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Covert inflammation may trigger many forms of cancer

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A previously unidentifiable type of low-grade inflammation may explain why common anti-inflammatory drugs such as aspirin have shown promise against some types of cancer – even when patients don't display typical signs of inflammation.

A team led by researchers in the labs of Atul Butte, MD, PhD, director of the Institute for Computational Health Sciences and a professor of pediatrics at UC San Francisco, and Yinon Ben-Neriah, MD, PhD, a professor of immunology and cancer research at the Lautenberg Center of Immunology of Hebrew University Medical School in Jerusalem, identified the role of a subtle form of inflammation in human and mouse cancer cells. According to the authors, this so-called "parainflammation" may explain how a number of different forms of cancer begin.

"Understanding the initial triggers of tumor formation is one of the main challenges in cancer research," said Dvir Aran, PhD, a postdoctoral scholar in the Butte lab who was co-lead author of the new paper with Audrey Lasry, a PhD student in Ben-Neriah's lab. "We think parainflammation could be a big part of this puzzle."

The research was published online on July 8, 2016, in the open-access journal *Genome Biology*.

Common Cancer Gene Mutations 'Turn Off the Brakes'

Growing evidence over the past decade suggests that people who take a regular dose of aspirin or other non-steroidal anti-inflammatory drug (NSAID) are significantly less susceptible to colorectal cancer, breast cancer and a number of other malignancies. This relationship is mysterious, because most of the cancers that aspirin appears to prevent typically show no overt signs of inflammation.

Aran and colleagues hypothesized that there must be some sort of low-level of inflammation, undetectable with standard methods, that could interact with gene mutations to trigger cancer.

In a previous study, Ben-Neriah's lab showed that they could induce just such a state of low-level tissue inflammation in mice, which they categorized as parainflammation. They found that non-immune cells, including cells known to give rise to cancer, were able to activate some of the same genetic pathways typically used by the immune system. These pathways then interacted with p53, a regulator of cellular division, to prevent the cells from continuing to grow and divide, driving them toward a state known as cellular senescence.

But when p53 becomes mutated, as it does in many different forms of cancer, the researchers found that parainflammation loses its protective role and becomes dangerous for the tissue.

"Without p53, the brakes are off, and the previously protective energy of parainflammation can drive the formation of tumors," Ben-Neriah said.

The new study identified a specific pattern of gene expression characteristic of carcinogenic parainflammation in mice with both experimentally induced intestinal parainflammation and mutated p53. This newly identified gene-expression signature, which gave the researchers a way to detect the previously invisible phenomenon, allowed them to detect parainflammation in an array of mouse organoid

tumors, human cancer cell lines, and human tumor samples.

The new work is an important advance in understanding the link between inflammation and cancer, said Yale School of Medicine immunobiologist Ruslan Medzhitov, PhD, who coined the term parainflammation in 2008 to describe a theoretical state of low-level inflammation, which he hypothesizes could play a beneficial role in helping cells respond to tissue stress or damage. "The ability to molecularly detect parainflammation should help devise cancer treatments that are tailored to these stereotypic paths the tumors follow," he said.

Linking Parainflammation to Human Cancer Mortality

To determine the role of parainflammation in human cancers, the researchers mined The Cancer Genome Atlas (TCGA), a National Institutes of Health electronic database, and retroactively examined 6523 primary tumors of 18 different cancer types for the molecular signature of parainflammation. They found that more than a quarter of all tumor samples exhibited parainflammation, and that it was much greater in some cancer types than others: for example, more than three quarters of pancreatic adenocarcinomas exhibited parainflammation, while no kidney cancers showed significant signs of parainflammation.

The researchers found that tumor samples with the highest levels of p53 mutations also had the highest levels of parainflammation, corresponding with their hypothesis that parainflammation is permissive of p53-driven cancers. High parainflammation was particularly apparent in fast-growing cancers, such as pancreatic and bladder cancers. Within cancer types, higher rates of parainflammation were linked to increased mortality.

In line with their initial hypothesis, the researchers also showed that NSAIDs dampened parainflammation in both cancerous mouse intestinal tumors and cancer cell lines of oral, pancreatic and colorectal origin. These results suggest that the newly developed genetic signature of parainflammation could also be used to better predict which patients would benefit from an aspirin regimen following cancer surgery.

Though the results suggest aspirin may have great promise in fighting cancer, the researchers also cautioned that it is not without side effects. Aran envisions a genetic test for parainflammation, similar to existing tests for predicting breast cancer recurrence, to identify patients who would be most likely to benefit from a course of NSAIDs.

Identification of the parainflammation signature is the result of a multi-year collaboration. The work began when Aran, whose background is in bioinformatics, was a PhD student in the lab of co-author Asaf Hellman, PhD, a researcher at Hebrew University Medical School. While Lasry led the animal and cell-line experiments from Ben-Neriah's lab at Hebrew University, Aran joined Butte's lab at UCSF to take advantage of the lab's techniques for computationally analyzing public biomedical data sets.

"The public genomic data allowed us to connect the dots and draw significance from mouse models to humans," Aran said.

Butte cited the new paper as a key example of what can be done when research data is shared broadly across the research community. "This paper shows how years of research data can be reused to study cancer immunology, one of the newest areas of cancer therapeutics," he said. "More importantly, it shows the benefits of our efforts to connect research models of cancer, like cell lines and mouse models, with actual cancer therapy in humans, which remains a major challenge in cancer immunology, and one we have been specifically funded to address."

More information: Dvir Aran et al. Widespread parainflammation in human cancer, *Genome Biology* (2016). DOI: 10.1186/s13059-016-0995-z