Remote Controlled CARs: Towards a Safer Therapy for Leukemia

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Genetic engineering of patient T cells with chimeric antigen receptors (CAR T cells) provides a powerful tool for inducing remissions in patients with various cancers derived from B cells. Challenges stemming from the inability to control the CAR T cells once given pose significant safety concerns. An article in Cancer Immunology Research presents an approach to circumvent this issue. Cancer Immunol Res; 4(8); 643. ©2016 AACR.

See article by Sakemura et al., p. 658.

B-cell malignancies are the most common cancers derived from the hematopoietic system. A number of groups have shown that chimeric antigen receptors (CAR T cells) that target lineage-restricted molecules expressed on the surface of B-cell cancers hold great promise for a variety of cancers. The use of engineered T cells, redirected to CD19 for B-cell acute lymphoblastic leukemia, has shown the greatest promise in the field to date. Recent clinical updates from several biotechnology and pharmaceutical companies presented at the 2016 American Society of Clinical Oncology indicate that CD19 CAR T cells are on the fast track to commercial approval in the United States.

The CAR T cells currently under evaluation in clinical trials are constitutively expressed on the surface of the infused T cells. These cells are "always on" and will eliminate all cells expressing CD19, including both malignant B cells and normal B cells. Therefore, B-cell aplasia is one consequence of constitutive CAR T cells that target CD19. In adults, acquired B-cell aplasia has been well tolerated, because humoral immunity is maintained by long-lived plasma cells that do not express CD19 (1). However, in children, B-cell aplasia may present an increased risk of infection because many children have not yet established immunologic memory, and it is not possible to vaccinate children with B-cell aplasia.

Sakemura and colleagues describe "switchable" CARs that may present a solution to the complications other researchers have encountered with constitutive CARs. They designed a system in which expression of their CD19 CAR is controlled by a tetracycline-inducible system that is "on" only in the presence of the commonly used antibiotic doxycycline. The tetracycline (Tet)-On system is an inducible gene-expression system that functions in mammalian cells. To control when the genes are induced, a fusion protein, the reverse Tet transactivator (rtTA), is engineered to respond to the presence of doxycycline; rtTA comprises the doxycycline-binding Tet-repressor mutant protein and the C-terminal activator domain from the herpes simplex virus VP16 protein. In the presence of doxycycline, rtTA activates the promoters for the CD19 CAR constructs that are fused downstream of an array of repeated Tet-operator sequences.

The main issue with such technologies has been the amount of baseline activity or "leakiness" while in the "off" state. In principle, the gold standard of efficiency required for a switchable application for B-cell directed CAR T-cell therapies would be a system that permits recovery from B-cell aplasia when the CARs are in the "off" state. Functionally, the "on" state of the inducible CAR would need to retain a potent antitumor activity equivalent to that of the current CD19 CAR T cells that are constitutively expressed.

One of the major concerns with new forms of engineered T cells is whether the process will render the CAR T cells immunogenic, leading to rejection by the patient. Here, the relevant issue will be the immunogenicity of the tetracycline-based inducible system, in particular the rtTA fusion protein that is derived from various prokaryotic and viral components. This issue is more than a theoretical concern, as previous studies have shown that engineered T cells containing a suicide system incorporating components from herpes simplex virus were rejected (2).

Other investigative groups are also actively developing switchable CAR designs using different approaches (3, 4). Indeed, it is likely that the principles of synthetic biology combined with cellular engineering will permit the design of an array of CAR T cells that fulfill the various activity states of Boolean logic gated circuits, such as AND, OR, and NOT gates that are switchable. These next-generation designs should enable increasing precision and potency of CARs that will be controllable by the medical team.

Disclosure of Potential Conflicts of Interest

C.H. June holds intellectual property and serves as a consultant to Novartis and Tmunity.

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References

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