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Stability of exhausted T cells limits durability of cancer checkpoint drugs

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Checkpoint inhibitor drugs that boost the immune system to fight cancer owe part of their existence to infectious diseases. Microbes that cause diseases like HIV, malaria, and hepatitis C exploit and often activate the same checkpoint pathways—cell surface receptors such as CTLA4 and PD-1—to slow immune cells and prevent their elimination by the host.

T cells that are supposed to clear an infection, instead, become "exhausted." The cell-surface receptors naturally act like brakes to tell the immune system to not react as strongly during normal situations and help the immune system avoid damaging healthy tissue or causing autoimmunity. Blocking PD-1 can reinvigorate exhausted T cells and improve control of chronic infections and cancer. However, whether blocking PD-1 can reprogram exhausted T cells into durable memory T cells is unclear.

E. John Wherry, PhD, director of the Institute for Immunology at Penn and the Barbara and Richard Schiffrin President's distinguished professor of Microbiology, in the Perelman School of Medicine at the University of Pennsylvania, and colleagues found that reinvigorating exhausted T cells in mice using a PD-L1 blockade caused very few T memory cells to develop. After the blockade, re-invigorated T cells became re-exhausted if antigen from the virus remained high, and failed to become memory T cells when the virus was cleared. They published their findings in this week's issue of *Science*.

The team found that exhausted T cells acquired an epigenetic profile

distinct from effector or memory T cells. These latter two cell types can mount effective immune responses to viruses and tumors; whereas, exhausted T cells fail and memory T cells, in particular, for long-lasting durable effects.

Epigenetics is the way chemical modifications to DNA and the proteins binding DNA determine which genes are expressed by a cell type. Epigenetic profiles can be highly stable and confer long-term identity to a cell. (In other words, the reason a liver cell stays a liver cell and doesn't become a lung cell is due largely to epigenetics since both liver and lung cells have the same genes.)

"What these new findings on exhausted T cells tells us is that the unique epigenetic profile of exhausted T cells causes these cells to express a different overall set of genes compared to memory or effector T cells," Wherry said. However, this epigenetic pattern was only minimally changed following the PD-L1 blockade. This prevented these exhausted T cells from changing into the more protective effector or memory cell types.

"We were surprised that the exhausted T cell epigenetic profile was not reprogrammed," Wherry said. "Instead, the benefit we see after PD-1 pathway blockade is caused by only transient changes in gene expression that is not durable, rather than permanent epigenetic reprogramming."

These findings suggested that exhausted T cells are a distinct lineage of T cells in and of themselves instead of just being effector or memory T cells restrained by checkpoint pathways. "We predicted that exhausted T cells would not have a distinct epigenetic profile but have the molecular flexibility to obtain immune memory," Wherry said. "But we found that exhausted T cells are quite set in their ways."

"We think this shows that epigenetic fate inflexibility may limit current

immunotherapies based on PD-1 checkpoint inhibitors," said first author Kristen Pauken, PhD, a postdoctoral researcher in the Wherry lab. Most cancer patients respond well to PD-1 blockades at first, but the response is not sustained. This study shows how exhausted T cells do not maintain a durable switch to an effector T cell profile, although in the clinic, checkpoint inhibitors are well tolerated and their side effects such as autoimmunity are usually manageable. This lack of durability clinically is not well characterized, but these results suggest it is likely, at least partially, due to the lack of sustained or permanent reprogramming of exhausted T cells.

In a companion study also published in Science, Nick Haining, MD, and colleagues from Dana-Farber Cancer Institute, also found a distinct epigenetic landscape for exhausted T cells in mice and humans, and they were able to ascribe key functions in T cell exhaustion to some of these epigenetic changes. Wherry and Pauken are co-authors on this study.

Wherry, together with his colleagues in the Parker Institute for Cancer Immunotherapy at Penn, are involved in multiple checkpoint-related trials, in melanoma, lung cancer, renal cell carcinoma, and others, including combining checkpoint blockade with radiation. The ultimate goal is to precisely understand the mechanisms of checkpoint blockade effectiveness and bring next generation, sustainable immunotherapies to even more patients, perhaps using by using epigenetic drugs in combination with checkpoint blockade to allow epigenetic reprogramming of exhausted T cells into durable and functional memory T cells.

More information: "Epigenetic stability of exhausted T cells limits durability of re-invigoration by PD-1 blockade," *Science*, science.sciencemag.org/cgi/doi … 1126/science.aaf2807

"The epigenetic landscape of T cell exhaustion," *Science*,