

'Eat me' signal whets appetites for tumor-devouring dendritic cells

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By changing the mouse model they use to study how the immune system responds to cancer, a team of researchers hopes to shift the focus for one emerging form of cancer immunotherapy back to the standard approach—relying on antigen-presenting dendritic cells—and away from the current upstart, macrophages.

Although [macrophages](#), like [dendritic cells](#), also take up antigens, they are more likely to degrade them than present them to T [cells](#). The recent emphasis on macrophages stems, in part, from promising, but problematic, efforts to develop an effective macrophage-driven T cell-mediated immunotherapy.

In a paper published online Aug. 31, by *Nature Medicine*, researchers report that using a monoclonal antibody called anti-CD47, which blocks the "don't-eat-me" signal on [malignant cells](#), to treat mice with an intact [immune system](#) provides a much more lifelike way to study and develop an immune-based cancer therapy.

The paper also suggests ways to improve the relative timing of the combination of anti-CD47 antibodies and chemotherapy.

"Our results point to a new and more personalized strategy to modulate the tumor microenvironment," said study director Yang-Xin Fu, MD, PhD, professor of pathology at the University of Chicago. "Tumor rejection requires both innate and adaptive immune responses against [tumor cells](#). We think our approach, along with further investigation of scheduling and dosing, could improve survival and quality of life for patients battling advanced cancer."

The shift of focus from one set of scavengers, dendritic cells, to another, macrophages, was initiated by ground-breaking studies at Stanford University. A team there, led by stem-cell pioneer Irving Weissman, MD, demonstrated that many aging cells, and most cancer cells, display a protein called CD47 on the cell surface.

The presence of CD47 protects these cells; it instructs circulating macrophages not to devour them. But as cells age or evolve, many slowly lose their protective CD47 and the macrophage system can confront them.

The Stanford investigators found that when they used antibodies against CD47 to negate this "don't-eat-me" signal, macrophages were able to chew up many of these [cancer cells](#).

In their *Nature Medicine* paper, Fu and colleagues point out that these initial studies relied on human tumors transplanted into mice. The mice also had significant immune defects. They argue that a more appropriate model, transplanting tumors from mice into genetically identical hosts with fully intact immune systems, would be more informative and clinically relevant.

When they used such mice to test their approach, they found that the bulk of therapeutic effect from CD47 blockade relied not on macrophages but on dendritic cells. These triggered the secretion of interferons, an immune system activator, and the priming of CD8+ T cells. They note that anti-CD47-mediated tumor rejection "requires both innate and adaptive immune responses."

Using their more life-like model, the Chicago researchers show:

- Dendritic cells are more potent than macrophages at priming killer T cells.
- Dendritic cells cause the immune stimulant, type-1 interferon, to boost adaptive immunity.
- The STING pathway (stimulator of interferon genes), activated by dendritic cells, is "absolutely essential for the antitumor effect of anti-CD47 therapy."
- A single treatment with chemotherapy before, rather than after, CD47 treatment appeared to be most effective.

"Our data clearly demonstrate in an immune-competent, syngeneic host that the therapeutic effect of CD47 blockade requires functional dendritic cells and T cells," they conclude.

More information: CD47 blockade triggers T cell–mediated destruction of immunogenic tumors, [DOI: 10.1038/nm.3931](https://doi.org/10.1038/nm.3931)

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