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Dialing back treg cell function boosts the body's cancer-fighting immune activity

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By carefully adjusting the function of crucial immune cells, scientists may have developed a completely new type of cancer immunotherapy—harnessing the body's immune system to attack tumors. To accomplish this, they had to thread a needle in immune function, shrinking tumors without triggering unwanted autoimmune responses.

The new research, performed in animals, is not ready for clinical use in humans. However, the approach, making use of a key protein to control immune function, lends itself to further study using candidate drugs that employ the same mechanisms.

"This preclinical study demonstrates proof of principle that using a drug to regulate the function of a special, immunosuppressive subset of so-called T-regulatory (Treg) cells safely controls tumor growth," said study leader Wayne W. Hancock, M.D., Ph.D., of the Division of Transplant Immunology at The Children's Hospital of Philadelphia (CHOP). "It really moves the field along towards a potentially major, new cancer immunotherapy."

Hancock and colleagues published the study today in *Nature Medicine*.

"There's a basic paradox in immunology: why doesn't the immune system prevent cancer in the first place?" said Hancock. The answer is complicated, he adds, but much of it involves a delicate balancing act among elements of the immune system: while immunity protects us

against disease, an overly aggressive immune response may trigger dangerous, even life-threatening, autoimmune reactions in which the body attacks itself.

In the current study, Hancock focused on a subtype of immune cells called Foxp3+ Tregs, for short. Tregs were already known to limit autoimmunity, but often at the cost of curtailing immune responses against tumors. "We needed to find a way to reduce Treg function in a way that permits antitumor activity without allowing autoimmune reactions," he said.

Hancock's group showed that inhibiting the enzyme p300 can affect the functions of another protein, Foxp3, which plays a key role in controlling the biology of Tregs. By deleting the gene that expresses p300, the researchers safely reduced Treg function and limited tumor growth in mice. Notably, they also achieved the same effects on p300 and Tregs in mice by using a drug that inhibits p300 in normal mice.

Hancock will pursue further investigations into targeting p300 in immunotherapy. The preclinical findings offer encouraging potential for being translated into the clinic, said Hancock, who added that pharmaceutical companies have expressed interest in researching this approach as a possible cancer therapy.

The antitumor study, down-regulating Treg function, is the flip side of another part of Hancock's Treg research. In a 2007 animal study, also in *Nature Medicine*, he increased Treg function with the goal of suppressing the immune response to allow the body to better tolerate organ transplants. In the current study, decreasing Treg activity permitted the immune system to attack an unwelcome visitor—a tumor. In both cases, he relied on epigenetic processes—using groups of chemicals called acetyl groups to modify key proteins—but in opposite directions. "This is the yin and yang of immune function," he added.

More information: Yujie Liu et al., "Inhibition of p300 impairs Foxp3+ T regulatory cell function and promotes antitumor immunity," *Nature Medicine*, published online Aug. 18, 2013. doi.org/10.1038/nm.3286