

Adoptive Immunotherapy with Antigen-Specific T Cells Expressing a Native TCR

Wingchi Leung and Helen E. Heslop



Abstract

Although T cells genetically modified with chimeric antigen receptors became the first immune effector product to obtain FDA approval, T-cell products that recognize their antigenic targets through their native receptors have also produced encouraging responses. For instance, T cells recognizing immunogenic viral antigens are effective when infused in immunosuppressed patients. A large number of tumor antigens are also expressed on nonviral tumors, but these antigens are less immunogenic. Many tumors can evade a transferred immune response by producing variants, which have lost the targeted antigens, or inhibitory molecules that recruit suppressive cells, impeding persistence and function of immune effectors. Nevertheless, infusion of antigen-specific T cells has been well-tolerated, and clinical responses have been consistently associated with immune

activity against tumor antigens and epitope spreading. To overcome some of the obstacles mentioned above, current research is focused on defining *ex vivo* culture conditions that promote *in vivo* persistence and activity of infused antigen-specific T cells. Combinations with immune checkpoint inhibitors or epigenetic modifiers to improve T-cell activity are also being evaluated in the clinic. Antigen-specific T cells may also be manufactured to overcome tumor evasion mechanisms by targeting multiple antigens and engineered to be resistant to inhibitory factors, such as TGF β , or to produce the cytokines that are essential for T-cell expansion and sustained antitumor activity. Here, we discuss the use of T cells specific to tumor antigens through their native receptors and strategies under investigation to improve antitumor responses.

Introduction

Adoptive transfer of T cells genetically modified with chimeric antigen receptors (CAR) recognizing the CD19 molecule has produced encouraging response rates in several CD19-expressing malignancies, resulting in FDA approvals of CD19.CAR T cells for the treatment of relapsed acute lymphoblastic leukemia and non-Hodgkin lymphoma (1). Another type of T-cell therapy utilizes endogenous T cells with native receptor specificities for tumor-associated antigens (TAAs), which can be expanded *ex vivo* to produce antigen-specific T cells for subsequent administration (2). This approach encompasses tumor-infiltrating lymphocytes (TILs) isolated in association with tumor tissues and endogenous T cells obtained from peripheral blood. The antigen-specific T cells can be selected directly from peripheral blood using HLA-peptide streptamers or by capture of T cells that secrete IFN γ after antigenic stimulation, but these strategies are challenging when few circulating T-cell precursors are present, thus, the strategies are mainly used to select T cells specific for viral antigens. Most manufacturing methodologies to expand tumor antigen-reactive T-cell lines rely on *ex vivo* culture with repetitive antigenic stimulation with the appropriate antigen-presenting cells and cytokines while preserving specificity and function.

Advantages of this approach include the ability to target multiple antigens, which addresses clonal heterogeneity to reduce the risk of tumor escape, and the induction of epitope spreading—a process in which endogenous T cells with new specificities arise in patients postinfusion. Epitope spreading has consistently been shown to correlate with clinical responses (3, 4). However, one challenge of targeting antigens with the native T-cell receptor (TCR) is that most candidate TAAs expressed are less immunogenic than viral antigens, which have been successfully targeted in multiple studies. This article will focus on adoptive immunotherapy strategies using endogenous T cells that recognize tumor antigens through their native TCR, highlighting their current status and potential future research directions.

Target Antigens

An ideal TAA would be universally and selectively expressed on tumor cells and essential for the maintenance of the oncogenic phenotype of the tumor. Many candidate antigens have been validated through the detection of T cells specific for the antigen during a clinical response to donor lymphocyte infusion following allogeneic hematopoietic stem cell transplant (HSCT), TIL infusion, or a vaccine (Table 1). TAAs can be classified into several categories, as summarized in Table 1.

Virus-Specific T Cells for the Treatment of Malignancies

Virus-derived antigens represent optimal targets for a T-cell immune response, as they are usually immunogenic and widely expressed on the tumor cells. Five major oncogenic virus groups—human papillomaviruses (HPV), Epstein-Barr virus (EBV),

Center for Cell and Gene Therapy, Baylor College of Medicine, Houston Methodist Hospital and Texas Children's Hospital, Houston, Texas.

Corresponding Author: Helen E. Heslop, Baylor College of Medicine, 1102 Bates St, Suite 1630, Houston, TX 77030. Phone: 832-824-4662; Fax: 832-825-4668; E-mail: hheslop@bcm.edu

doi: 10.1158/2326-6066.CIR-18-0888

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Table 1. Tumor-associated antigens

Tumor antigen	Examples	Targeting strategies
Viral	EBV Merkel cell polyoma virus HPV	Donor virus-specific T cells (VST) post HSCT (7, 8) Autologous EBVSTs (10, 11, 34) Third party EBVSTs (8, 9, 38) Autologous VSTs (39) TILs (13)
Shared mutated antigens and fusion proteins	BCR-ABL	Autologous and normal donor-specific T cells (16)
Lineage-restricted antigens	MART WT1 PR1	Autologous MART-1-specific T cells (35) Donor-derived WT1-specific T cells (26) Vaccine (40)
Cancer testis antigens	NY-ESO PRAME SSX MAGE	Autologous TAA-specific T cells (22, 41)
Antigens overexpressed in tumors	hTERT Survivin	T cells with vaccine (42) Autologous TAA-specific T cells (41, 42)
Individual neoantigens	Mutation in ERBB2-interacting protein	TILs enriched for mutation-specific T cells (19)
Minor histocompatibility antigens	HA1	Donor-derived minor specific T cells (43)

human herpesvirus 8, human T-cell leukemia virus (HTLV 1), and Merkel cell polyoma virus—are associated with up to 15% of malignancies. EBV-specific T cells have been the most used T cells for immunotherapy targeting viral cancers, with evidence of specificity, safety, and clinical responses in multiple trials (5). The most immunogenic EBV-associated malignancy is posttransplant lymphoproliferative disease (PTLD), which develops in the setting of immunosuppression following HSCT or solid organ transplant (SOT; ref. 6). PTLD shows a type III latency pattern that expresses all nine latent cycle EBV antigens, including the immunostimulatory EBNA-3 antigens. Many studies have evaluated whether EBV-specific T cells generated from the stem cell donor can prevent and treat this complication (5). Our group has reported that none out of 101 high-risk allogeneic HSCT patients who received donor-derived EBV-specific T cells as prophylaxis developed PTLD compared with 12% in a historical cohort, whereas 11 of 13 patients with active PTLD attained complete clinical responses to treatment without significant GVHD or toxicity (7). Several other groups have observed similar response rates (5, 8). EBV-related PTLD post-SOT is a more challenging problem, as the malignant clones are usually derived from recipient B cells, and the patients usually need to remain on immunosuppression regimens. Several groups have reported activity with autologous EBV-specific T-cell treatment, but more studies now focus on third-party EBV-specific T cells generated from normal donors, which have the advantage of being immediately available and producing similar response rates without evidence of GVHD (9).

EBV is also associated with approximately 40% of Hodgkin (HL) and non-Hodgkin lymphoma (NHL) in immunocompetent hosts, and 95% of cases of nasopharyngeal cancer (NPC; ref. 6). However, tumor cells in these diseases express a more limited array of antigens, including EBNA1, LMP1, LMP2, and BARF1 that are less immunogenic, but still can act as targets. Bollard and colleagues (3) manufactured autologous virus-specific T cells (VST) that were enriched for T-cell clones recognizing the subimmunodominant LMP1 and LMP2 antigens and reported that 28 of 29 patients with relapsed EBV⁺ HL or NHL infused with these cells as adjuvant therapy remained in remission, whereas 13 of 21 patients with relapsed or resistant disease had clinical responses. Of note, epitope spreading was detected in the peripheral blood of patients with

clinical responses but not in nonresponders. Responses have also been reported in NPC by several groups (10, 11), and a study combining standard chemotherapy with EBVSTs in patients with relapsed NPC resulted in an encouraging response rate of 71.4% with survival rates significantly higher than those observed in historical controls receiving chemotherapy alone (12).

HPV strains 16 and 18, which are found in over 70% of cervical cancers, express the E6 and E7 oncoproteins. In a study at the NCI, 5 of 18 patients with cervical cancer infused with autologous TIL products containing T cells specific for HPV had objective responses with two complete responses being sustained for more than 50 months (13). Tumor responses were also seen in 2 of 11 (18%) patients in a noncervical cancer cohort (13). Merkel cell carcinoma (MCC) is an aggressive skin cancer caused by the Merkel cell polyomavirus. Adoptive transfer of polyomavirus-specific T cells was described in a patient with MCC, resulting in durable complete response in two of three metastatic lesions. In a follow-up study, two patients received autologous polyomavirus-specific CD8⁺ T cells in combination with immune checkpoint inhibition and had responses associated with infiltration of CD8⁺ T cells (14). Of note, both patients sustained late relapses, and the investigators were able to demonstrate transcriptional suppression of the HLA genes that presented the targeted viral epitope as a cause of tumor escape (14).

Nonviral Antigen-Specific T Cells

The successful clinical responses attained with virus-specific T cells provided a rationale for exploring this strategy in nonvirus-mediated malignancies, where it is more challenging to identify optimal target tumor antigens. Because most of these antigens are "self-antigens," T cells that recognize these antigens with high affinity should be deleted through central and peripheral tolerance mechanisms, leaving only T cells with relatively weak affinities. The ideal tumor antigen is a tumor-specific mutation, and candidates include single-nucleotide variants, insertions, or deletions. These mutations can be identified following mass spectrophotometric analysis of peptides eluted from the MHC of tumor cells or RNA-sequencing/whole-exome sequencing. However, not all such mutations are immunogenic, and intensive efforts to

validate bioinformatic algorithms to identify the most immunogenic antigens are underway (15).

Recurrent mutations

Unfortunately, few mutations are recurrent and expressed in multiple tumors. Fusion proteins, such as BCR-ABL, are one example of a recurrent mutation unique to tumor cells but are immunogenic only in the context of particular HLA alleles. Nevertheless, Comoli and colleagues reported that infusion of autologous or allogeneic Bcr-Abl-specific T cells induced molecular or hematologic complete remissions in three patients with acute lymphoblastic leukemia having the *p190 BCR-ABL* fusion (16). *JAK2 V617F* is another recurrent mutation that occurs in >50% of myeloproliferative neoplasms and T cells targeting this mutation have shown antitumor activity in preclinical studies (17). Ongoing studies will provide more data on the feasibility of targeting these mutations.

Neoantigens

Neoantigens arise from nonsynonymous genetic alterations in the tumor, and tumor transcriptome analysis has revealed that tumors express a diverse range of mutated proteins. Neoepitopes have been identified as the targets of *in vitro*-cultured TILs or peripheral lymphocytes and are known to contribute to responses (18). For example, a patient with metastatic cholangiocarcinoma exhibited tumor regression after infusion of CD4⁺ T cells targeting a mutated ERBB2IP epitope expressed by the tumor (19), and TILs reactive against a neoantigenic epitope for K-ras (identified from a patient with colorectal cancer) could reject metastatic lesions following adoptive transfer (20). Immunoglobulin neoantigens are also recognized as targets for immunotherapy in a study that interrogated tumor peptides presented by MHC class I and class II molecules in patients with mantle cell lymphoma (21). The identified peptides were all derived from the lymphoma immunoglobulin heavy- or light-chain variable regions, and CD4⁺ T cells recognizing these neoantigens could kill autologous lymphoma cells (21). However, a limitation of targeting neoantigens is that they can be unique to each tumor, increasing the time and complexity of generating a product that will only be applicable to one patient.

Antigens overexpressed in tumor cells

Targeting cancer-testis antigens, including MAGE, NY-ESO-1, SSX, and PRAME, which are expressed by many malignancies but not in normal cells other than germline tissues, is a more broadly applicable strategy. Another class of tumor-specific antigens are proteins that are overexpressed in many different tumors, but are absent from or have low expression in healthy tissues, such as hTERT and survivin. Several studies have targeted either individual antigens or multiple antigens, which can reduce the risk of single-antigen editing and, thus, tumor immune evasion. One of the earliest reports describes a patient with metastatic melanoma who achieved a durable complete response upon receiving NY-ESO-1-specific CD4⁺ T cells, which associated with antigen spreading to other melanoma antigens (4). Our group has used overlapping peptides that can present both HLA class I- and class II-restricted epitopes to reactivate TAA-specific T cells and to overcome the possibility of tumor escape by targeting multiple epitopes in five antigens

(PRAME, SSX2, MAGEA4, NY-ESO-1, and survivin) with promising clinical responses in lymphoma and myeloma (22). Responses correlate with the detection of T cells specific for the targeted tumor antigens and with detection of epitope spreading *in vivo* (22).

Lineage-restricted antigens

Some lineage-restricted antigens may also be targets if they are expressed on tumor cells as well as the normal tissue of origin. Such antigens include the melanoma-associated antigens MART, gp100, or Melan-A that were first identified as targets of melanoma-infiltrating lymphocytes, and PR1 and WT1 expressed on acute myeloid leukemia (23, 24). One limitation of targeting lineage antigens is their potential to also target normal cells, as evidenced by the vitiligo observed in patients treated with MART-specific T cells (23). T cells recognizing WT1 and PR1 can be detected in recipients after HSCT (25). For example, Chapuis and colleagues infused donor-derived WT1-specific CD8⁺ T-cell clones after HSCT and observed long-term persistence of the transferred T cells and clinical responses, with a transient response in one patient with extensive disease and a remission in a patient with minimal residual disease (26).

Strategies to Enhance Antigen-Specific T Cells

Defining optimum T-cell populations

Although infusion of antigen-specific T cells has shown benefit in many clinical studies, the results could be further improved if trafficking, function, and persistence of transferred T cells could be enhanced. High-throughput TCR tracking analysis has been undertaken to define the attributes associated with persistence. An analysis in patients receiving adoptive T-cell therapy targeting melanoma antigens or NY-ESO-1 revealed that many of the clonotypes in the infused autologous polyclonal lines were derived from a low frequency T-cell population that likely represented naïve cell populations in the patients' peripheral blood, which was used to manufacture the infused product (27). Clinical responses associated with expansion of these low frequency populations in the infused lines, supporting the contention that early differentiation phenotypes are beneficial for adoptive transfer (27).

Tumor microenvironment milieu

Another major avenue of research to improve antigen-specific T-cell therapy is to overcome the immunosuppressive milieu of the tumor microenvironment (TME) that consists of immune cells, fibroblasts, and endothelial cells in a robust extracellular matrix. Optimal T-cell activation and proliferation requires a distinct set of signals, which consist of antigen-specific CD3ζ activation (signal 1) via TCRs and costimulation (signal 2). Upon proper costimulation, cytokines (signal 3) are produced, which are critical for T-cell expansion and their sustained antitumor activity. Components of the TME can block the activity of immunostimulatory cytokines that are essential for preserving the optimal activity of T cells. Modulation of cytokine activity is, therefore, a strategy to enhance the proliferation and activity of infused antigen-specific T cells (Fig. 1).

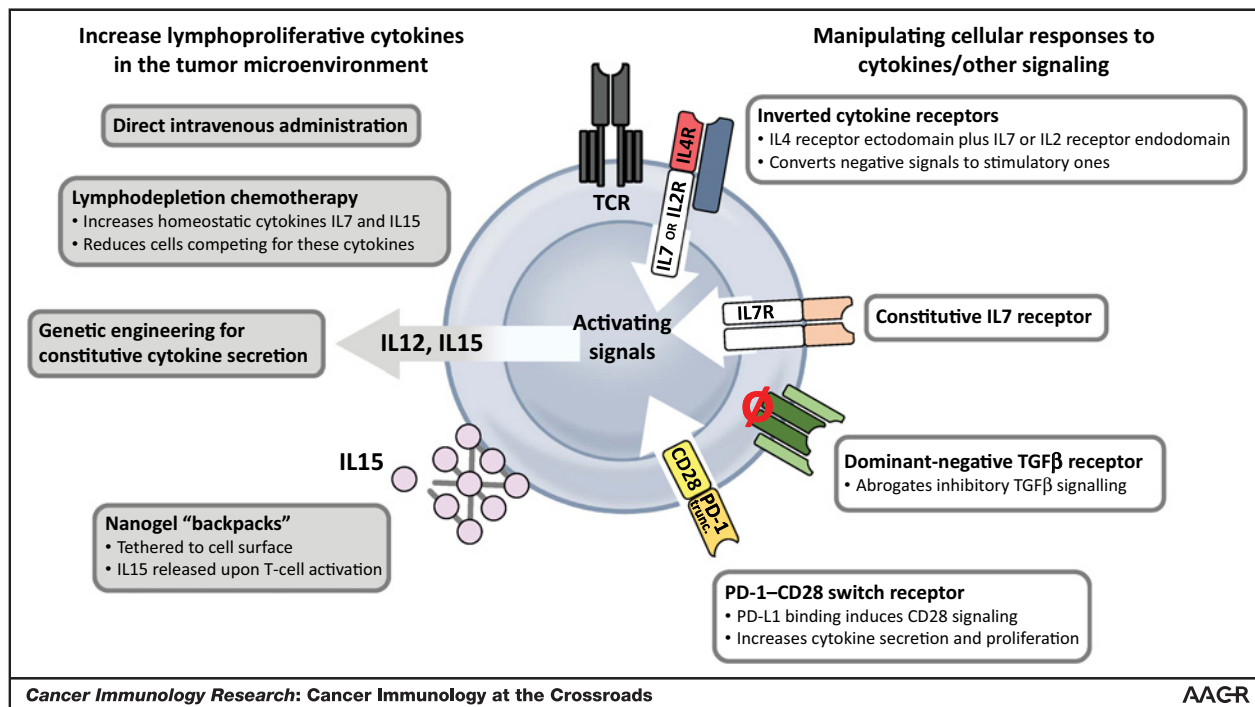


Figure 1.

Modulation of cytokines to augment T-cell responses. Several different strategies to increase lymphoproliferative cytokines in the TME exist, including direct administration of cytokines, use of lymphodepletion to produce homeostatic cytokines, or modification of the infused T cells by genetic engineering or a nanogel "backpack" (left). An alternative strategy is to transduce the cell with a switch receptor to convert a negative signal into a positive signal or to activate a cytokine receptor (right).

Robust evidence from studies of CAR-T cells shows that lymphodepletion chemotherapy, such as cyclophosphamide and fludarabine, which reduce suppressive cellular cytokines while promoting the production of IL7 and IL15, is a crucial step that produces an environment where the infused T cells can thrive. A variety of mechanisms for this benefit have been proposed, including increased homeostatic cytokine availability (Fig. 1), abrogation of an anti-CAR immune response, and depletion of indoleamine deoxygenase in the TME (28, 29). An alternative approach to chemotherapy is to genetically modify infused antigen-specific T cells to constitutively secrete immunostimulatory cytokines such as IL15 and IL12 (Fig. 1). This strategy is being tested in the clinic for patients with solid tumors. Genetic engineering can also be used to overexpress cytokine signaling systems. Shum and colleagues (30) constructed a constitutively signaling cytokine receptor (C7R) to augment T-cell function following antigen exposure, and others have devised nanogel "backpacks" of IL15 molecules linked by synthetic disulfide cross-linkers on T cells, which are released upon encountering tumor cells, driving antitumor activity (31) (Fig. 1).

Genetic modification

In addition to altering the cytokine composition, T-cell responses can be manipulated to convert negative signals into stimulatory ones. Chimeric cytokine receptors in which the IL4 receptor exodomain is fused to the IL7 receptor endodomain (32) or a genetically engineered switch receptor construct

comprising the truncated extracellular domain of PD-1 and the transmembrane and cytoplasmic signaling domains of CD28 (33) can both boost the activity of CAR T cells in murine solid tumor models. In a clinical study, EBV-specific T cells were genetically modified to express a dominant-negative TGFβ receptor rendering them resistant to this inhibitory cytokine (34). These cells safely expanded with no acute or long-term toxicities, and 4 of the 7 evaluable patients with active disease attained clinical responses (34). Overall, these studies demonstrate that immunosuppressive pathways can be circumvented and potentially manipulated to provide stimulatory signals to T cells (Fig. 1).

Combination therapies

Interest to combine immune checkpoint inhibition and epigenetic drugs with adoptive T-cell therapies is rising. A study evaluating the combination of CTLA-4 inhibition with infusion of MART-1-specific T cells in 10 patients with advanced melanoma showed that the clinical responses seen (2 complete remissions, 2 partial responses, and 3 stable disease) were associated with epitope spreading and detection of cells in the recipients with phenotypic T-cell characteristics of long-lived memory cells (35). Epigenetic drugs can increase the expression of tumor antigens to engage cognate TCRs, thereby, potentially activating the adoptively transferred T cells (36). Several trials are exploring the combination of epigenetic drugs with adoptive T-cell therapy. For instance, histone deacetylase inhibitors can induce the expression of lytic cycle antigens in EBV-associated malignancies (37).

Conclusion

Adoptive transfer of endogenous T cells with the native TCRs directed at viral or nonviral antigens is an attractive cancer treatment option due to the ability of these cells to discriminate between normal and malignant tissues. Multiple clinical studies have demonstrated significant clinical responses in the absence of short- or long-term toxicities, and a consistent finding is the development of epitope spreading in responders. Numerous ongoing studies should identify methods to further enhance the activation, antitumor activity, and persistence of these infused T cells.

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