A one-molecule immune evasion system: New discovery could land one-two punch against cancer

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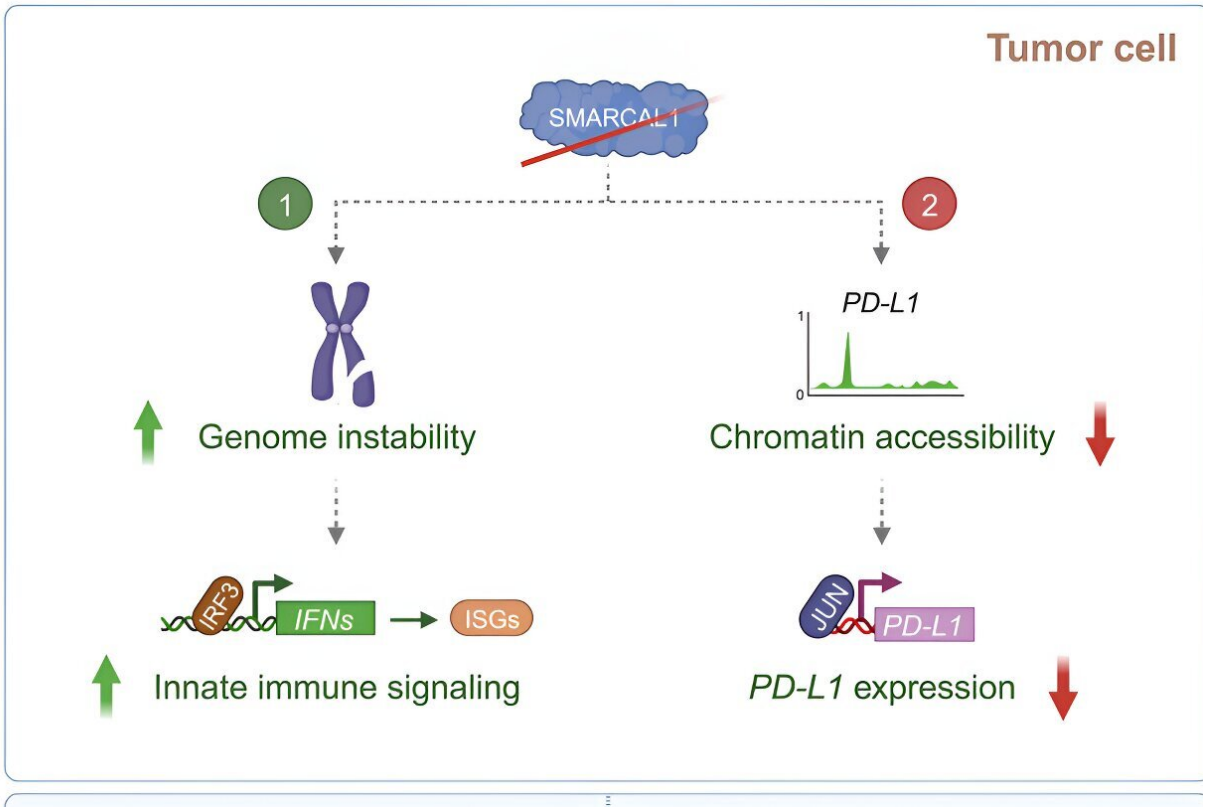

Graphical abstract. Credit: *Cell* (2024). DOI: 10.1016/j.cell.2024.01.008

A multinational team of researchers led by Columbia University has discovered that tumors can repurpose a single cellular protein to hide

themselves from the immune system in two distinct ways. Drugs targeting that protein could strike a double blow against many cancers, and make immunotherapy, one of the newest types of tumor therapies even more effective.

One of the hallmarks of cancer is genome instability, an increased tendency of the genome to acquire mutations during cell division. This genome instability in turn triggers innate immune sensors within the cell, who then recognize the bits of genetic material that leak outside the cell nucleus into the surrounding cytoplasm.

"This can be beneficial in the context of cancer treatment because it can lead to the release of chemokines that attract immune cells into the tumor," says Alberto Ciccia, associate professor of genetics and development at Columbia and a member of the Herbert Irving Comprehensive Cancer Center. The responding immune cells can then kill the cancerous cell before it gets out of control.

Unfortunately, some cancers manage to activate an immune checkpoint response, essentially a "nothing to see here" signal, to evade the initial response. Recently developed therapies, a type of immunotherapy called checkpoint inhibitors, can overcome that problem by suppressing the checkpoint response, but these immune checkpoint blockade treatments still fail in some patients.

SMARCAL1: A one-molecule immune evasion system

"We were interested to study the interplay between the innate immune response and the immune checkpoint response," says Ciccia, who is the senior author on the paper describing the new results, published in the journal *Cell*. A postdoctoral fellow in Ciccia's lab, Giuseppe Leuzzi, led the study, using a clever genetic screen to identify cellular proteins linked to both responses. "We were expecting to find factors that would

up-regulate both responses," says Ciccia. However, the team discovered a subset of proteins with opposite effects on the two responses.

One protein in particular, called SMARCAL1, seems to suppress innate immune signaling while inducing the production of immune checkpoint proteins; it's a one-molecule immune evasion system. "When you inactivate this factor, you activate the innate immune pathway, and reduce the expression of one of the immune checkpoint proteins," says Ciccia.

Working with an international team of collaborators at several other institutions, the investigators demonstrated that the two functions work through two distinct mechanisms. SMARCAL1 operates as a factor that maintains genome stability during DNA replication, and also as a transcription regulator that can induce the production of immune checkpoint proteins.

A promising target for new therapies

"By targeting this factor, we could achieve a dual benefit, increasing innate immunity and infiltration of tumors by immune cells, and limiting the ability of the cancer cells to evade the immune system through immune checkpoints," says Ciccia. The team tested that idea in a mouse model of tumor immune responses, with promising results. They also analyzed patient data from The Cancer Genome Atlas, and found that high SMARCAL1 expression correlates with poor clinical outcomes.

"We are hoping to be able to develop small-molecule inhibitors of SMARCAL1 and see whether we can recapitulate the effects that we are observing in our genetic models," says Ciccia. Though he emphasizes that many hurdles remain to turning the new findings into effective therapies, Ciccia is optimistic about the prospects. Indeed, SMARCAL1 wasn't the only potential target the team identified in the initial screen.

"These are factors that when you inactivate them, they might allow you to achieve multiple different responses that could be beneficial," says Ciccia.

More information: Giuseppe Leuzzi et al, SMARCAL1 is a dual regulator of innate immune signaling and PD-L1 expression that promotes tumor immune evasion, *Cell* (2024). DOI: 10.1016/j.cell.2024.01.008

Provided by Columbia University Irving Medical Center

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