Reinvigorating exhausted engineered CAR-T cells by giving them a break

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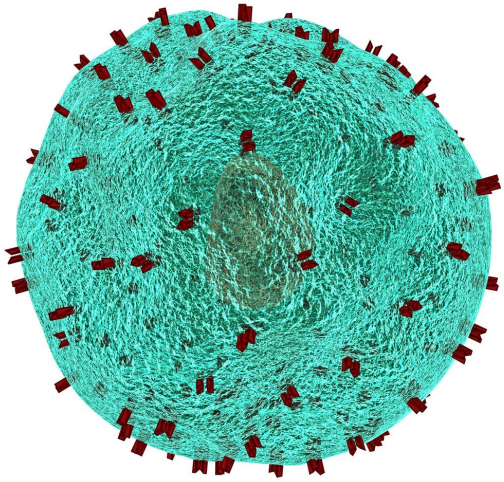

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A team of researchers at Stanford University has found a way to reinvigorate exhausted engineered CAR-T cells by giving them a time-out period to recover. In their paper published in the journal *Science*, the group describes giving the cells a time-out period, and how well it worked in giving them a new lease on life. Maksim Mamonkin and Malcolm Brenner with Texas Children's Hospital have published a Perspective piece in the same issue outlining exhaustion in engineered CAR-T cells and the work done by the team in this new effort.

Chimeric antigen receptor T-cells (CAR-T) cells are T-cells that have been altered genetically to provide therapeutic benefits, such as attacking cancerous tumors. They do their work by producing T-cell receptors that can be used with immunotherapy. Unfortunately, their effectiveness diminishes over time due to what is known as exhaustion. In this new effort, the researchers looked into the factors that contribute to CAR-T cell exhaustion and what happens if the engineered cells are given a rest period now and then.

Prior research has shown that CAR-T cell exhaustion arises due to continuous stimulation via antigen receptors, which impair their expansion and slow the destruction of targeted cells. In studying the process, the team at Stanford found that continuous stimulation of the cells induced epigenetic, functional and transcriptional changes to the CAR-T cells. But they also found that periodically blocking the signals produced by the cells reversed such changes. They also found that blocking could be accomplished in two ways. The first involved making changes to the turnover of the cells themselves, and the second involved temporarily administering the drug dasatinib.

In testing both approaches, the researchers found that the temporary pause they induced resulted in reinvigoration of the CAR-T cells. The rejuvenation, they found, was due primarily to histone methylation rather than DNA methylation, though they were not able to explain why that was the case. The researchers suggest that intermittently inhibiting CAR–T cell signaling may be in order for patients being treated with CAR-T cells, though more work is required to determine the best approach.

More information: Evan W. Weber et al. Transient rest restores functionality in exhausted CAR-T cells through epigenetic remodeling, *Science* (2021). DOI: 10.1126/science.aba1786

Maksim Mamonkin et al. Reversal of exhaustion in engineered T cells, *Science* (2021). DOI: 10.1126/science.abh0583