New paradigm *for immunotherapy*

When the immune system detects a disruption of the status quo—an injury, an infection—it sends T-cells and B-cells to overpower the invader. But cancer cells can avoid these protectors by sending out chemical signals that lull, confuse, or even stop the immune response.

Researchers have recently succeeded in countering this trickery with drugs called checkpoint inhibitors. The inhibitors block the cancer cells' misleading signals, enabling the immune system to wake up and fight the invaders. These new immunotherapies can be miraculously effective against certain cancers with specific biomarkers, most notably PD-1/PD-L1.

That's very good news for some cancer patients. Unfortunately, many cancers—including brain, breast, ovarian, pancreatic, and colon—do not respond to current checkpoint inhibitors. Among all cancer patients, only about 14 percent are helped by the new immunotherapies. In some cases, a strong initial response fades away as the cancer develops resistance to the inhibitor.

Two scientists at Yale Cancer Center are developing a new paradigm for immunotherapy. It could radically improve and expand current approaches by moving beyond checkpoint inhibitors that target specific biomarkers in a few types of cancer.

"This approach is not the next anti-PD-L1," said Carla Rothlin, PhD, Dorys McConnell Duberg Professor of Immunobiology and Pharmacology and Howard Hughes Medical Institute Faculty Scholar. "It's a completely different way of thinking about how to increase anti-tumor responses from the immunological side."

"The concept evolved out of our studies of the fundamental principles that regulate the immune response against viruses, bacteria, and so on," added Sourav Ghosh, PhD, Associate Professor of Neurology and of Pharmacology. "Now we are applying this fundamental understanding to cancer. If we can improve the anti-tumor immune response, that should be applicable to many types of cancer, not just lung cancer or colon cancer."

Current immunotherapies work by re-activating T-cells that have been put to sleep. T-cells are specialists trained to recognize and attack specific antigens. Their narrow focus is their strength. But cancer cells exploit this specialization by emitting a signal that prevents a T-cell from reacting against its particular target. When a checkpoint inhibitor blocks the false signal, T-cells wake up and attack. T-cells, like B-cells, are part of the adaptive immune system.

Drs. Rothlin and Ghosh want to move upstream of T-cells, beyond the adaptive immune system, to the ultimate command center—the innate immune system. It's older and more primitive, and it's primary. It activates the adaptive immune system and trains T-cells what to do and where to go. The innate immune system, like the adaptive immune system, contains checkpoints that regulate the immune response. Drs. Rothlin and Ghosh think these checkpoints can be manipulated to stimulate a greater array of T-cells into hyperactivity and thus boost the overall immune response to cancer, irrespective of a tumor's type or location.

It's often said that immunotherapy "takes the brakes off of T-cells." Dr. Rothlin uses a different image to illustrate what she and Dr. Ghosh have in mind. "Imagine that the anti-tumor response is an army," she said. "Your T-cells are the soldiers at the site of the battle, the tumor. But the soldiers are tired or don't have weapons. Current immunotherapies make the soldiers better. But what if you don't have any soldiers at the battle site?" That is, some tumors don't have T-cells, so there are no soldiers to be activated by current immunotherapies. "So we go further upstream," continued Dr. Rothlin, "to your innate immune response,

which makes sure that soldiers get the right instructions and the right weapons and are transported to the right place to kill the cancer cells."

"The innate immune cells train the T-cells," added Dr. Ghosh. "We are trying to make the trainers better. The way we do that is that there are molecules in the trainers that are brakes, and some of these molecules are receptor tyrosine kinases. We can generate small molecule inhibitors or even use biologics to inhibit the inhibitors—to break the brakes. That makes the trainers hyperactive, so they train the T-cells better to get to the site of the tumor."

If T-cells could be sent into the large group of tumors that lack them, the effect would be profound. Tumors without T-cells cannot mount an immune response and are not affected by immunotherapies that depend on T-cells. Such tumors can be referred to as "cold" compared to "hot" tumors with active T-cells. Drs. Rothlin and Ghosh are comparing cold and hot tumors, looking for mechanisms and pathways in the innate immune system that can be manipulated to direct T-cells to where they are needed, making cold tumors hot with cancer-fighters.

"That's a big need that we want to fill," explained Dr. Ghosh.

Their research is focused on a group of receptor tyrosine kinases called TAM (TYRO3, AXL, and MERTK) that help regulate the immune system's response to inflammation. TAMs gradually decrease the inflammatory response and assist in tissue repair.

"That's important when you want to survive an infection," said Dr. Rothlin, "but it turns out that in cancer, this resolution also turns off the immune response. But if you inhibit the TAMs, you release the brake of the innate immune response and mount a much stronger response to the cancer."

They have also learned that some tumor cells overexpress TAMs to drive growth, so inhibiting them might also damage the tumors themselves. "That's almost a bonus," said Dr. Ghosh, "because you can simultaneously boost the immune response and also target the tumor. But our focus is the immune system because that's more widely applicable."

Another bonus, he continued, is that going upstream to the adaptive immune system offers access to cell types that don't occur in the adaptive immune system, such as natural killer cells.

The scientists are currently studying this in mouse models. Once they are satisfied with their understanding of the basic biology, they will hand off their findings to drug developers who can design the inhibitors.

They hope that the result of their work will be immunotherapies that are more powerful, sustained, effective, and broadly applicable. "We are super excited," said Dr. Ghosh. "We are attacking cancer in many ways, not just with one weapon or one target."

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