Molecular Garbage on Tumors Makes Easy Target for Antibody Drugs

Cancer's rapid growth and messy waste disposal could mark it for destruction.

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For five decades, scientists have known about a notorious cancer-causing enzyme called SRC. But they always assumed it only appeared on the inside of cells, where it sent signals that fueled tumor growth and stayed hidden from the immune system.

But now researchers at UC San Francisco have discovered that the SRC enzyme also appears like a flag on the surface of bladder, colorectal, breast, pancreatic, and probably many other tumor cells.

As cancer cells furiously divide, they produce a lot of garbage. In healthy cells, the trash gets broken down. But in tumors, the recycling system gets overwhelmed, and the cells expel some of their trash. This pushes the SRC enzyme onto the surface of the cell, where it is visible to potential therapies, like antibodies.

Researchers targeted the SRC enzyme with antibodies that carried radioactive payloads or summoned immune cells. This killed the cancer cells, shrinking tumors in mice. The new target could apply to up to half of all tumors.

"No one thought to look for it on the outside, said Jim Wells, PhD, professor of Pharmaceutical Chemistry at UCSF and senior author of the paper, which appears in Science on March 12. "Our discovery enables us to test proven immunotherapies on this new tumor target."

SRC takes unexpected journey to cell surface

In the 1970s, UCSF's J. Michael Bishop, MD, and Harold Varmus, MD, identified the SRC gene — which contains the instructions for building the SRC enzyme — as the very first oncogene, or cancer-causing gene. It launched the modern field of cancer genetics and won the researchers a Nobel Prize in 1989.

Ever since, scientists have tried to block the SRC enzyme with drugs that slip inside cells. But the therapies have not worked well because they disable SRC enzymes in both cancerous and healthy cells that need it to function.

To understand how SRC enzymes reached the cell surface, the scientists tracked the protein in cancer cells grown in petri dishes. They found that SRC enzymes were getting caught up in the cell's overactive disposal system.

Cells normally trap waste in small sacs that they break down and reuse. But in fast-growing cancer cells, the system can become overloaded. Instead of being digested, the sacs containing waste fuse with the cell membrane and dump their contents outside the cell.

"We saw that SRC was getting swept out onto the outer membrane, where it sat exposed like a red flag," said Corleone Delaveris, PhD, first author of the paper, who did the work as a post-doctoral researcher in Wells' lab and is now at Inversion Therapeutics.

The researchers found that the SRC enzyme was present on the surface of bladder tumor cells taken from patients at UCSF, but it was not present on healthy bladder tissue or on immune cells. This suggests it is specific enough to steer cancer-killing antibodies to the right target.

In collaboration with UCSF professor of Radiology Michael Evans, PhD, the team aimed experimental radioactive antibodies at the SRC enzyme in mice that had been implanted with human tumor cells, and they confirmed that these antibodies accumulated in the cancer. They also engineered antibodies to help immune cells recognize and kill human cancer cells in mice.

UCSF has licensed the antibodies and related molecules to Inversion Therapeutics to explore their therapeutic potential.

"We went all the way from the discovery to developing two preclinical therapies that target SRC — and they worked," Wells said. "It's truly exciting."

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