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Every step you take: STING pathway key to tumor immunity

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A recently discovered protein complex known as STING plays a crucial role in detecting the presence of tumor cells and promoting an aggressive anti-tumor response by the body's innate immune system, according to two separate studies published in the Nov. 20 issue of the journal *Immunity*.

The studies, both from University of Chicago-based research teams, have major implications for the growing field of cancer immunotherapy. The findings show that when activated, the STING pathway triggers a natural immune response against the tumor. This includes production of chemical signals that help the immune system identify tumor cells and generate specific killer T cells. The research also found that targeted high-dose radiation therapy dials up the activation of this pathway, which promotes immune-mediated tumor control.

These findings could "enlarge the fraction of patients who respond to immunotherapy with prolonged control of the tumor," according to a commentary on the papers by the University of Verona's Vincenzo Bronte, MD. "Enhancing the immunogenicity of their cancers might expand the lymphocyte repertoire that is then unleashed by interference with checkpoint blockade pathways," such as anti-PD-1.

STING, short for STimulator of INterferon Genes complex, is a crucial part of the process the immune system relies on to detect threats—such as infections or cancer cells—that are marked by the presence of DNA that is damaged or in the wrong place, inside the cell but outside the

nucleus.

Detection of such "cytosolic" DNA initiates a series of interactions that lead to the STING pathway. Activating the pathway triggers the production of interferon-beta, which in turn alerts the immune system to the threat, helps the system detect cancerous or infected cells, and ultimately sends activated T cells into the battle.

"We have learned a great deal recently about what we call checkpoints, the stumbling blocks that prevent the immune system from ultimately destroying cancers," said Thomas Gajewski, MD, PhD, professor of medicine and pathology at the University of Chicago and senior author of one of the studies. "Blockade of immune checkpoints, such as with anti-PD-1, is therapeutic in a subset of patients, but many individuals still don't respond. Understanding the role of the STING pathway provides insights into how we can 'wake up' the immune response against tumors. This can be further boosted by checkpoint therapies."

The two published studies, he said, help move this approach forward.

In a series of experiments in mice, both research teams found tumor cell-derived DNA could initiate an immune response against cancers. But when tested in mice that lacked a functional gene for STING, the immune system did not effectively respond.

"Innate immune sensing via the host STING pathway is critical for tumor control by checkpoint blockade," Gajewski's team noted in their paper. They found promising drugs known as checkpoint inhibitors—such as anti PD-1 or anti PD-L1, which can take the brakes off of an immune response—were not effective in STING-deficient mice. New agents that stimulate the STING pathway are being developed as potential cancer therapeutics.

A second University of Chicago team, led by cancer biologist Yang-Xin Fu, MD, PhD, professor of pathology, and Ralph Weichselbaum, MD, chairman of radiation and cellular oncology and co-director of the Ludwig Center for Metastasis Research, found that high-dose radiation therapy not only kills targeted cancer cells but the resulting DNA damage drives a systemic immune response.

"This result unifies traditional studies of DNA damage with newly identified DNA sensing of immune responses," Fu said.

"This is a previously unknown mechanism," Weichselbaum added.

In mice that lacked STING, however, there was no therapeutic immune response. The induction of interferons by radiation and consequent cancer cell killing, they conclude, depends on STING-pathway signaling.

They did find that combining cyclic guanosine monophosphate-adenosine monophosphate (cGAMP), an earlier step in the STING pathway, with radiation, could greatly enhance the antitumor efficacy of radiation.

"This opens a new avenue to develop STING-related agonists for patients with radiation-resistant cancers," Fu said.

Provided by University of Chicago Medical Center