T-cell Receptor Gene Therapy Clinically Targeting a *TP53* Public Neoantigen

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T-cell receptors (TCR) are an antigen receptor class that can uniquely respond to epitopes resulting from cytosolic and intranuclear proteins. In this issue, Kim and colleagues report the first successful application of TCR gene therapy targeting a shared, or public, neoantigen resulting from a *TP53* hotspot mutation. These results establish clinical proof of concept that an off-the-shelf TCR targeting a recurrent mutation in a molecular driver of oncogenesis can benefit patients with metastatic cancer.

See related article by Kim et al., p. 932 (4).

Unlike antibody-based therapies, which include chimeric-antigen receptors (CAR), TCRs can uniquely respond to epitopes derived from intracellular proteins (1). This attribute dramatically expands the universe of cancer cell antigens that can be therapeutically targeted. TCRs recognize a composite structure formed by a polypeptide bound to a specific HLA molecule. Diverse classes of proteins can generate TCR epitopes following proteasomal degradation, including neoantigens, which have received considerable attention because correlative evidence implicates epitopes resulting from such proteins as a major determinant of successful immunotherapies.

Nearly all (∼99%) neoantigens result from passenger mutations that are unique to individual patients (2). The therapeutic targeting of patient-specific, or private, neoantigens poses significant challenges. On the one hand, private neoantigens are time consuming and costly to identify because they require bespoke reagents tailored to a single patient's cancer. On the other hand, private neoantigens are subject to clonal heterogeneity, a major mechanism of immune escape. In contrast, a rare subset of neoantigens—public neoantigens—are clonally conserved and shared among patients because they result from recurrently mutated genes encoding oncogenic drivers. Public neoantigens resulting from mutated driver oncogenes, such as *KRAS* (2) and *PIK3CA* (3), have been described. Public neoantigens resulting from tumor suppressor genes (TSG), such as *TP53*, can also occur and are the subject of the study by Kim and colleagues (4).

TP53 is the most commonly mutated gene across human cancers, making it an attractive candidate to develop public neoantigen TCRs against. While many TSGs possess mutational hotspots, these regions are typically more numerous than the tightly constrained hotspots associated with mutated oncogenes. Consequently, the number of patients who share a particular TSG hotspot mutation is proportionally smaller. To overcome this limitation, Kim and colleagues curated a library of patient-derived TCRs that confer specificity to different mutant p53–HLA allele pairs. Among the library members are several novel TCRs, including an HLA-A*02:01–restricted TCR that recognizes an epitope resulting from the prevalent $TP53^{Y220C}$ mutation. TCRs recognizing rare *TP53* variants were also discovered and characterized. The clinical utility of these latter TCRs may not be high, but they serve to buttress the conclusion that T-cell responses to mutant *TP53* are surprisingly common in patients with cancer.

The pièce de résistance of the study is an instructive case report of a patient who received adoptive transfer of autologous T cells transduced with a $TP53^{R175H}$-specific TCR. The subject, a 48-year-old HLA-A*02:01^{+} woman with treatment-refractory breast cancer harboring a $TP53^{R175H}$ mutation, received a single T-cell infusion following lymphodepleting chemotherapy. Shortly after the patient received TCR-modified cells, she developed cytokine release syndrome (CRS), a toxicity frequently observed with CAR therapies but notably less common with TCR therapies. Two weeks later, the patient received a single dose of the PD1-specific antibody pembrolizumab, which precipitated a second CRS event. Despite these acute toxicities, which were manageable, the patient experienced an objective response involving multiple metastatic sites lasting 6 months. Genomic sequencing of a new skin metastasis revealed *HLA-A*02:01* loss of heterozygosity, a likely mechanism of acquired immune escape.

These findings establish that targeting a public neoantigen using TCR gene transfer is both feasible and efficacious. Moreover, these data provide the most compelling evidence yet that neoantigen targeting can directly trigger cancer regression in patients.

Authors' Disclosures

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