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Ancient anti-inflammatory drug salicylic acid has cancer-fighting properties

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Scientists from the Gladstone Institutes have identified a new pathway by which salicylic acid—a key compound in the nonsteroidal anti-inflammatory drugs aspirin and diflunisal—stops inflammation and cancer.

In a study published in *eLife*, the researchers found that both salicylic acid and diflunisal suppress two key proteins that help control gene expression throughout the body. These sister proteins, p300 and CREB-binding protein (CBP), are epigenetic regulators that control the levels of proteins that cause inflammation or are involved in cell growth. By inhibiting p300 and CBP, salicylic acid and diflunisal block the activation of these proteins and prevent cellular damage caused by inflammation. This study provides the first concrete demonstration that both p300 and CBP can be targeted by drugs and may have important clinical implications.

"Salicylic acid is one of the oldest drugs on the planet, dating back to the Egyptians and the Greeks, but we're still discovering new things about it," said senior author Eric Verdin, MD, associate director of the Gladstone Institute of Virology and Immunology. "Uncovering this pathway of inflammation that salicylic acid acts upon opens up a host of new clinical possibilities for these drugs."

Earlier research conducted in the laboratory of co-author Stephen D. Nimer, MD, director of Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, and a collaborator of

Verdin's, established a link between p300 and the leukemia-promoting protein AML1-ETO. In the current study, scientists at Gladstone and Sylvester worked together to test whether suppressing p300 with diflunisal would suppress leukemia growth in mice. As predicted, diflunisal stopped cancer progression and shrunk the tumors in the mouse model of leukemia.

"The ability to repurpose drugs that are already FDA-approved to be part of novel therapies for cancer patients is incredibly exciting," said Nimer. "We have conducted a clinical trial of salicylic acid in patients with hematologic cancers and found it to be safe. Thus, this collaborative effort to develop novel epigenetic therapies is an important next step in our journey to find more effective treatment for leukemia patients."

The scientists are now pursuing a clinical trial that will test the ability of salicylic acid to treat patients with leukemia as part of novel combination therapies. Other possible clinical applications for salicylic acid include other forms of cancer, type 2 diabetes, inflammatory diseases, and even neurodegenerative disorders, such as Alzheimer's disease. Prior Gladstone research showed that another drug containing salicylic acid prevented the accumulation of tau in neurons and protected against cognitive decline in a mouse model of dementia.

More information: Kotaro Shirakawa et al, Salicylate, diflunisal and their metabolites inhibit CBP/p300 and exhibit anticancer activity, *eLife* (2016). DOI: 10.7554/eLife.11156

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