Modified Stem Cells Create Tumor-Attacking T Cells

Researchers have tried many techniques to produce T cells that home in on and attack cancers. One group of scientists now reports in *PNAS* that genetic modification of hematopoietic stem cells (HSC) can spur humanized mice to generate human T cells that destroy melanoma tumors.

Approaches that involve manipulating T cells outside the body and then replacing them have shown promise. However, researchers worry that such cells could provoke autoimmunity because they don’t pass through negative selection, the weeding-out of self-targeted T cells in the thymus. Other concerns are that the re-introduced T cells won’t survive very long and that they won’t generate the memory cells needed for continued protection.

To try to overcome these potential limitations, a team led by immunologist Jerome A. Zack of the University of California, Los Angeles (UCLA) engineered HSCs and then infused them into humanized mice whose bone marrow had been destroyed by radiation. The HSCs received DNA encoding a T-cell receptor (TCR) that recognizes a particular melanoma antigen, with the idea that the stem cells will spawn T cells targeted against this antigen. Moreover, the mice incorporated human thymus tissue that can remove T cells that might trigger autoimmune attacks.

Four to 6 weeks after the procedure, the mice carried large numbers of CD8+ T cells that displayed the melanoma-recognizing TCR. To test the cells' melanoma-fighting abilities, the team implanted the mice with melanoma tumors that carried the matching antigen and with control tumors that sported non-matching molecules. The cells attacked—and in some cases eliminated—tumors with matching antigens. However, the T cells overlooked the control tumors. T cells generated by the implanted HSCs appeared to undergo negative selection. The HSCs also yielded memory cells, suggesting they could provide long-term benefits.

“This gives us the opportunity to generate a population of targeted T cells” that could combat melanoma or other cancers, says first author Dimitrios N. Vatakis, PhD, also at UCLA.
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