Study identifies critical regulator of tumor-specific T cell differentiation

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Immune checkpoint therapy has revolutionized cancer therapy, leading to long-term remission for patients with advanced cancer. However, most cancer patients either do not respond or have only short-term responses to checkpoint therapy, which targets inhibitory receptors on T cells.

A study published June 17 in *Nature* offers clues as to why blocking inhibitory receptors on tumor-infiltrating T cells may not always work. Mary Philip, MD, Ph.D., assistant professor of Medicine in the Division of Hematology and Oncology and a senior author on the story, together with Andrea Schietinger, Ph.D., of the Sloan Kettering Institute, found that the thymocyte selection-associated high-mobility group box protein, TOX, is expressed at high levels in dysfunctional tumor-infiltrating T cells in mice and humans.

The investigators found that TOX controls the high expression of inhibitory receptors such as PD1 on dysfunctional tumor-infiltrating T cells. These inhibitory receptors act like brakes on T cells. The team deleted TOX from tumor-infiltrating T cells to see if that would restore their function. To their surprise, though the tumor-infiltrating T cells no longer expressed PD1 and other inhibitory receptors, the T cells were still dysfunctional and unable to eliminate cancers. Even more surprising, the T cells without TOX were unable to survive long term. The study demonstrates that control of the killing machinery in T cells is uncoupled from regulation of inhibitory receptors.

"Taking off the brakes is not enough to restore the killing capacity of anti-tumor cells. In fact, T cells need the brakes to avoid getting over-activated and dying," Philip said.

The study follows a previous investigation published in *Nature* on May 25, 2018, by Philip and colleagues on T cell dysfunction in liver cancer using mouse models. Philip was the lead author of that study.

The overarching goal of Philip's research group is to decipher the mechanisms regulating T cell dysfunction in cancers and to design new strategies to override these mechanisms to improve cancer immunotherapy.

More information: Andrew C. Scott et al. TOX is a critical regulator of tumour-specific T cell differentiation, *Nature* (2019). DOI: 10.1038/s41586-019-1324-y