New "blueprint" of exhausted T cell lifespan could help build better immunotherapies

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E. John Wherry, PhD. Credit: Perelman School of Medicine at the University of Pennsylvania

Mapping out the lifespan of the immune cells that lose steam in the body's fight against cancer is giving Penn Medicine researchers a better understanding of how future immunotherapies could reinvigorate them to help attack disease.

In a new study published in Cell Press, the lab of E. John Wherry, Ph.D., chair of the department of Systems Pharmacology and Translational Therapeutics and director of the Penn Institute of Immunology in the

Perelman School of Medicine at the University of Pennsylvania, for the first time showed four key stages of so-called "exhausted" T cell development and the molecular mechanisms driving the transition from one stage to the next.

Past studies, including some conducted at Penn, have identified various developmental stages of exhausted T cells, but none have produced a picture as full as this study. More advanced genomic sequencing, and lineage tracing at a higher resolution (a lab technique to study essentially the "family tree" of cells in vivo) using melanoma mouse models and human tumor samples provided much more detail.

The immune system struggles to defeat cancer because many of the T cells that leap into action end up exhausted, rendering them ineffective against disease. That path to exhaustion is a crucial one that researchers aim to understand.

"When we look at cancer in patients, we're just capturing a snapshot of their biology, so we're often not sure what stage of exhausted T cell development they're in. This hampers our ability to target the cells and coax them in a different direction," said Wherry, the senior author of the paper. "Here, we've laid out a developmental blueprint and identified and dissected the underlying molecular and transcriptional switches that initiate these steps along the way."

The four stages of development include: stem-cell like progenitor cells that remain dormant; progenitor cells that proliferate and circulate; "intermediate" cells that circulate and are slightly cytotoxic; and terminally exhausted cells. The transcriptional and epigenetic factors, including the proteins TCF-1, TOX, and T-bet, driving the developmental stages were also identified at each stage as T cells barreled toward exhaustion.

Knowing the intricate step-by-step process of T cell differentiation opens up more opportunities for immunologists to exploit them using cellular therapies. That could include, for example, rewiring T cells at one stage to "stop," so they don't advance to the next stage, or manipulating later stage T cells into early ones that possess more fighting power. Using a series of genetic modifications of the T cells, the researchers showed they could give rise to T cells at the different stages.

The blueprint could be also utilized to study how current interventions interact with exhausted T cells, which may reveal more about why some therapies are successful, while others are not.

This latest study builds off of several publications over the last year from Wherry's lab, including a study in the journal *Immunity* that uncovered the early makings of an exhausted T cell and in *Nature* that showed the role of the protein TOX as the key regulator of exhaustion.

Next, the researchers plan to study external factors in the surrounding environment to see how they may affect the lifespan of these T cells, such as cytokines, which are proteins also released by the immune system that regulate immunity and inflammation.

"We need to better understand the developmental biology so that when we profile tumor biopsies or blood of patients, we can actually reflect that data back onto a more comprehensive map, even if it's from a preclinical model," Wherry said. "Because now we're only getting a piece of the information, and we need the full picture."

More information: Jean-Christophe Beltra et al. Developmental Relationships of Four Exhausted CD8+ T Cell Subsets Reveals Underlying Transcriptional and Epigenetic Landscape Control Mechanisms, *Immunity* (2020). DOI: 10.1016/j.immuni.2020.04.014

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