Cancer Immunology Research

Tales of Antigen Evasion from CAR Therapy

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Both T cells bearing chimeric antigen receptors and tumor-specific antibodies can successfully target some malignancies, but antigen escape can lead to relapse. Two articles in this issue of *Cancer Immunology Research* explore what effective countermeasures may prevent it. *Cancer Immunol Res; 4(6); 473. ©2016 AACR.*

See articles by Zah et al., p. 498, and Rufener et al., p. 509.

The use of chimeric antigen receptors (CAR) for cancer immunotherapy is gaining momentum, propelled by the CD19 paradigm (1). CARs are synthetic receptors that retarget T cells to selected antigens and, depending on their design, reprogram T-cell functionality, metabolism, and persistence. The pursuit of CD19 as the target antigen has resulted in remarkable clinical results in patients with B-cell malignancies, especially acute lymphoblastic leukemia (1), and has rapidly generated substantial knowledge on the therapeutic potential and limitations of second-generation CARs. Thus, CARs effectively target both $CD4^+$ and $CD8^+$ T cells against tumors; CD19 CARs can induce complete responses in patients with chemorefractory disease and patients for whom an allogeneic bone marrow transplant would have very little chance of success, and CAR T cells can be manufactured for the vast majority of patients. Based on these exciting outcomes, research on CAR therapy is rapidly expanding in both academia and industry.

Trials of CD19 CAR therapy have also yielded valuable insights into the complications and limitations of this approach. Current CD19 CAR therapy is more effective in acute lymphoblastic leukemia (ALL) than in chronic lymphocytic leukemia or non-Hodgkin lymphoma, for unknown reasons. CD19 CAR T cells occasionally induce strong cytokine responses that require a medical intervention, as well as transient neurotoxicity, which also awaits a mechanistic explanation. Finally, some tumors may resist CD19 CAR therapy or relapse, most often within the first year after CAR T-cell infusion. The relapsed tumors may still express CD19, or read out as CD19-negative, a relatively common occurrence in post-CAR therapy relapse of pediatric ALL (2). Antigen escape is a classic mechanism of tumor immune evasion.

Two research articles in this issue of *Cancer Immunology Research* shed new light on antigen escape in the context of CAR therapy (3, 4). In the first study, researchers from Yvonne Chen's group (Zah et al.; ref. 2) explore a novel dual targeting CAR design, which they term OR-gate, as a means to minimize the escape of an antigen-negative variant. Dual targeting strategies have been previously reported, either admixing two CAR T-cell populations, coexpressing two CARs in the same T cells, or generating a bispecific CAR. The OR-gate approach differs in that a single CAR is used to target both antigens, CD19 and CD20. The authors demonstrate that their bispecific CAR effectively kills targets expressing either antigen, similarly to a monospecific CAR. This CAR design is simple in concept but challenging to implement. One of the peculiarities of CARs is that they do not engage epitopes at a constant distance from the cell surface, in contrast to the physiologic T-cell receptor (TCR), which binds to a myriad of peptides and HLA molecules under constant spatial constraints. This topology is critical to the productive formation of a T-cell synapse with the antigen-presenting cell. This constraint needs to be adjusted for each CAR and further reconciled for each epitope within the structure of a dual-specific CAR. These authors resolved this issue by selecting epitopes, one on CD19 and the other on CD20, such that each one was positioned within its optimal spatial range. This elegant resolution places a significant restriction on the ability to pair epitopes. Most gratifyingly, however, this approach prevented the emergence of CD19- or CD20-negative escape variants in the context of mixed tumor populations.

Researchers from Brian Till's group (Rufener et al.; ref. 4) explore another circumstance that could precipitate antigen escape, in the scenario where an antibody could mask the CAR target. This may plausibly occur in subjects infused with CD20 CARs after being treated with the CD20-specific monoclonal antibody rituximab. This concern was previously explored when targeting antigens known to be cell bound as well as secreted, such as carcino-embryonic antigen (CEA) or Lewis-Y antigen, in which moderate concentrations of soluble antigen did not preclude CAR target recognition. Rufener and colleagues looked at a broad range of antibody concentrations and their effect on CD20 recognition. Antibody levels as high as 100 μg/mL did not impede CAR T-cell function against high-expressing CD20 lymphoma cell lines—a concentration exceeding the median residual serum rituximab measured in 103 patients with lymphoma. *In vivo*, rituximab administration did not inhibit CAR T-cell–mediated rejection of rituximab-refractory cell lines. Recipients of rituximab are thus unlikely to resist CD20 CAR T cells and should not be excluded from CAR therapy protocols.

These studies not only bring more good news for the prospects of CAR therapy—they also illustrate the rapid pace of progress in the CAR field.

Disclosure of Potential Conflicts of Interest

The author reports having an ownership interest and serving as a consultant for Juno Therapeutics.

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