Review

Approaches for generation of anti-leukemia specific T cells

Zhenyi Jin [a, b], Ling Xu [a, c, **], Yangqiu Li [a, c, *]

[a] Key Laboratory for Regenerative Medicine of Ministry of Education; Institute of Hematology, School of Medicine; Jinan University, Guangzhou, 510632, China
[b] Integrated Chinese and Western Medicine Postdoctoral Research Station, Jinan University, Guangzhou, 510632, China
[c] Department of Hematology, First Affiliated Hospital, Jinan University, Guangzhou, 510632, China

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ABSTRACT

As three decades ago, it was reported that adoptive T cell immunotherapy by infusion of autologous tumor infiltrating lymphocytes (TILs) mediated objective cancer regression in patients with metastatic melanoma. A new era of T cell immunotherapy arose since the improvement and clinical use of anti-CD19 chimeric antigen receptor T cells (CAR-T) for the treatment of refractory and relapsed B lymphocyte leukemia. However, several challenges and difficulties remain on the way to reach generic and effective T cell immunotherapy, including lacking a generic method for generating anti-leukemia-specific T cells from every patient. Here, we summarize the current methods of generating anti-leukemia-specific T cells, and the promising approaches in the future.
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1. Introduction

Leukemia is a group of blood cancers arising from hematopoietic stem/progenitor cells. Treatment of leukemia can be complex due to the variable types of leukemia and patient-related factors such as age. Stem cell transplantation is the major form of treatment, which most likely led to complete remission (CR). Moreover, targeted therapy and biological therapy are also commonly used in the clinic. The first targeted drug, anti-CD20 antibody, was approved for use in CD20 + B cell leukemia and lymphoma in 1997,[1] and the first successful small molecule drug, the tyrosine kinase inhibitor (TKI) imatinib, which targets BCR-ABL, was introduced in clinical practice in 1998 to treat chronic myelogenous leukemia (CML).[2] The benefit from TKI treatment is that greater than 90% of CML patients could live without leukemia burden. All-trans-retinoic acid (ATRA) treated patients with acute promyelocytic leukemia (APL) has a even higher remission rate.[3] Increasing numbers of targeted drugs, such as BTK inhibitors, BCL-2 inhibitors, FLT3 inhibitors, and IDH inhibitors, have been used in clinical trials for treating different leukemia subtypes.[4–6]

Cancer-associated immune suppression can cause defectiveness of T cell-mediated anticancer immunity, which is an important factor for prognosis of leukemia.[7] Reasonably, adoptive T cell immunotherapy may significantly improve the clinical outcome of leukemia. Evidence that tumor-infiltrating lymphocytes (TILs) could eliminate tumor cells was first described by Rosenberg.[2] Subsequently, in the setting of allogeneic hematopoietic stem cell transplantation (allo-HSCT), donor NK and T cells were found to be capable of destroying both leukemic and leukemic stem cells, which is referred to as the graft-versus-leukemia (GVL) effect.[8] In the same year, Kolb et al. reported that donor lymphocyte infusion

* Corresponding author. Key Laboratory for Regenerative Medicine of Ministry of Education, Institute of Hematology, Department of Hematology, First Affiliated Hospital, School of Medicine, Jinan University, No.601 West of Huangpu Avenue, Guangzhou 510632, China. Fax: +86 20 85220262.
** Corresponding author. Key Laboratory for Regenerative Medicine of Ministry of Education; Institute of Hematology, Department of Hematology, First Affiliated Hospital, School of Medicine; Jinan University, Guangzhou, 510632, China.
E-mail addresses: jinzhenyijnu@163.com (Z. Jin), lingxu114@163.com (L. Xu), yangqiuli@hotmail.com (Y. Li).
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(DLI) is effective for treating CML patients who suffer disease relapse after HSCT and other types of refractory and relapsed leukemia.[9] Based on these discoveries, generation of anti-leukemia specific T cells has become a core interest for scientists in cell therapy field over the past several decades. Together with the success of second-generation CAR-T cells treating B cell leukemia, T cell immunotherapy, alone or in combination with other traditional leukemia treatments, has gradually become a powerful therapeutic strategy for B cell leukemia. While the challenges and difficulties remain in generating anti-leukemia-specific T cells, here we summarize and emphasize the current methods used for generation of anti-leukemia-specific T cells, and discuss promising methods that might be used in the future.

2. Resources and approaches for generating anti-leukemia-specific T cells

The direct resources of anti-leukemia T cells generating include patient autologous peripheral blood (PB), bone marrow (BM) and human leukocyte antigen (HLA) matched allogeneic individuals. While, there are several approaches for generating anti-leukemia-specific T cells, including ex vivo expansion, gene-modification as well as reprogramming. When using the method of reprogramming, the resource of T cell generation could be enlarged a great degree. Theoretically, all kinds of stem cells and somatic cells are reprogrammable. Here, we would like to introduce the methods had been tested either in clinical or in laboratory following the development of these techniques.

3. Autologous T cells from leukemia patients

Anti-tumor T cells were first identified from TILs in melanoma patients. After in vitro culture with interleukin-2 (IL-2), amplified autologous T cells from TILs were enriched and re-infused into patients, which consequently demonstrated an anti-melanoma effect.[10] Similarly, anti-leukemia-specific cytotoxic T cells (CTLs) could be identified in peripheral blood and bone marrow from patients with leukemia. Candidate antigens for these cells should be unique or up-regulated by leukemic cells to reduce the risk of side effects on normal cells. Diverse autologous CTLs targeting different leukemia-associated antigens have been identified, including preferentially expressed antigens of Wilm's tumor antigen 1 (WT1) CTLs, preferentially expressed antigen of melanoma (PRAME) CTLs, the receptor for hyaluronic acid mediated motility (RHAMM/CD168) CTLs, and *FLT3* internal tandem duplication (*FLT3-ITD*) CTLs from patients with leukemia.[11–14] Isolation and amplification of such leukemia antigen-specific T cells from leukemia patients is a straightforward approach for producing autologous CTLs against leukemia. However, due to the limited cell number and effect of leukemia microenvironment, ex vivo expanded leukemic-specific CTLs always show short lifespan and limited cytotoxic activity in vivo.[15] Therefore, the use of allogeneic T cells to generate anti-leukemia T cell is an efficient and feasible approach.[16]

4. Allogeneic anti-leukemia T cells from donors

DLI could eliminate CML cells in CML relapse patients after allo-HSCT.[17] Currently, DLI targeting multiple leukemia-associated antigens enhanced GVL effects for the treatment of leukemic relapse after allo-HSCT.[18] However, graft-versus-host disease (GVHD) remains a major complication after DLI.[19] Therefore, developing specific anti-leukemia T cells is important for improving the effects of allogeneic T cell treatment. The identification of T cells recognizing a specific leukemia antigen is an important step in developing autologous or allogeneic anti-leukemia T cells. Molecular and immunological techniques, such as GeneScan, Sanger sequencing, high-throughput TCR gene sequencing, tetramer analysis, and flow-cytometry combined with T cell function evaluation, allow for identification of leukemia-specific CTLs.[20–22] In addition, co-administration of cytokines and antibodies further augment the potency of the DLI. In general, allogeneic anti-leukemia T cells could be induced after stimulation with leukemia antigen peptides derived from various leukemia-associated antigens such as WT-1, BCR-ABL, hTERT, PR-1, and NY-ESO-1.[23,24] For example, human leukocyte antigen A2 (HLA-A*0201)-restricted, WT1-specific, donor-derived CD8$^+$ T cells were induced by the WT1 peptide, which showed anti-leukemia activity in treating relapsed or high-risk leukemia patients after HSCT.

Additionally, the transferred T cells even maintained a long half-life.[21] However, challenges remain in generating sufficient numbers of high-quality, antigen-specific T cells using autologous and allogeneic-derived antigen-specific T cells.[25] Alternatively, engineered T cells may overcome the above limitations.

5. Redirected T cells

Screening and expansion of autologous or allogeneic T cells are laborious, time-consuming, and inefficient.[26] Thus, engineered T cells have emerged as a new stage in precision cancer therapy. In this review, engineered T cells mainly mean TCR gene-modified T (TCR-T) cells and CAR-T cells. The idea is to enforce the expression of TCR or CAR genes on autologous or donor T cells so that they are supposed to specifically recognize leukemia antigens and enlarge their anti-leukemia cytotoxic signaling.[25,27] Except for mature T cells, HSCs are also can be endowed with those recognition and killing 'weapons'. All of these methods have their unique advantages and disadvantages respectively, although the most successful method is CAR-T cell therapy right now. The progression of these three methods is summarized in the review.

5.1. TCR-T cells

TCR-T cells are engineered by transducing autologous αβ or γδ T cells with a retroviral or lentiviral vector encoding TCR (an α chain noncovalently bound with a β chain) that recognizes peptides of interest and CD3ζ genes. When the engineered T cells recognize peptides bound to the major histocompatibility complex (MHC) on the surface of antigen-presenting or tumor cells, they become activated and start expanding.

The first TCR-T cell therapy was used in clinical trial for metastatic melanoma, whose TCR recognizing an HLA-A2−restricted peptide from a melanocytic differentiation antigen, melanoma antigen recognized by T cells 1 (MART-1).[28] Afterward, to achieve the goal of sensitively recognizing malignant cells expressing low MART-1 antigen, higher-avidity TCR targeting the mutated MART-1 epitope was developed. However, despite an improved response rate, these higher-avidity TCR-T cells showed 'on-target, off-tumor' toxicity. The side-effect was induced by lower tumor-associated antigen (TAA) expression on normal tissue and cross-reactive epitopes present on normal cells occurred in more than half of the treated patients. Thus, killing tumor cells by TCR-targeting approaches brings safety concerns. Nonetheless, numerous studies have explored the potential of engineered TCRs both at the bench and in the clinic for treating hematological malignancies. NY-ESO-1 TCR-modified T cells demonstrated efficacies against MM.[29] Engineered NY-ESO-1-TCR-T cells are now under evaluation in a late-stage clinical trial (NCT01343043, clinicaltrials.gov). WT-1 is also an interesting target for TCR transfer studies because it is persistently and highly expressed in AML, CML, and myelodysplastic syndrome (MDS). WT1-TCR-T cells successfully eliminated leukemia cells in xenograft

mouse models and leukemia-bearing NOD/SCID mice.[30–32] During the ASH (American Society of Hematology) meeting in 2014, Bar et al. reported that the infusion of escalating doses of donor-derived, virus-specific CD8$^+$ T cells expressing high-affinity TCRs specific for the HLA A*02:01-restricted WT1126-134 (RMFPNAPYL) epitope showed persist anti-leukemic activity in four of nine AML patients who belonged to high-risk AML and post-transplantation or who relapsed.[33] To investigate safety and the kinetics of TCR-T cells, the first clinical trial using WT1-TCR-T cells (HLA-A*24:02) in eight patients with refractory AML and high-risk MDS was performed. Four of five patients who had persistent WT1-TCR-T cells survived over 12 months. These results firstly demonstrate the potential of applying WT1-specific TCR-T cells in the clinic for leukemia immunotherapy.[34]

In general, engineered TCR-T cells are constructed using the recombinant TCR α and β chains to redirect the αβ T cells. However, major concerns include the mispairing of transferred TCRs with those endogenous TCRs and usage limitations by MHC restriction. To avoid mispairing, γδ T or NK cells are alternative TCR-T cell resources.[35] More recently, the introduction of TCR αβ genes to HSC or reprogrammed T cells also showed feasibility in solving this problem.[36,37] While to overcome the MHC restriction barrier, CAR-T cells are a fantastic cell model against leukemia.

5.2. CAR-T

CAR-T cells overcome some of the limitations of engineered TCR-T by using a single-chain variable fragment (scFv) derived from immunoglobulin (Ig) variable domains that can specifically recognize antigens combined with costimulatory domains from receptors such as CD28, OX40, and CD137 (also known as 4-1BB). T cells armed with CARs possess strong anti-tumor cytotoxicity based on their direct targeting of tumor antigens without the necessity of recognizing MHC binding domains, which are commonly down-regulated on tumor cells.[38,39] Anti-CD19 CAR-T cell therapy was the first great success based on CAR-T approach, which was approved by the U.S. Food and Drug Administration (FDA) for the treatment of refractory pre-B cell acute lymphoblastic leukemia (B-ALL) and diffuse large B cell lymphoma.[38] In addition to CD19, CARs targeting different tumor cell-surface antigens, such as CD33, CD123, CD138, and BCMA, have been developed for clinical trials in treating AML and MM.[38,40,41]

5.3. HSC-TCR/CAR-T

As mentioned above, although TCR-T cells show the efficacy of anti-leukemia in vivo, the introduction of exogenous TCR genes into terminally differentiated T cells also brings disadvantages. First, the activation and expansion process also activate the existing endogenous TCRs, and the exogenous TCR chains can mispair with the endogenous TCR chains. These unwanted chimeric TCRs might cause unknown antigen specificity or result in autoimmune effects, or reducing the efficacy of leukemia-specific TCRs, although that these lethal autoimmune disorders only detected in mouse models but not yet verifying in human beings. Second, to generate adequate dose of T cells for infusion, TCR and CAR gene-redirected T cells always experience multiple-rounds of ex vivo divisions. Consequently, the expanded T cells demonstrate a terminally differentiated T cell phenotype (Loss of CD62L and/or CCR7) and reduced regenerative potential. The reduced persistence and activity of these cells in vivo might partially address the leukemia relapse after T cell infusion. An alternative approach to generate redirected T cells avoiding these weaknesses is the introduction of leukemia-specific TCR or CAR genes into autologous or exogenous HSCs.[36,42] An additional advantage of CAR-engineered HSCs is that not only long-term persistent CAR-specific T cells can be generated but also

CAR-specific NK and myeloid cells can be produced, providing broader and quicker anti-tumor activity. Several pre-clinical studies using CAR-HSC-derived TCR-T cells, by approaches including in vitro murine OP9-DL1/4 co-culture system,[43,44] CAR-HSC transplantation of NOD/SCID/IL2Rg−/− (NSG) immune-deficient mice or a NSG humanized mouse model simultaneously transplanted with human thymus and fetal liver tissues (BLT mice),[42,45–47] have demonstrated their therapeutic efficacies comparable to those TCR-T cells from other resources. In addition, De Oliveira et al. demonstrated that anti-CD19 CAR-engineered HSC-derived T cells carrying a suicide gene gave rise to a persistent, multi-cell lineage, HLA-independent immunotherapy against B-lineage malignancies in xenograft animal model,[48] however, it may further need to confirm the feasibility of those CAR-HSC derived T cells which development in a human thymic like micro-environment in the humanized BTL mouse models.[49] Recently, cord blood hematopoietic progenitor cells (HPCs) transduced with a CAR/TCR with or without CD28 co-stimulatory domains could differentiate ex vivo into mature T cells when co-cultured with an OP9-DL1 stromal feeder layer, implying their potent as a new CAR-T/TCR-T resource in clinical settings where autologous HSC transplants are performed to add a GVL effect.[36,48,50] However, this type of engineered HSC might lead to neoplasia caused by insertional mutagenesis in the engineered HSCs. Further, the speed of T cell generation by engineered HSCs is slow and the efficacy of T cells is seriously dependent on the status of individual patients' thymus environment. Taken together, TCR- or CAR-modified HSCs show potential advantages and disadvantages. Overcoming these drawbacks requires technique innovation.

5.4. Reprogramed T cells

The ACT usually use T cells that directly infiltrated the tumor microenvironment after being transferred with TCRs or CARs; however, T cells from cancer patients occasionally demonstrate functional exhaustion, senescence, and reduced response to activation.[7,51–53] To overcome the disadvantages faced in CAR-T and TCR-T cell production, an alternative approach has been attempted in the T cell regenerative field i.e., generating tumor-targeting T cells from human embryonic stem cell (hESC) or induced pluripotent stem cells (iPSCs).[52,54,55] In contrast to T cells generated from mouse ESCs, the induction of T cells from hESCs demonstrated limited success due to the failure of mimicking human thymus microenvironment in vivo. Generation of T cells from patient somatic cell-reprogrammed iPSCs demonstrated great potential in recent years. Certain types of somatic cells, such as B and CD8$^+$ antigen-specific T cells, could be reprogrammed into iPSC cells by transduction with Yamanaka, and further differentiated into T cells.[56–58] iPSCs reprogrammed from T cells are called T-iPSCs. In 2013, two groups demonstrated that terminally differentiated antigen-specific CD8$^+$ T cells (MART-1 and HIV-1-epitope) could be rejuvenated through reprogramming. These rejuvenated T cells can recognize their cognate peptides while possessing prolonged telomeres, a memory T cell phenotype, and an anti-specific antigen immune response.[56,59]

Interestingly, induced functional T cells (iT) can be generated via the expression of the HSC-specific transcription factor Hoxb5 in mouse pro-pre-B cells in vivo.[60] This trans-differentiation approach implicates a de novo method producing engineered CAR-T/TCR-T in vivo if the role of HOXB5 is conserved in human cell trans-differentiation.[61]

5.5. Summary and future directions

T cell therapy plays a vital role in the treatment of leukemia, particularly for refractory and relapsed patients after HSCT. A large
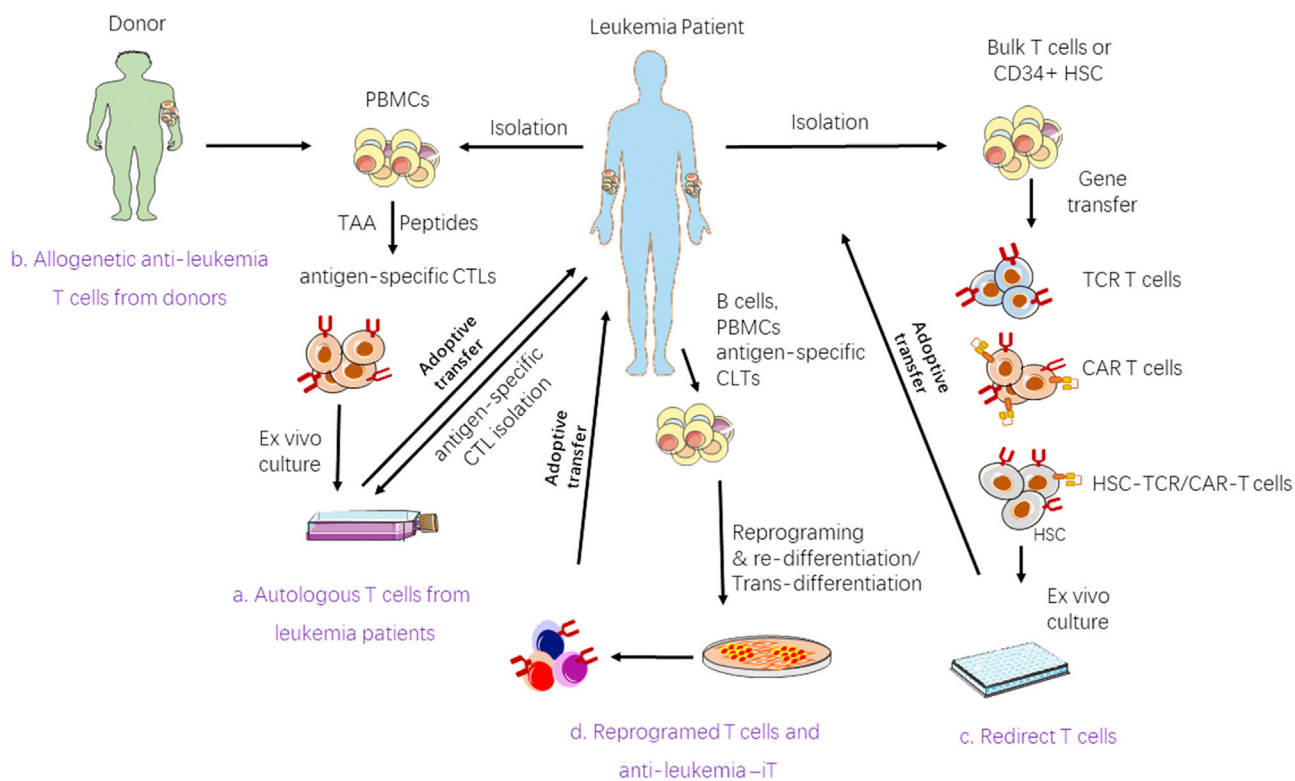
Fig. 1. Schematic diagram of approaches for generating anti-leukemia T cells for adoptive T cell immunotherapy. (a) PBMCs from patients are either stimulated with appropriate specificity against leukemia antigens, or antigen-specific CTLs isolated directly from patients. After initial stimulation, leukemia-specific T cells are selected and expanded ex vivo and then re-infused into the same patients. (b) Generation of antigen-specific CTLs from healthy donors targeting patient leukemia cells. (c) Flowchart of redirected T-cell-based adoptive immunotherapeutic. Bulk T cells/CD34$^+$ HSCs from patients/donors can be redirected with TCRs/CARs and then cultured in a suitable environment ex vivo to generate antigen-specific T cells for the ACT. (d) B cells or antigen-specific T cells can be reprogrammed into iPSCs and re-differentiated or directly trans-differentiated into rejuvenated antigen-specific T cells ex vivo for ACT. PBMCs: peripheral blood mononuclear cells; CTLs: cytotoxic T cells; TCR: T-cell receptor; CAR: chimeric antigen receptor; HSC: hematopoietic stem cells; T-iPSC: T cell-induced pluripotent stem cell.

number of clinical trials have demonstrated that adoptive transfer of CAR-T cells induces remarkable responses and durable remission in patients with relapsed/refractory B cell leukemia and lymphoma. Similar strategies are even extended to the treatment of AML and MM. However, cytokine release syndrome (CRS), neurotoxicity, CAR-T cell exhaustion, and unpredictable pharmacology toxicity due to heterogeneity of individual products remain in CAR-T cell therapy. Universal CAR-T cells derived from healthy donors, knocked out endogenous TCR gene and exhaustion genes which could prevent the generation of GVHD in MHC-mismatched recipients and functioning in long-term would be an ideal CAT-T cell product which is the so called off the shelf CAR-T cells.[62–64] A great challenge is disease relapse after CAR-T cell therapy, the production of the 'off shelf therapy T cells' which targeted different leukemia antigens may meet the salvage therapy needs of T cells when detection of leukemia relapse with a changed leukemia cell clone. An advantage of TCR-T cells is that they are capable of recognizing intracellular antigens and covering the shortage of CAR-T cells that can only recognize surface antigens.[38] With the development of non-viral human genome-targeting T cell techniques such as CRISPR-Cas9, the utilization of TCR-T cells for leukemia therapy may rapidly grow.[65] Moreover, reprogrammed T cells may be a source for producing anti-leukemia-iTs (Fig. 1).[61]

Funding

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