Boosting the Potency of T-cell Therapies

Manipulating proliferative, persistent T-cell subsets produces durable antitumor responses

Although adoptive T-cell therapies have yet to be approved by the FDA, this area of cancer immunotherapy is gaining ground “at a torrid pace,” says Stanley Riddell, MD, of the Fred Hutchinson Cancer Research Center in Seattle, WA. Riddell shared his research team’s progress in synthesizing and evaluating chimeric antigen receptor (CAR) T cells at the annual meeting of the American Association for the Advancement of Science in February.

CAR T-cell therapy involves inserting a synthetic receptor in patients’ T cells, which then recognize and destroy tumors expressing a specific antigen. So far, researchers have had remarkable success—albeit in small clinical trials—directing this therapy against CD19, which is expressed on the surface of all B cells, including B-cell malignancies like acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL). Riddell reported a complete remission rate of 93% in 29 patients with ALL who had relapsed after chemotherapy and, in some cases, a bone marrow transplant. He also showed that NHL tumors were “completely wiped out by CAR T cells.”

These data mirror the findings of other groups investigating CAR T-cell therapy’s potential, Riddell notes. “What distinguishes our work is that we only engineer CARs in the T cells best able to proliferate and persist in patients,” he says. T cells aren’t a single lineage with shared attributes; they “exist in phenotypically distinct subsets, with different properties in host immunity,” he explains. Additionally, patients slated for CAR T-cell therapy have often already received multiple other treatments, which “skews the ratios of their T cells toward the least effective subsets.” Selecting the best T cells is key, therefore, to ensure “a uniformly potent product,” he says.

Riddell’s group has found that CAR-bearing naïve and central memory T cells cooperate to eradicate tumors in mice. They’re now isolating these subsets from patients to test this tumor-killing synergy in the clinic. By engineering CARs only in defined, highly proliferative T cells, the researchers have also found that escalating doses is unnecessary. “Each patient receives a rice grain–sized cell pellet, which rapidly expands in vivo to combat enormous tumor burdens,” Riddell says.

Chiara Bonini, MD, of the San Raffaele Scientific Institute in Milan, Italy, describes T-cell receptor (TCR) gene editing as a different way to tweak T-cell specificity. “TCRs specific for tumor antigens are rare,” she explains. “Our group has designed zinc finger nucleases that act as molecular scissors. We can snip out the gene for any T cell’s endogenous receptor and replace it with one for a tumor-specific TCR.”

However, these modified cells can be as toxic as they are potent: Patients risk life-threatening side effects, chiefly cytokine release syndrome, so current experimental therapies often include “kill switches” to mitigate severe toxicity. Bonini favors having T cells co-express the herpes simplex virus thymidine kinase suicide gene; if necessary, the cells can be depleted by administering the antiviral drug ganciclovir. Meanwhile, Riddell has collaborated with Dirk Busch, MD, of the Technical Institute of Munich in Germany, on a different switch—their CAR T cells co-express truncated EGFR and can be eliminated with cetuximab (Erbitux; Eli Lilly).

“Rather than relying on one type of kill switch, we should have a repertoire,” Busch says, “because the level of T-cell depletion needed to prevent or reduce toxicity may vary in different clinical situations.”

The flip side of kill-switch activation is that “you’re eliminating the therapy at the same time,” says Michel Sadelain, MD, PhD, director of the Center for Cell Engineering at Memorial Sloan Kettering Cancer Center in New York, NY. “My personal view is that these switches are a valuable adjunct, but if they’re frequently required, you should really be changing your CAR design.”

Meanwhile, because engineering T cells to recognize single antigens is a one-dimensional, limited approach, Sadelain and others are exploring combinatorial antigen targeting. His team has developed CAR T cells that are, broadly speaking, primed to go after tumors containing a pair of antigens—A and B—and suboptimally active if only one of those antigens is present (Nat Biotechnol 2013;31:71–5). Another group has built a sequentially activated T-cell “circuit” in which recognition of antigen A by one CAR is necessary to induce a second CAR targeting antigen B (Cell 2016;164:770–9). Unless both antigens exist, the T cells can’t attack the tumor. Such strategies aim to expand this immunotherapy’s applicability, especially in solid tumors, and ensure discrimination of tumor from normal tissue.

Ultimately, the adoptive T-cell concept “isn’t just about creating tumor killers—at least, it shouldn’t be,” Sadelain says. “We have a living drug that could be exploited for much more…. The reach of current therapies is still limited, but in terms of ideas to improve them, the sky’s the limit.”

—Alissa Poh
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