhance the body's ability to fight chronic viral infections and possibly cancer.

Their study was published March 23 in *Nature Medicine*.

Viruses that cause chronic infection, such as HIV and Hepatitis B and C, are able to persist in the body despite attack from T cells, the body's main line of defense against pathogens. They persist because, over time, our T cells weaken to the point of "T-cell exhaustion." To circumvent this process, the research team—led by Susan Kaech, associate professor of immunobiology at Yale School of Medicine—investigated two pathways that cause T cell suppression.

The first pathway is triggered by prostaglandin E2 (PGE2), a lipid known to suppress the immune system's response to tumors. To explore the relationship between PGE2 and T cells, the research team studied mice with viral infections and observed that PGE2 levels increased, particularly during chronic infection. The enhanced PGE2 reduced both the number of T cells that attack the infected cells and their anti-viral functions.

As Kaech explained, T cells have receptors keeping them in balance by telling them to either stop or go. "What we have discovered is that PGE2 is another type of receptor giving a stop signal," said Kaech, who is also a member of Yale Cancer Center. In fact, when the team studied mice

lacking PGE2 receptors, or the ability to synthesize normal amounts of PGE2, T cells thrived.

The researchers next tested the combined effect of systemically reducing PGE2 while simultaneously blocking another pathway known as PD-1. In previous studies, PD-1 had also been shown to inhibit T cells. The researchers treated virus-infected mice lacking normal PGE2 production with anti-PD-1 antibodies, and observed that the combined blockade of PGE2 and PD-1 resulted in even greater increased T-cell function and enhanced viral control.

"Blocking both pathways leads to an augmentation of the antiviral response that is bigger than either treatment alone," Kaech explained.

In a final step, the researchers found they could achieve the same boost to T cells by administering celecoxib (Celebrex), a non-steroidal anti-inflammatory drug (NSAID) commonly used to manage pain. "Since these inhibitors are already in common use, we wondered if using them to decrease PGE2 signaling would also improve T-cell responses," said Jonathan Chen, first author on the study and a resident in pathology at Massachusetts General Hospital.

One important implication of the study is the potential use of NSAIDs as adjunct therapy to treat patients with chronic infections and cancer. "By administering a medicine many of us take routinely, we could potentially augment the effects of PD-1 blockade, which is showing remarkable outcomes in cancer trials," said Kaech.

More information: Prostaglandin E2 and programmed cell death 1 signaling coordinately impair CTL function and survival during chronic viral infection, *Nature Medicine*, dx.doi.org/10.1038/nm.3831

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