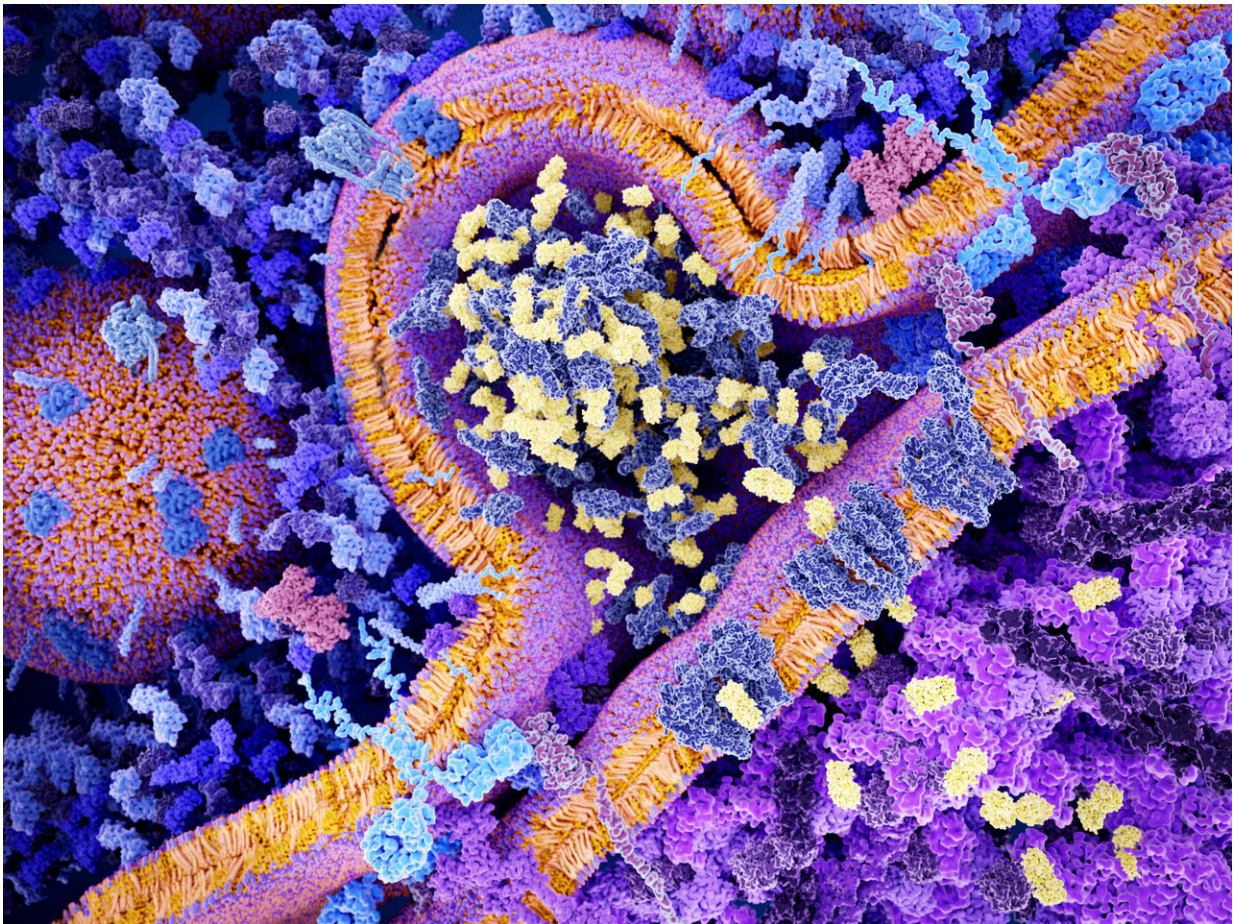


De-TOXing exhausted T cells may bolster CAR T immunotherapy against solid tumors

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Chimeric antigen receptor therapy. CAR molecules (light blue) bind to CD19 molecules on a cancer cell leading to segregation of granzyme vesicles (yellow) that activate apoptosis. Credit: La Jolla Institute for Immunology

A decade ago researchers announced development of a cancer immunotherapy called CAR (for chimeric antigen receptor)-T, in which a patient is re-infused with their own genetically modified T cells equipped to mount a potent anti-tumor attack. Since then CAR T approaches (one of several strategies collectively known as "adoptive T cell transfer") have made headlines as a novel cellular immunotherapy tool, most successfully against so-called "liquid cancers" like leukemias and lymphomas.

Sarcomas and carcinomas have proven more resistant to these approaches, in part because engineered T-cells progressively lose [tumor](#)-fighting capacity once they infiltrate a tumor. Immunologists call this cellular fatigue T cell "exhaustion" or "dysfunction."

In efforts to understand why, La Jolla Institute for Immunology (LJI) investigators Anjana Rao, Ph.D., and Patrick Hogan, Ph.D., have published a series of papers over the last years reporting that a transcription factor that regulates gene expression, called NFAT, switches on "downstream" genes that weaken T cell responses to tumors and thus perpetrates T cell exhaustion. One set of these downstream genes encodes [transcription factors](#) known as NR4A, and a previous graduate student, Joyce Chen, showed that genetic elimination of NR4A proteins in tumor-infiltrating CAR T cells improved tumor rejection. However, the identity of additional players cooperating with NFAT and NR4A in that pathway has remained unknown.

Now a paper published in this week's online edition of the *Proceedings of the National Academy of Sciences (PNAS)* from the Rao and Hogan labs provides a more complete list of participants in an extensive gene expression network that establishes and maintains T cell exhaustion. The study employs a [mouse model](#) to show that genetically eliminating two new factors, TOX and TOX2, also improves eradication of "solid" melanoma tumors in the CAR T model. This work suggests that

comparable interventions to target NR4A and TOX factors in patients may extend the use of CAR T-based immunotherapy to solid tumors.

The group began by comparing [gene expression](#) profiles in samples of normal versus "exhausted" T cells, searching for factors upregulated in parallel with NR4A as co-conspirators in T cell dysfunction. "We found that two DNA binding proteins called TOX and TOX2 were consistently highly expressed along with NR4A transcription factors," says Hyungseok Seo, Ph.D., a postdoctoral fellow in the Rao lab and the study's first author. "This discovery suggested that factors like NFAT or NR4A may control expression of TOX."

The group then recapitulated a CAR T protocol in mice by first inoculating animals with melanoma tumor cells to establish a tumor, and then a week later infusing mice with one of two collections of T cells: a "control" sample from a normal mouse, versus a sample derived from mouse genetically engineered to lack TOX and TOX2 expression in T cells.

Remarkably, mice infused with TOX-deficient CAR T cells showed more robust regression of melanoma tumors than did mice infused with normal cells. Moreover, mice treated with TOX-deficient CAR T cells exhibited dramatically increased survival, suggesting that loss of TOX factors combats T cell exhaustion and allows T cells to destroy tumor cells more effectively.

Additional analysis led the investigators down a pathway ending with a well-known immune adversary. The researchers showed that TOX factors join forces with both NFAT and NR4A to promote expression of an inhibitory receptor called PD-1, which decorates the surface of exhausted T cells and sends immunosuppressive signals.

PD-1 is blocked by numerous monoclonal antibodies called checkpoint

inhibitors, which combat immunosuppression and activate an innate anti-cancer immune response. Convergence of TOX, NFAT, and NR4A on PD-1 makes molecular and immunological sense and puts it at the convergence of both cellular and antibody immunotherapy approaches.

"Currently, CAR T cell therapy shows amazing effects in patients with "liquid tumors" such as leukemia and lymphoma," says Seo. "But they still do not work well in patients with [solid tumors](#) due to T cell exhaustion. If we could inhibit TOX or NR4A by treating CAR T [cells](#) with a small molecule, this strategy might show a strong therapeutic effect against solid cancers such as melanomas."

More information: Hyungseok Seo et al., "TOX and TOX2 cooperate with NR4A transcription factors to impose CD8+ T cell exhaustion," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1905675116

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