Cell Biol Toxicol (2017) 33:323–327
DOI 10.1007/s10565-017-9397-6

EDITORIAL

T cell modulation in immunotherapy for hematological malignancies

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Received: 10 March 2017 / Accepted: 30 April 2017 / Published online: 4 May 2017

We have come to realize that T cell-centered immunotherapy is a promising approach for patients with hematological malignancies and may result in a disease cure. Hematological malignancies can downregulate target antigens and generate an immunosuppressive environment to escape the host immune response. It has become clear that the goal of immunotherapy is to exploit the patient immune system or confer immunity with T cells, NK cells, or monoclonal antibodies to kill tumor cells, and inducing and/or recovering T cell activation is a key aspect of these immunotherapies.

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Direct target immunotherapy by genetic engineering cytotoxicity T cells

T cells perform a key function in cell-mediated immunity against tumor cells. It has been demonstrated that adoptively transferred antigen-specific T cells including T cell receptor (TCR) redirected T cells (TCR-T) and chimeric antigen receptor (CAR) T cells (CAR-T) could have intense antitumor effects. CAR-T usually consisted of the single-chain variable fragment of an antibody specific for a tumor antigen linked to an intracellular signaling domain that could contain co-stimulatory domains and T cell activation moieties. In contrast to TCR-T, CAR-T are cytotoxic to antigens in an MHC-unrestricted fashion. Eshhar et al. pioneered the first generation of CAR-T cells in 1989. CAR-T treatment provided a novel option for patients who failed multiple lines of chemotherapy or hematopoietic stem cell transplantation (HSCT). The first CAR-T used for clinical trials is CAR-T targeting CD19, which is expressed on malignant B cells, such as B cell acute lymphocytic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), or B cell lymphoma (Kalos et al. 2011; Kochenderfer et al. 2012; Porter et al. 2011). CD19-CAR-T has produced dramatic anti-tumor effect in patients with relapsed/refractory B-ALL with high complete remission rates of 61–93% and durable remissions (Lee et al. 2014; Maude 2017). Recently, more and more types of CAR-T to target different antigen such as CD20- and CD22-CAR for B-ALL; CD139 (CS1)-,

CD138-, and CD38-CAR for MM; CD33- and CD123-CAR for acute myeloid leukemia (AML); CD116-CAR for myeloid leukemia; and CD30-CAR for Hodgkin lymphoma (HL) were reported in preclinical or in ongoing clinical trials (Haso et al. 2013; Lee et al. 2014; Maude et al. 2014; Nakazawa et al. 2016; Rufener et al. 2016; Thokala et al. 2016; Wang et al. 2017).

Indirect target immunotherapy by bispecific T cell engaging antibody inducing T cell activation

In addition to the adoptively transferred T cell therapy, a number of other exciting new immunotherapeutic approaches has emerged for inducing or recovering T cell activation to kill tumor cells in recent clinical trials. One of these approaches is bispecific T cell engaging antibodies (BiTEs). BiTEs are designed to avoid the drawback that antibodies do not directly recruit T cells to tumors to promote antitumor immune responses. BiTEs comprise minimal binding domains containing two distinct antibodies via a short peptide, which crosslink T cells with tumors. Most researchers use BiTEs directed against the ε chain of the CD3 complex to target host T cells because all mature T cells express CD3, and its engagement activates them. It has been demonstrated that BiTEs mediate robust T cell activation, leading to the apoptosis of tumor cells and secretion of the cytokines IL-2, TNF-α, and IFN-γ. Bargou et al. performed the first BiTE (blinatumomab) trial with seven non-Hodgkin's lymphoma (NHL) patients, targeting $CD3^+$ T cells to $CD19^+$ B lymphocytic malignant cells and leading to elimination of target cells in the blood (Bargou et al. 2008). In 2016, this group released the final results from their phase I study. In 76 heavily pretreated patients with relapsed/refractory NHL, including 14 with diffuse large B cell lymphoma (DLBCL), the overall response rate was 69% across the NHL subtypes and 55% for diffuse large B cell lymphoma (n = 11), and the median response duration was 404 days (Goebeler et al. 2016). Thus, as a single agent, blinatumomab has anti-lymphoma activity. A phase 2 study of blinatumomab in relapsed/refractory DLBCL is in progress (Viardot et al. 2016). Recently, novel bispecific T cell engaging antibodies, such as CD33-CD3 and B cell maturation antigen (BCMA)-CD3 were developed as a potential therapy for relapsed/refractory AML, multiple myeloma (MM) (Fan et al. 2015; Hipp et al. 2017).

Indirect T cell activation by inhibiting T cell co-inhibitory factors

T cell activation is not only based on upregulating T cell stimulators but also related to downregulating T cell inhibitors. T cells express a number of co-stimulatory and co-inhibitory molecules on the cell surface. Co-stimulatory molecules allow T cell activation, whereas co-inhibitory molecules are negative counterparts that act as immune regulators, leading to a state of anergy. The balance between co-stimulatory and co-inhibitory signals on T cell membranes ultimately affects their overall activation and function. In most cancer contexts, co-inhibitory factors called as immune checkpoints, such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death 1 (PD-1), can accumulate at the membranes of T cells. Immune checkpoint inhibitors have also demonstrated good proof of efficacy for inducing or recovering T cell activation against tumor cells. Therefore, it is the third approach for enhancing anti-tumor T cell function in hematologic malignancies. Obviously, immunotherapy by anti-CTLA-4 and anti-PD-1/PD-L1 have shown astonishing results by promoting immune responses against cancers as well as disrupting tumor resistance in hematologic malignancies. For example, in a phase I clinical trial of ipilimumab (anti-CTLA4 monoclonal antibody for relapsed hematological malignancies including HL, AML, multiple myeloma (MM), CLL, CML, and NHL following allo-HSCT), the clinical effect is associated with T cell activation (Zhou et al. 2011). Similar to CTLA-4 blockade, PD-1 inhibition was found to mediate the clinical activity in a variety of cancers. PD-1 inhibition using a humanized monoclonal antibody has been evaluated in patients with refractory AML, CLL, HL and NHL, and MM. In a cohort with 28 patients with relapsed or refractory HL, treatment with nivolumab (PD-1 inhibitor) showed that an objective response was demonstrated in 20 patients (87%), including 17% with a CR and 70% with a PR; the remaining 3 patients (13%) had stable disease (SD). The progression-free survival rate at 24 weeks was 86% (Ansell et al. 2015).

It has been proven that the amount of $CD4^+CD25^{high}$ regulatory T cells (Treg cells) is elevated in patients with both solid tumors and hematologic malignancies. Treg cells are important mediators of active immune evasion in cancer. Thus, there is a need to devise effective immunotherapies targeting Treg cells to improve

antitumor immunotherapy. Interruption of PD-1/PD-L1 interactions not only leads to antigen-specific CTL activation but also to a decrease in Treg suppressive function (Ascierto et al. 2010). Surprisingly, it was found that Tregs could be converted into cytotoxic lymphocytes (CTL) via cross-linking with tumors via the BiTE format (Choi et al. 2013). This phenomenon occurs in mice, and the mechanisms by which BiTEs potentiate the antitumor activity of Tregs remains to be elucidated. Using immunostimulatory adjuvants, such as agonistic ligands for TLRs, have revealed their therapeutic potential. In lung carcinoma, leukemia, and melanoma mouse models, treatment with a synthetic bacterial lipoprotein (BLP) TLR1/2 agonist mediates tumor regression by reducing the Treg suppressive effects and increasing the $CD8^{+}$CTL cytotoxic function (Zhang et al. 2011).

Overall, with the novel techniques and products, immunotherapy becomes a critical role for hematologic malignancies, while T cell modulation is the important step. To improve the effects, CAR-T have been developed as first, second, third, and fourth generation agents based on the number of intracellular signaling domains of the cell surface receptors (Allegra et al. 2016). Moreover, combination CAR-T with different factors which can improve T cell function or inhibit tumor cell proliferation, such as ibrutinib (Bruton tyrosine kinase (BTK) inhibitor), BiTEs, or PD-1, may be the effective strategy. For example, in CLL, ibrutinib therapy improved the expansion of CD19-CAR T (CTL019), and it was associated with decreased expression of PD-1 on T cells and CD200 on CLL cells; this finding may guide the combination therapy of clinical trials for CLL (Fraietta et al. 2016). Because PD-1 upregulation within the tumor microenvironment inhibited T cell function, CAR-T with cell-intrinsic PD-1 shRNA blockade or through PD-1 antibody blockade can improve CAR-T function (Cherkassky et al. 2016).

Summary and prospect

Most antitumor immunotherapies are based on inducing the activation of antitumor T cells, which corresponds to resulting clinical effects. However, several issues needed to be discussed: (1) Currently, CAR-T therapy is restricted by the requirement of generating individual cellular products for each patient (Cheadle et al. 2014). Therefore, how to generate the universal CAR-T is an interesting issue; a recent finding showed that directing a CD19-specific CAR to the T cell receptor α constant (TRAC) locus CRISPR/Cas9 genome editing, these CAR-T without TCRα expression not only result in uniform CAR expression in human T cells but also enhances T cell potency (Eyquem et al. 2017); moreover, pluripotent stem cell-derived T cells, or CAR-modified human-induced pluripotent stem cell (hiPSC)-derived engineered T cells may be considered as the novel approach for uniform CAR-T application in the future. On the other hand, engineered γδ T cells without MHC-restricted may be also considered as a new platform for T cell immunotherapy. (2) The differences of T cell activation status in different patients may influence responses to immunotherapies, so-called immune heterogeneity**,** which may be due to factors including the status of immunosuppression and T cell signaling pathway activation. Therefore, to improve the effect of immunotherapy, detection of immune biomarkers must be established and to determine how to enhance the T cell reactivation before or during immunotherapy, it is worthy to discuss. On the other hand, donor T cells with normal activated function derived CAR-T may have high anti-tumor activity, in which graft-versus-host activity (GVHD) is under control (Ghosh et al. 2017). (3) Novel approach for persistence and high effect of engineered T cells is needed to improve continually. (4) Finally, for prediction of immunotherapy effect, as well as the possibility and risk of severe side effects such as cytokine release syndrome and CNS toxicity, it is needed to establish an effective immune evaluation system.

Acknowledgements This study was supported by grants from the National Natural Science Foundation of China (Nos. 81570143 and 91642111), the Guangdong Provincial Basic Research Program (No. 2015B020227003), the Guangdong Provincial Applied Science and Technology Research & Development Program (No. 2016B020237006), the Guangzhou Science and Technology Project of China (No. 201510010211), and the Fundamental Research Funds for the Central Universities of China (No. 21616108).

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