A new method for fighting 'cold' tumors

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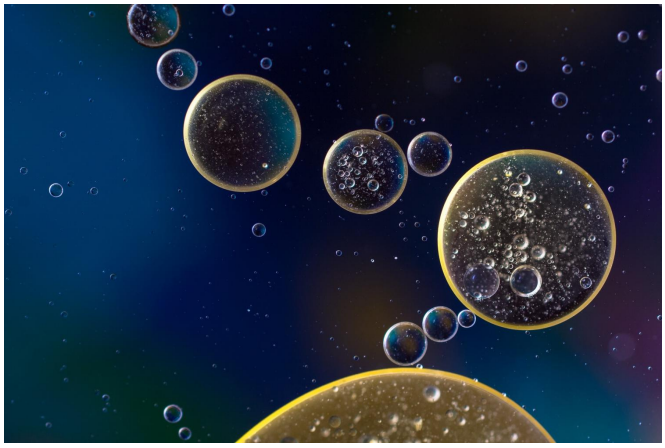

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Not all cancerous tumors are created equal. Some tumors, known as "hot" tumors, show signs of inflammation, which means they are infiltrated with T cells working to fight the cancer. Those tumors are easier to treat, as immunotherapy drugs can then amp up the immune response.

"Cold" tumors, on the other hand, have no T-cell infiltration, which means the immune system is not stepping in to help. With these tumors, immunotherapy is of little use.

It's the latter type of tumor that researchers Michael Knitz and radiation oncologist and University of Colorado Cancer Center member Sana Karam, MD, Ph.D., address in new research published this week in the *Journal for ImmunoTherapy of Cancer*. Working with mouse models in Karam's specialty area of head and neck cancers, Knitz and Karam studied the role of T cells in tumor treatment.

"What we found is that the cells that normally tell the T cell, 'Hey, here's a tumor—come and attack it,' are being silenced," Karam says.

She and her team found that regulatory T cells (Tregs), a specialized T cell type that suppresses immune response, are essentially telling the T cells to stop fighting the cancer.

"Tregs normally serve as an important balance in a healthy immune system," Knitz says. "They prevent autoimmune disease and put the brakes on the T cells when needed. However, in many tumors, Tregs are too numerous or overly suppressive, bringing the T cell response to a halt."

Using medication that deactivates the Tregs can help boost the immune response in patients with cold tumors, the researchers found, as can radiation treatment that causes enough injury that the immune cells known as dendritic cells work to put the regular T cells into fight mode.

But this is only part of the story. The T cells need to know what to attack. "You need the radiation to create injury and bring in the immune cells so that the tumor can be recognized and targeted," says Karam, also an associate professor of radiation oncology at the University of Colorado School of Medicine. "That way, the dendritic cells trigger the immune system to produce a lot of T cells, similar to what a vaccine does. Those T cells then go back to the tumor to kill cancer cells. The pieces are already in place; they just need the proper signals. Activating the dendritic cells is a crucial step in allowing radiation to heat up these cold tumors."

Importantly, Karam and her team, which includes post-doctorate fellow Thomas Bickett, found that the radiation must be administered in a specific way.

"A specific dosing is needed," Karam says. "You have to pulse it. You can't just give one dose. You have to give it again and combine it with things that remove the suppression—the Tregs—while simultaneously keeping those antigen-presenting dendritic cells active and on board."

Karam says the next step in her research is clinical trials she hopes will eventually change the

treatment paradigm from surgery and weeks of chemotherapy and radiation to just three sessions of radiation and immunotherapy, then surgery. She is driven to change the standard of care for cold tumors, she explains, because of the horrendous effects they have on patients.

"These tumors resemble those in patients who are heavy smokers," she says. "They're very destructive to bone and muscle, infiltrating the tongue, jaw, gum, and lymph nodes. It's horrible. We have very high failure rates with them, and the treatment often involves removing the tongue and weeks of radiation and chemotherapy, only for the patient to fail. I'm confident that we can do better for our patients."

More information: Michael W Knitz et al, Targeting resistance to radiation-immunotherapy in cold HNSCCs by modulating the Treg-dendritic cell axis, *Journal for ImmunoTherapy of Cancer* (2021). DOI: 10.1136/jitc-2020-001955