Chimeric antigen receptors redirect T cells to surface antigens. Discovery and validation of appropriate target antigens expand the possible indications for chimeric-antigen receptor (CAR)-T cells. B-cell maturation antigen (BCMA) is expressed only on mature B cells and plasma cells and promotes their survival. BCMA is a promising target for CAR-T cells in multiple myeloma. 

In this issue of *Clinical Cancer Research*, Carpenter and colleagues (1) explore the potential of targeting the B-cell maturation antigen (BCMA) with chimeric-antigen receptor (CAR)-transduced T cells, with the goal of developing a clinical T-cell therapy to treat multiple myeloma.

CAR-T cells are autologous or allogeneic T cells genetically engineered to express a CAR specific for a cell surface structure, typically a protein or carbohydrate. The specificity of the CAR is based on the Fab region of an antibody, typically engineered into a single-chain variable fragment, whereas the CAR’s signaling domains are derived from native human T-cell receptor signaling domains (CD3z), which may be fused in tandem to additional costimulatory proteins that promote T-cell proliferation, cytokine release, and resistance to apoptosis. CAR-T cells are emerging as a powerful therapy with the curative potential of allogeneic stem cell transplant but without the complications of allogeneic graft versus host disease. In the last 2 years, pilot studies of CD19-directed CAR-T cells have been reported by several groups to induce prolonged remissions in chemotherapy-resistant or -refractory CD19+ malignancies (2, 3). Clinical trials of CAR-T cells directed to CD20 (4) and GD2 (in neuroblastoma; ref. 5) have been reported, and there are many ongoing studies of CAR-T cells in various tumors.

Although there is still an ongoing effort in the field to determine the optimal molecular and biomechanical aspects of CAR design, the biggest hurdle to widespread development of CAR-T cells for malignancies is finding suitable antigenic targets. The requirements for an appropriate target antigen for directing CAR-T are conceptually simple but strict:

1. The target must be expressed on the surface.
2. Off-tumor expression of the target, even at low levels, must not be present in an essential organ or cell type (i.e., hematopoietic stem cells).
3. To avoid antigen escape, all the tumor cells must express the target or, alternatively, the target must be essential for maintenance of the tumorigenic phenotype.

The first requirement is a consequence of the nature of MHC-independent antibody binding. The second requirement is based on the toxicity profile of CAR-T cells, which has shown that cells expressing low levels of the target antigen are rapidly lysed. In the case of the Her2/neu (6) antigen, for example, low-level expression in the lungs resulted in rapid and fatal toxicity; similarly, CARs directed to carbonic anhydrase IX resulted in T-cell-mediated cholangitis due to low-level expression of the target in the bile duct epithelium (7). This type of toxicity reflects the sensitivity of the T cell to signaling from engagement of its target, and has also been seen in T cells that have been redirected to MHC-restricted tumor antigens. The third requirement has now been clinically shown; in a recent trial of CD19-directed CAR-T for B-cell acute lymphoblastic leukemia, a patient whose tumor expressed CD19 heterogeneously relapsed with CD19-negative disease after an initial complete response induced by the CAR-T (8). Thus, choosing the most appropriate target antigen, in the context of the targeted disease, is arguably the most crucial component in developing CAR-T therapies.

BCMA is a TNF receptor (TNFR) member that is expressed on terminally differentiated B cells; engagement of BCMA by its ligands delivers prosurvival signals to mature B cells, plasma cells, and multiple myeloma cells. The 2 ligands for BCMA are B-cell maturation antigen (BAM) and a proliferation-inducing ligand (APRIL). Two other related TNFR family members, BAFF-R and transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI), are expressed in earlier stages of B-cell development. The primary ligand for BAFF-R is BAFF, whereas the...
primary ligand for BCMA is APRIL (9). TACI, which is coexpressed with both BCMA and BAFF-R in memory B cells, and only with BCMA in plasmablasts, long-lived plasma cells, and some multiple myeloma cells, binds to BAFF independently but requires CD138 to act as a coreceptor to bind APRIL (10). In human multiple myeloma, BCMA is thought to play a critical role in protecting the myeloma cells from apoptosis; the tumor microenvironment, and osteoclasts in particular, secrete APRIL and BAFF (Fig. 1).

The BAFF pathways are highly active in some autoimmune diseases. BCMA is mostly known for its functional activity in mediating the survival of plasma cells that maintain long-term humoral immunity (11), but it may not be absolutely required for this function, as mature B cells from BCMA-deficient lupus-prone mice could still differentiate into plasma cells and have a worsened autoimmunity (12); this is thought to occur via TACI signaling. Whether compensatory signaling through TACI could or will occur in humans is unknown because BCMA has not yet been directly targeted with an antibody or CAR-T in humans. It is unknown whether BCMA–TACI+ antigen escape variants of myeloma will be selected by CAR-T cells, and this question is best answered by clinical testing.

In this article, Carpenter and colleagues have focused on defining BCMA as a suitable antigen for CAR-T cell therapies. They begin by showing bright surface expression on primary myelomas, which confirms previous studies of surface expression of BCMA on mature B cells. What is not clear is whether the expression of BCMA is homogeneous in primary myeloma cells, though it is encouraging that BCMA signals are functionally involved in the maintenance of the tumor phenotype. They also conduct an in-depth analysis of protein expression of BCMA in many normal organs, with particular attention to gut tissues that were thought to express BCMA on the basis of mRNA expression; reassuringly, a beautiful immunohistochemical analysis showed that BCMA expression in the gut is a result of resident B cells and plasma cells that form part of the gut-associated lymphoid tissues. Ultimately, the disappointing experience in the field is that clinical toxicities may not be predicted from in vitro and xenogeneic models.

Given the early successes with CD19-CARs for B-cell malignancies, it is logical to target multiple myeloma as a...
malignancy because of the extensive prior characterization of plasma cells. One caveat is that myeloma tends to be a heterogeneous disease; it is possible that some myeloma cells will express TACI over BCMA, though the potential for antigen escape should be relatively straightforward to assess by flow cytometry from bone marrow aspirates. Finally, the predisposition of CAR-T cells to home to the bone marrow weighs the odds in favor of developing CAR-T cells for myeloma and other hematologic malignancies.

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