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Review

T-cell receptor gene therapy — ready to go viral?☆

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ABSTRACT

T lymphocytes can be redirected to recognize a tumor target and harnessed to combat cancer by genetic introduction of T-cell receptors of a defined specificity. This approach has recently mediated encouraging clinical responses in patients with cancers previously regarded as incurable. However, despite the great promise, T-cell receptor gene therapy still faces a multitude of obstacles. Identification of epitopes that enable effective targeting of all the cells in a heterogeneous tumor while sparing normal tissues remains perhaps the most demanding challenge. Experience from clinical trials has revealed the dangers associated with T-cell receptor gene therapy and highlighted the need for reliable preclinical methods to identify potentially hazardous recognition of both intended and unintended epitopes in healthy tissues. Procedures for manufacturing large and highly potent T-cell populations can be optimized to enhance their antitumor efficacy. Here, we review the current knowledge gained from preclinical models and clinical trials using adoptive transfer of T-cell receptor-engineered T lymphocytes, discuss the major challenges involved and highlight potential strategies to increase the safety and efficacy to make T-cell receptor gene therapy a standard-of-care for large patient groups.

Abbreviations: ACT, adoptive cell therapy; allo-SCT, allogeneic stem cell transplantation; APC, antigen-presenting cell; BLAST, basic local alignment search tool; CAR, chimeric antigen receptor; CTL, cytotoxic T lymphocyte; DC, dendritic cell; EGFR, epidermal growth factor receptor; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HPA, Human Protein Atlas; IL, interleukin; ImmTAC, Immune-mobilizing monoclonal TCR Against Cancer; MDSC, myeloid-derived suppressor cell; MHC, major histocompatibility complex; MiHA, minor histocompatibility antigen; MPO, myeloperoxidase; NK, natural killer cell; NKT, natural killer T cell; PBMC, peripheral blood mononuclear cell; PD-1, programmed cell death protein 1; pMHC, peptide-MHC complex; SCT, stem cell transplantation; TAA, tumor-associated antigen; T_{CM}, central memory T cell; TCR, T-cell receptor; T_{EM}, effector memory T cell; T_E, effector T cell; T_H, helper T cell; TIL, tumor infiltrating lymphocytes; T_N, naïve T cell; T_{reg}, regulatory T cell; T_{SCM}, stem cell memory T cell; WT1, Wilms tumor antigen 1.

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1. Introduction

Solid evidence that the immune system can eradicate cancer came from studies of bone marrow transplantation from healthy donors to patients with hematological malignancies, first performed in the late 1950s by E. Donnall Thomas (Thomas et al., 1957). Although the transfer of donor-derived T cells with up to 10^7 different and unknown specificities might not have received approval if suggested for the first time today, as proof of its curative potential this treatment still remains part of the standard therapeutic regimen for patients with leukemia or lymphoma. The transfer of a heterogeneous donor-derived T-cell repertoire to a human leukocyte antigen (HLA)-matched donor is, however, frequently associated with severe adverse effects caused by T-cell recognition of polymorphic antigens expressed in normal tissues of the patient. The occurrence of so-called graft-versus-host disease (GVHD) thereby limits the application of this treatment (reviewed by Jedema and Falkenburg, 2015). This safety hazard is omitted by use of the endogenous T-cell repertoire to target cancer. In a series of pioneering studies, Rosenberg and colleagues were the first to demonstrate that, following *in vitro* expansion and adoptive transfer back to the patient, tumor-infiltrating lymphocytes (TIL) can efficiently treat malignant melanoma (Dudley et al., 2008; Rosenberg et al., 2011, 1994; Topalian et al., 1988). However, the efficacy of TILs in other types of cancers is uncertain (TIL therapy is reviewed by Geukes Foppen et al., 2015). Another approach that relies on the natural T-cell repertoire is the blocking of negative immune checkpoints by therapeutic antibodies. Recent results indicate that checkpoint inhibition can induce remarkable clinical responses, including durable complete remissions (Hodi et al., 2010; Topalian et al., 2012; and reviewed in Lesokhin et al., 2015; Sharma and Allison, 2015; Sledzinska et al., 2015). The curative potential of TIL therapy as well as immune checkpoint inhibition is, however, likely limited by T-cell tolerance to tumor. This tolerance can be circumvented by equipping large numbers of patient-derived T cells with immune receptors recognizing a defined tumor-associated antigen (TAA) with high affinity. Recently, adoptive transfer of T cells genetically modified to express chimeric antigen receptors (CARs) consisting of CD19-specific antibodies grafted onto T-cell receptor (TCR) signaling domains have successfully induced long-lasting remissions in patients with hematological malignancies (Brentjens et al., 2013, 2011; Grupp et al., 2013; Kochenderfer et al., 2013, 2012, 2015; Maude et al., 2014; and reviewed in Whilding and Maher, 2015). However, CARs are limited to engaging native cell surface molecules. In spite of an extensive search, it has proven difficult to identify membrane targets that are cancer-specific or, in addition to tumor, are expressed only on cells that are expendable to the host (Lamers et al., 2013; Morgan et al., 2010). Thus, redirecting T cells with TCRs, which in principle are capable of recognizing peptides from all cellular proteins, might be an attractive alternative to allow application of T-cell gene therapy to a wider selection of cancers.

The first studies describing that TCR gene transfer can redirect T lymphocytes and provide them with antitumor reactivity *in vitro* (Clay et al., 1999) paved the way for studies demonstrating that both CD8 and CD4 T lymphocytes redirected by TCR gene transfer are functional and capable of mediating potent antitumor effects *in vivo* using mouse models (Chamoto et al., 2004; Kessels et al., 2006, 2001; Morris et al., 2005; Tahara et al., 2003; Xue et al., 2005). Immunotherapy based on TCR gene transfer rapidly followed. The first published clinical trial of TCR gene therapy was conducted with melanoma patients who received T lymphocytes targeting the melanoma/melanocyte differentiation antigen MART-1, but relatively modest clinical responses were observed (Morgan et al., 2006) (Table 1). The TCR was derived from a TIL clone that was obtained from a melanoma patient who demonstrated a nearly complete regression of the metastatic cancer after adoptive cell therapy (ACT) with TILs (Hughes et al., 2005). A higher affinity TCR against the MART-1 antigen derived from the same patient (Johnson et al., 2006) provided more potent antitumor responses, but on-target toxicities in healthy tissues occurred (Johnson et al., 2009). An affinity-enhanced TCR targeting the cancer/testis antigen NY-ESO-1 (Robbins et al., 2008) proved, however, safe and effective in therapy of melanoma, synovial cell sarcoma and myeloma, and 55%, 61% and 80% of treated patients had objective clinical responses, respectively (Rapoport et al., 2015; Robbins et al., 2015, 2011) (Table 1).

Studies targeting other antigens raised, however, concerns about the safety of TCR gene therapy (Linette et al., 2013; Morgan et al., 2013; Parkhurst et al., 2011) and demonstrated the need for developing preclinical methods to evaluate potential toxicities. Here, we discuss the increasing experience gained from preclinical and clinical studies with adoptive transfer of TCR gene-modified T cells, and emerging solutions to address the safety concerns as well as the need for enhanced therapeutic efficacy. The major challenges include 1) identification of antigens for safe and effective tumor-targeting, 2) identification of TCRs with optimal affinity and desired specificity, 3) development of preclinical assays and models that give information about safety and efficacy before clinical use, 4) improvement of *ex vivo* genetic engineering, cell selection and expansion procedures to generate a highly potent T-cell infusion product, and 5) strategies to prepare the host to increase the persistence and therapeutic effect of the adoptively transferred T cells *in vivo* (Figure 1).

2. Identification of antigens for safe and effective tumor targeting

The choice of the target antigen forms the basis for the safety and efficacy of TCR-based gene therapy, and as such remains the most central challenge in the development of this therapeutic strategy. Thorough knowledge of the expression profile of the selected target antigen is the key to success. A major question is which lessons can be learned with regard to on-target toxicity from the clinical use of T cells genetically engineered with TCRs and CARs (off-target toxicity is discussed in Sections 3 and 4). In retrospect, could any of the detrimental effects seen in some of these trials have been avoided with the knowledge we have today? And more importantly, can