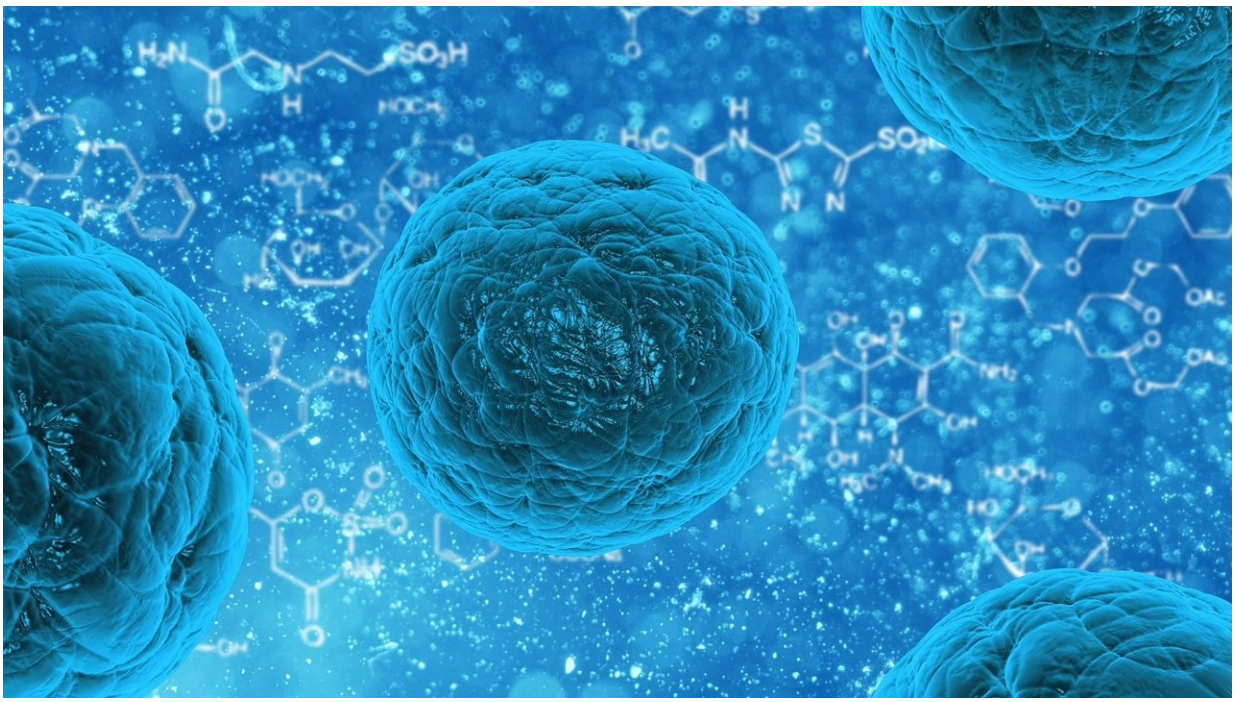
Researchers find that CD8 T cells remain in the bloodstream, do not enter organs and other tissues

December 11 2020



Credit: CC0 Public Domain

Immune cells called "killer T cells," also known as cytotoxic or cytolytic CD8 T cells, normally stay in the bloodstream and do not enter organs and other tissues, according to a new study from scientists in the Perelman School of Medicine at the University of Pennsylvania.

The discovery, published in *Cell*, may help resolve many conundrums in immunology, including mysteries with medical relevance—for example, why recently developed cancer therapies using modified killer T cells fail to work well against solid tumors, and why the AIDS-causing virus HIV, which is considered highly vulnerable to killer T cells, seems able to evade these immune cells indefinitely by hiding outside the bloodstream.

"This finding tells us that killer T cells normally do not migrate out of the bloodstream," said Michael Betts, Ph.D., Professor of Microbiology at Penn Medicine. "Now that we know this, we can, for example, start to engineer better solutions that employ these powerful cells."

Killer T cells have long been considered the main battle tanks of the immune system. Each killer T cell has a receptor that, like an antibody receptor, can recognize a specific target. Killer T cells are called "cytotoxic" or "cytolytic" because they possess special molecular weapons that enable them to directly attack and destroy other cells displaying targets they recognize, for example, a virus-infected cell or even a cancerous cell.

Traditionally immunologists have believed that killer T cells circulate more or less continuously from the bloodstream into tissues and then back again, ever-ready to destroy targets they recognize anywhere in the body. But this view is based mainly on studies in animals. Human studies of T cells have mostly been confined to sampling these cells from the bloodstream. In this study, Betts and his team were able to take a broader look at T-cell movement in the body by analyzing samples—from people as well as macaque monkeys—of both blood and lymph.

Lymph is a whitish, watery fluid that flows from various tissues and organs in the body into the bloodstream via a network of vessels and nodes called the lymphatic system. T cells and other immune cells that

move from the bloodstream into tissues flow back to the bloodstream via this lymphatic route. The scientists sampled from a part of the lymphatic network called the thoracic duct, through which most lymph flows.

In this way, the researchers for the first time were able to catalogue the detailed molecular characteristics of T cells sampled from thoracic duct lymph, comparing them to T cells collected from the bloodstream in the same subjects.

Of the many findings in the study, the most striking was that the CD8 T cells present in lymph—the CD8 T cells that had moved through organs and other tissues outside the bloodstream—generally were not the classic killer T cells that are abundantly present in blood. Virtually all of the CD8 T cells in lymph did not have a direct cell-killing capability; instead, they seemed equipped for producing chemicals called immune cytokines that summon other elements of the immune system. These non-cytotoxic CD8 T cells also seemed to recognize the same targets as their killer T cell counterparts in blood, hinting that these two sets of CD8 T cells develop from the same progenitor cells to have distinct but complementary roles in fighting the same pathogens.

The discovery is significant for basic immunology, the researchers say, because it extends the understanding of how these important immune cells work, and overturns the traditional assumption that killer T cells circulate from the bloodstream into tissues and back again. And while much remains to be learned, for example, about the role of the non-cytotoxic CD8 T cells that migrate through tissues beyond the bloodstream, the findings appear to have important implications for medicine.

One implication concerns CAR T-cell therapy for cancer, which uses engineered killer T cells from patients to home in on and kill their cancerous cells. CAR T-cell therapies have had significant successes

against leukemias and other cancers accessible via the bloodstream, but so far little success against solid tumors in organs and tissues outside the bloodstream. A possibility suggested by the new findings is that CAR-T cells could be further engineered to venture beyond the bloodstream and attack solid tumors effectively.

"It may be that cytotoxic T cells put into the blood cannot access tumors in the lungs or intestines or breast, for example, because they don't have the right properties to do so," Betts said.

Similarly, according to Betts, the new findings may help explain why some viruses, such as HIV, can elude the immune system indefinitely while infecting organs and tissues outside the bloodstream.

At the same time, the findings could lead to better ways of stopping killer T cells from inappropriately migrating outside the bloodstream and doing harm to the body, for example in the immune rejection of transplanted organs, and in autoimmune disorders that are caused in part by inappropriate T cell activity, such as multiple sclerosis, type 1 diabetes, and rheumatoid arthritis.

Betts and his colleagues are now following up with further research in several directions. In one project they will examine how to re-engineer CAR-T cells to migrate better to solid tumors. In another they will try to discover how maturing CD8 T cells become either bloodborne cytotoxic CD8 cells or tissue-transiting, non-cytotoxic CD8 T cells.

More information: Marcus Buggert et al. The Identity of Human Tissue-Emigrant CD8+ T Cells, *Cell* (2020). DOI: 10.1016/j.cell.2020.11.019

Provided by University of Pennsylvania