This time, it's personal: Enhancing patient response to cancer immunotherapy

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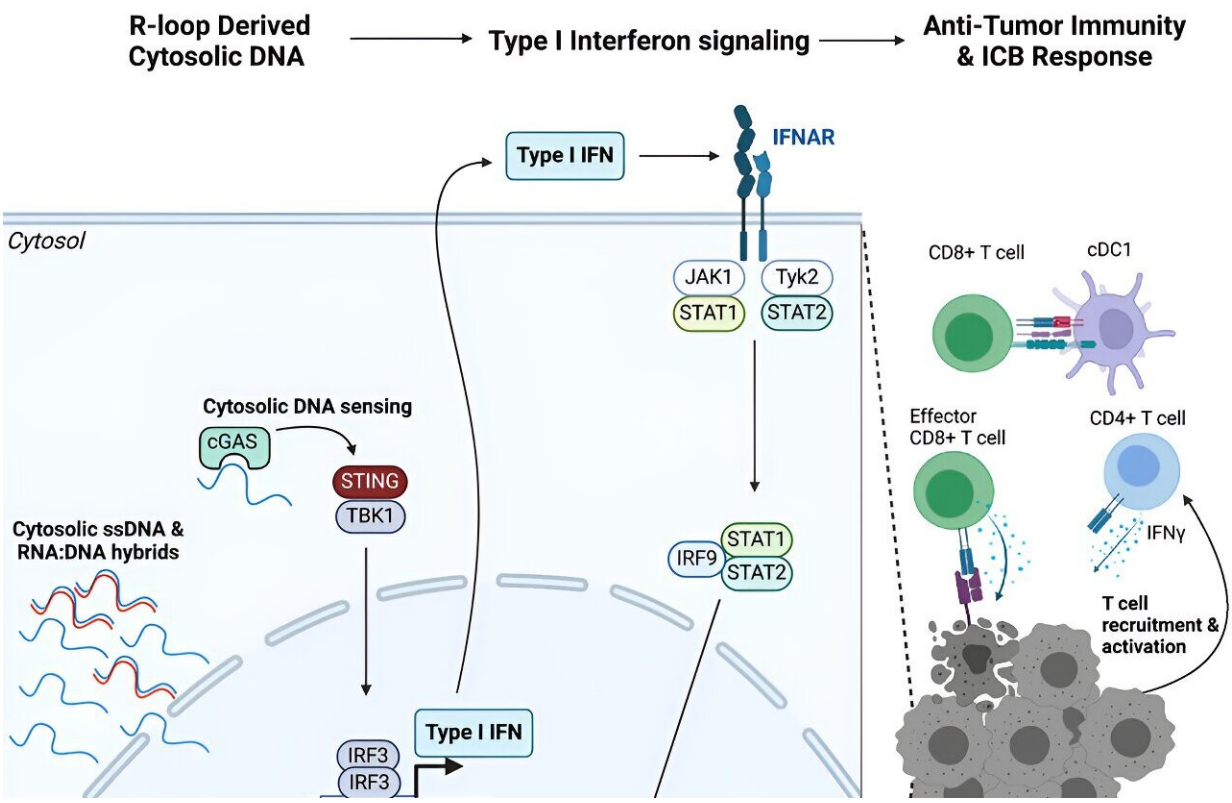

Credit: *Cell* (2024). DOI: 10.1016/j.cell.2024.04.025

Immunotherapy has revolutionized the way we treat cancer in recent years. Instead of targeting the tumor itself, immunotherapies work by directing patients' immune systems to attack their tumors more

effectively. This has been especially effective in improving outcomes for certain difficult-to-treat cancers. Still, fewer than half of all cancer patients respond to current immunotherapies, creating an urgent need to identify biomarkers that can predict which patients are most likely to benefit.

Recently, scientists have noticed that patients whose tumors have a mutation in a gene called ARID1A are more likely to respond positively to immune checkpoint blockade, a type of immunotherapy that works by keeping cancer-fighting immune cells called T cells turned "on" when they'd otherwise be turned "off."

Since this ARID1A gene mutation is present in many cancers—including endometrial, ovarian, colon, gastric, liver, and pancreatic cancers—researchers at the Salk Institute wondered how it might contribute to treatment sensitivity, and how clinicians could use this information to customize cancer treatments to each patient.

Their new study, published in *Cell*, reveals that ARID1A mutation renders tumors sensitive to immunotherapy by inviting cancer-fighting immune cells into the tumor through an antiviral-like immune response.

The researchers suggest this mutation and antiviral immune response could be used as a biomarker to better select patients for specific immunotherapies, like immune checkpoint blockade. The findings also encourage the development of drugs that target ARID1A and related proteins as a way of sensitizing other tumors to immunotherapy.

"This could really make a difference in patient outcomes from cancer treatment," says Associate Professor Diana Hargreaves, senior author of the study. "These ARID1A mutation cancer patients are already having an immune response, so all we need to do is upregulate that response using immune checkpoint blockade to help them destroy their tumors

from the inside."

While it was reported that people with ARID1A mutations responded well to immune checkpoint blockade, the exact relationship between the two remained unclear. To elucidate the mechanism behind this, Salk scientists turned to mouse models of melanoma and colon cancer with either mutated ARID1A or functional ARID1A.

The team observed a powerful immune response in all animal models with mutated ARID1A tumors but not those with functional ARID1A tumors, supporting the idea that the ARID1A mutation was, indeed, driving the response. But how did this work on a molecular level?

"We found that ARID1A plays an important role in the nucleus of keeping DNA properly arranged," says Matthew Maxwell, first author of the study and a graduate student in Hargreaves' lab. "Without functional ARID1A, loose DNA can be excised and escape into the cytosol, which activates a coincidentally desirable antiviral immune response that can be further enhanced by immune checkpoint blockade."

The ARID1A gene codes for a protein that helps regulate the shape of our DNA and maintain genome stability. When ARID1A is mutated, a microscopic chain of events analogous to a Rube Goldberg machine is set off in the cancer cell.

First, the lack of functional ARID1A leads to escape of DNA into the cytosol. Next, the cytosolic DNA activates an antiviral alarm system—the cGAS-STING pathway—since our cells are adapted to flag any DNA in the cytosol as foreign to protect us against viral infections. Finally, the cGAS-STING pathway calls on the immune system to recruit T cells into the tumor and activates them into specialized cancer-killing T cells.

With each step relying on the last, this chain of events—ARID1A mutation, DNA escape, cGAS-STING alarm, T cell recruitment—results in more cancer-fighting T cells in the tumor. Immune checkpoint blockade can then be used to ensure these T cells stay "on," supercharging them to defeat the cancer.

"Our findings provide a novel molecular mechanism by which ARID1A mutation can promote an anti-tumor immune response," says Hargreaves. "What's most exciting about these results is their translational potential. Not only can we use ARID1A mutations to help select patients for immune checkpoint blockade, but we now also see a mechanism by which drugs that inhibit ARID1A or its protein complex could be used to further enhance immunotherapy in other patients."

By outlining the mechanism by which immune checkpoint blockade is more effective for ARID1A mutant cancers, the researchers have provided cause for clinicians to prioritize the immunotherapy for patients with mutated ARID1A. The findings are a major step in personalizing cancer treatment and inspiring novel therapies that target and inhibit ARID1A and its protein complex.

In the future, the Salk team hopes its findings can improve patient outcomes across the many cancer types associated with ARID1A mutations and is set to explore this clinical translation with collaborators at UC San Diego.

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More information: Matthew B. Maxwell et al, ARID1A suppresses R-loop-mediated STING-type I interferon pathway activation of anti-tumor immunity, *Cell* (2024). DOI: 10.1016/j.cell.2024.04.025

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