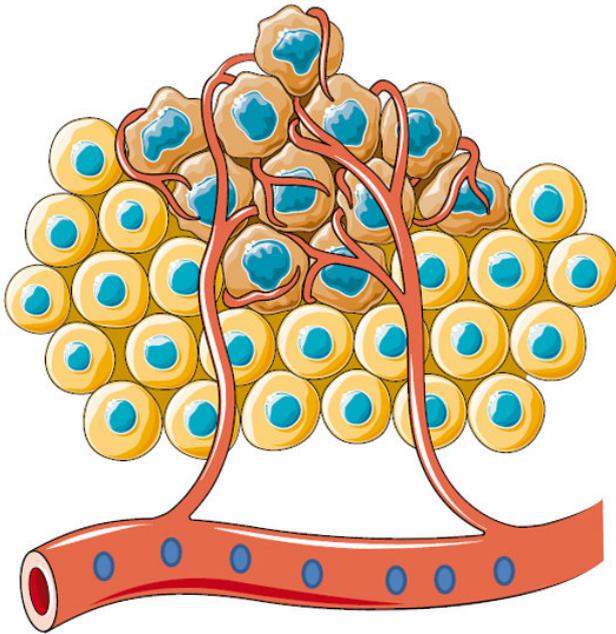


How a poorly explored immune cell may impact cancer immunity and immunotherapy

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Tumor cells secrete lactate (blue dots) that makes contact with naïve T cells and contributes to FIP200 expression that disables the balance between pro-apoptotic and anti-apoptotic gene expression in the cells. Credit: Xia et al., *Sci. Immunol.* 2, eaan4631 (2017)

The immune cells that are trained to fight off the body's invaders can become defective. It's what allows cancer to develop. So most research has targeted these co-called effector T-cells.

But a new study takes a step back and considers: What if the problem isn't with the effector T-cells but starts higher up the cellular chain?

And so researchers looked at naïve T-cells - a type of immune cell that hasn't yet been triggered to fight. Naïve T-cells differentiate into the fighter

effector T-cells.

"People didn't realize the problem may not only be directly from the effector cells themselves, but may also stem from a defect in the naïve cells. We found naïve cells already have a problem in patients who have cancer. If the naïve cells are functionally impaired, the [effector cells](#) cannot be healthy," says study author Weiping Zou, M.D., Ph.D., the Charles B. de Nancrede Professor of Surgery, Pathology, Immunology and Biology at the University of Michigan.

Naïve T-cells are not well understood in cancer, in part because the effector T-cells have direct control over [tumor](#) immunity. So that's where researchers have focused their attention. Also, naïve T-cells are rare in the tumor microenvironment - the traditional battlefield between cancer and [immune cells](#).

The new study, published in *Science Immunology*, finds that tumor metabolism impacts naïve T-cells. The [tumor cells](#) use a lot of glucose. When the glucose is metabolized, it produces lactate - and lactate turns out to be very bad for naïve T-cells. Once the tumor produces a certain level of lactate, it causes damage to the naïve T-cells, including cell death.

Currently, efforts to predict response to [cancer](#) immunotherapy focus on memory and effector T-cells. The new research suggests another path.

"Yes, you do see problems in effector T-cells, but you have to keep in mind that to begin with, the naïve T-cells are functionally impaired by the tumor metabolism," Zou says.

Researchers will look for ways to manipulate the metabolism to try to recover the function of the naïve T-cells in the hopes that it can make

immunotherapy more effective. Some early phase clinical trials are testing a way to target the lactate pathway. Researchers hope this could provide a rationale for combining immunotherapy with a therapy to regulate metabolism.

"When you have more healthy naïve T-cells to begin with, hopefully you will get more healthy effector T-cells, which will overcome some of the resistance we see with immunotherapy," Zou says.

More information: H. Xia et al., "Suppression of FIP200 and autophagy by tumor derived lactate promotes naïve T cell apoptosis and affects tumor immunity," *Science Immunology* (2017).

[immunology.sciencemag.org/look ...
6/sciimmunol.aan4631](https://immunology.sciencemag.org/look.../6/sciimmunol.aan4631)

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