Transition to exhaustion: Clues for cancer immunotherapy

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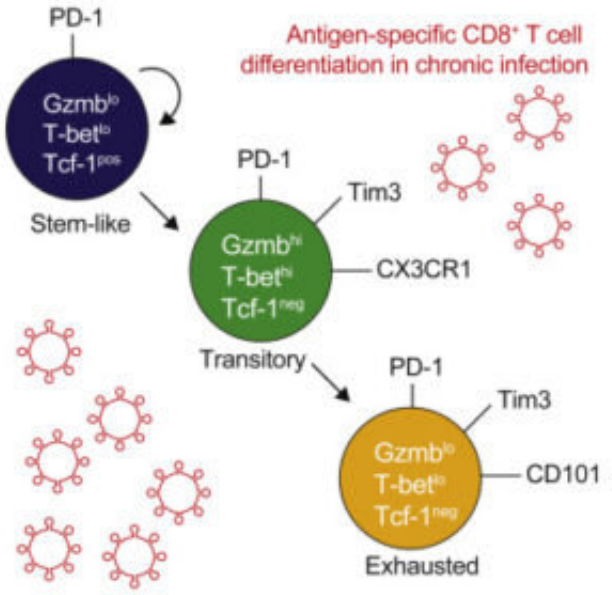


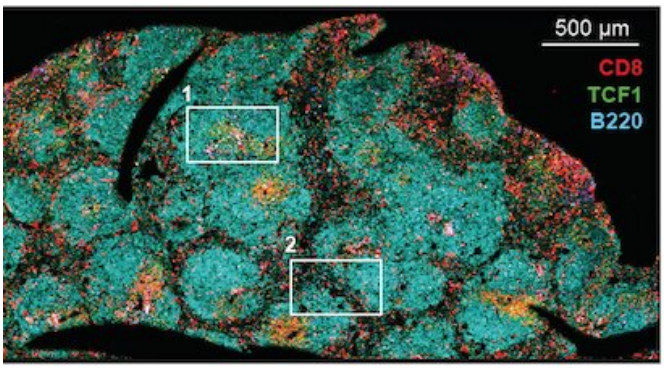
Credit: Emory University

Research on immune cells "exhausted" by chronic viral infection provides clues on how to refine cancer immunotherapy. The results are scheduled for publication in *Immunity*.

Scientists at Emory Vaccine Center, led by Rafi Ahmed, Ph.D., have learned about exhausted CD8 T cells, based on studying mice with chronic viral infections. In the presence of persistent virus or cancer, CD8 T cells lose much of their ability to fight disease, and display inhibitory checkpoint proteins such as PD-1 on their surfaces. PD-1 is targeted by cancer immunotherapy drugs, such as pembrolizumab and nivolumab, which allow CD8 T cells to regain their ability to attack and kill infected cells and cancers.

Those drugs are now FDA-approved for several types of cancer, yet some types of tumors do not respond to them. Studying exhausted CD8 T cells can help us understand how to better draw the immune system into action against cancer or chronic infections.

In previous research, Ahmed's lab found that exhausted cells are not all alike, and the diversity within the exhausted T cell pool could explain variability in responses to cancer immunotherapy drugs. Specifically, they observed that a population of "stem-like" cells proliferated in response to PD-1-blocking drugs, while a more differentiated population of exhausted cells stayed inactive. The stem-like cells are responsible for maintaining the exhausted T cell population, but cannot kill virus-infected or tumor cells on their own.



In the spleens of mice with chronic viral infections, a group of T cells is ready to expand when PD-1-blocking agents are introduced. From Im et al Nature (2016).

The current paper defines a transitional stage in between the stem-like and truly exhausted cells. The truly exhausted cells are marked by a molecule called CD101, and are unable to migrate to sites of infection and contain lower amounts of proteins needed to kill infected or tumor cells.

"The transitional cells are not completely exhausted," says postdoctoral fellow Will Hudson,

Ph.D., first author of the *Immunity* paper. "They are still capable of proliferating and performing their 'killer cell' functions. In our experiments, they contribute to viral control."

The transitional cells, lacking CD101, could be a good marker for response to PD-1 blocking drugs, Hudson says. Enhancing the proliferation or survival of these cells, or preventing their transition to lasting exhaustion, may be a novel therapeutic strategy for cancer.

"It is extremely exciting to have contributed to this project and know that our findings have the potential to inform cancer immunotherapy," says co-author Julia Gensheimer, an Emory graduate, now a MD/Ph.D. student at UCLA.

The *Immunity* paper also includes systematic identification of other markers for CD8 T cells in various stages of exhaustion, which could be a guide to efforts to promote their activity.

More information: William H. Hudson et al, Proliferating Transitory T Cells with an Effector-like Transcriptional Signature Emerge from PD-1+ Stem-like CD8+ T Cells during Chronic Infection, *Immunity* (2019). DOI: 10.1016/j.immuni.2019.11.002