In clinical trial, scientists hope to train immune system to attack cancer

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(Medical Xpress)—Training our immune systems to fight cancer is an appealing prospect. Why wouldn't we want to launch our own internal army against one of our most-hated foes? But the process is a bit like learning to spot a single traitor in a stadium full of innocent bystanders. After all, at the most basic level, cancer cells are simply our own tissue making bad choices about how to grow and spread.

And there's the rub: The immune system's ability to protect against foreign invaders like bacteria or viruses hinges on its ability to differentiate them from our body's own tissues, to which it must not react (a phenomena called immune tolerance). So it's a catch-22 when researchers attempt to prime B and T cells, macrophages and all of our many other immune cells to wipe out cancer cells. Often, what seems to be a promising response is dulled over time as immune cells called T regulatory cells, or Tregs, recognize the cancerous tissue as "self" and call off the attack.

Now, Ronald Levy, MD, professor of oncology at the School of Medicine and pioneer in the field of cancer immunotherapy, and postdoctoral scholar Aurelien Marabelle, MD, have shown it's possible to perpetuate an anti-cancer immune response in laboratory mice by blocking the activity of Tregs with specific antibodies injected directly into the tumor site. The work, which has resulted in the recent initiation of a phase-1 and -2 clinical trial in humans, was published May 24 in the *Journal of Clinical Investigation*.

"These monoclonal antibodies target and eliminate T regulatory cells mixed in with the tumor that dampen the immune response against it," Levy said. "With these negative regulatory cells out of the way, the killer T cells of the immune system are unleashed to seek and destroy the cancer cells wherever they are in the body, including in the brain."

Levy and his colleagues studied laboratory mice in which human lymphoma cells had been implanted under the skin or injected into the blood. Once tumors were established, they treated the mice with a combination of two highly specific, or monoclonal, antibodies that recognize and bind to two molecules on the surface of the Treg cells.

Although some of these anti-Treg antibodies have already been approved for use in humans (one, ipilimumab, marketed as Yervoy, is currently used to treat metastatic melanoma), they can have negative side effects. That's because they're injected in fairly large doses into a patient's blood stream, inhibiting the Tregs not just in the tumor, but throughout the body. As a result, even normal, healthy tissues is subject to attack from the immune system.

Levy and his colleagues found that injecting much smaller amounts of the anti-Treg antibodies directly into the animals' tumors effectively targeted the Treg cells. What's more, coupling this treatment with the local injection of a molecule known to rev up the anti-tumor immune response causes an effect that ripples throughout the body to other organs and the central nervous system.

"We have found in animal experiments that by injecting certain monoclonal antibodies into cancer in one place in the body we can trigger the immune system to fight cancer throughout the body," Levy said. "This result has the potential to change the way we use the immune system to treat cancer."

The researchers saw that the triple treatment—the two anti-Treg antibodies plus an injection of a molecule to stimulate the anti-cancer immune response—in one tumor site was highly effective even in mice with distant metastases. The animals lived longer and were resistant to a second administration of the cancer cells.

The ability of the treatment to induce a response in distant tumor sites is particularly interesting, say the researchers, because some sites in the central nervous system are very difficult to target or reach with conventional therapies. Holbrook Kohrt, MD, PhD, assistant professor of oncology, will now be leading a parallel phase-1 and -2 clinical trial in patients with melanoma, lymphoma and colon cancers.

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