Study of cancer-induced liver inflammation finds a promising therapeutic target

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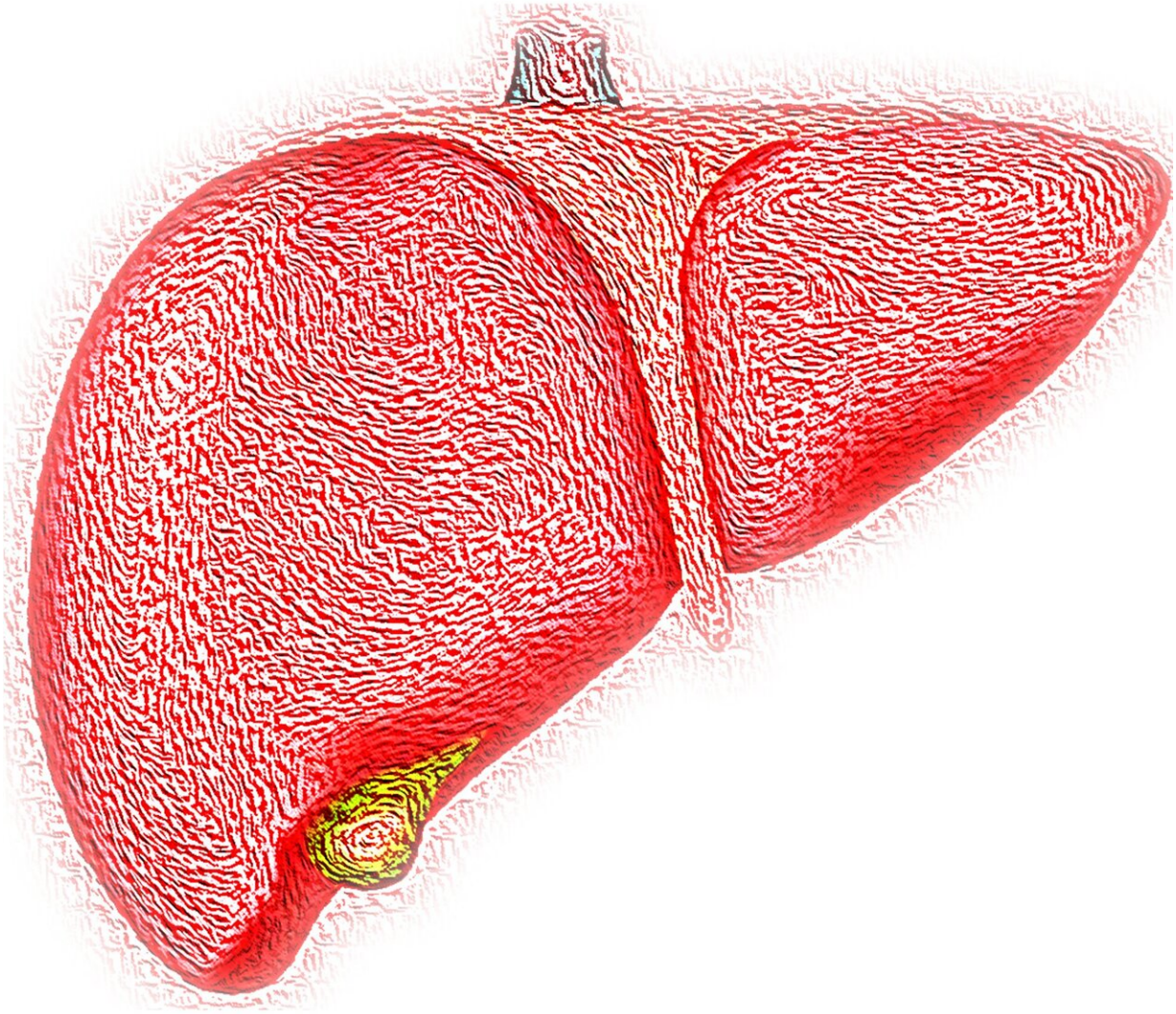

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Liver inflammation, a common side-effect of cancers elsewhere in the body, has long been associated with worse cancer outcomes and more recently associated with poor response to immunotherapy. Now, a team led by researchers from the Abramson Cancer Center and Perelman School of Medicine at the University of Pennsylvania has found a big reason why.

In their study, published today in *Nature Immunology*, the researchers discovered that cancer-induced liver inflammation causes liver cells to secrete proteins called serum amyloid A (SAA) proteins, which circulate through the body and hinder the ability of T cells—major anticancer weapons of the immune system—to infiltrate and attack tumors elsewhere.

"We want to better understand what causes cancer to resist or respond to immunotherapy to help design more effective strategies for patients," said senior author Gregory Beatty, MD, Ph.D., an associate professor of Hematology-Oncology and the director of Clinical and Translational Research for the Penn Pancreatic Cancer Research Center.

"Our findings show that liver cells—with their release of SAA proteins—effectively serve as an immune checkpoint regulating anti-cancer immunity, making them a promising therapeutic target."

The study builds on previous research from the team, including co-lead authors Meredith Stone, Ph.D., a research associate, and Jesse Lee, a graduate student, into liver inflammation in cancer: In a 2019 study, they showed how it promotes pancreatic tumor metastasis to that organ.

In 2021, researchers from the Beatty Laboratory observed that systemic inflammation, involving many of the same molecules implicated in liver metastasis, is associated with worse responses to immunotherapies in pancreatic cancer patients. The latest study was designed to investigate in more detail how liver inflammation may block the effects of these immune-boosting therapies.

First, they looked at mouse models of pancreatic cancer, measuring the amount of T-cell infiltration in pancreatic tumors—a basic indicator of anti-tumor immune activity. They found that mice with less T cell infiltration in their tumors tended to have more liver inflammation. These mice also showed stronger signs of an inflammatory signaling pathway called the IL-6/JAK/STAT3 pathway—the same one the team had implicated in liver metastasis in their 2019 study.

The researchers next showed that STAT3 activation in liver cells is associated with the reduced production of immune cells called dendritic cells, which are critical for normal T cell responses. When the scientists deleted STAT3 from liver cells, dendritic cell production and T cell activity picked up, and tumors that previously had only low T cell-infiltration developed high T cell-infiltration.

Ultimately the team found that STAT3 activation in liver cells has its dendritic cell- and T cell-suppressing effect by inducing the production of SAA proteins, which target receptors on immune cells. Deleting the SAA proteins had the same immune-restoring effect as deleting STAT3, and increased survival times and the likelihood of cures in mice that had pancreatic tumors surgically removed.

To get a sense whether the mouse model findings would translate to humans, the researchers measured SAA levels in tissue samples from patients whose pancreatic tumors had been surgically removed and found that those with low SAA levels at surgery went on to have significantly

longer survival times afterward.

"The translational findings in human patients highlight the likely clinical relevance of our discoveries in the mice," Beatty said. "Now that we've shown how liver inflammation puts up a roadblock to immunotherapy, our next step is to see if the same pathway can be targeted to reverse inflammation in patients who already have liver metastasis."

The research team is now working to set up further preclinical and eventually clinical studies of STAT3- and/or SAA-inhibiting agents as potential add-on therapies in combination with immunotherapy—for example, prior to surgery—that could improve cancer patient outcomes.

More information: Hepatocytes coordinate immune evasion in cancer via release of serum amyloid A proteins, *Nature Immunology* (2024). DOI: 10.1038/s41590-024-01820-1

Provided by Perelman School of Medicine at the University of Pennsylvania

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