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Challenges and Strategies to Turn Car-T Cells into A Tightly Controllable Therapeutic Tool in Acute Myeloid Leukemia

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Abstract

The treatment options for relapsed acute myeloid leukemia (AML) are limited and the median overall survival after disease relapse is only months. CAR-T cell therapy has shown promising results in the treatment of several hematological malignancies, especially chemotherapy-refractory B cell malignancies. Successful incorporation of CAR-T cell therapy in the treatment of AML patients is still dismal. The major limiting barrier in the application of CAR-T cell therapy in AML is the absence of a universal AML-specific antigen. Other factors include immunosuppression induced by AML, the interactions between leukemic stem cells and their microenvironment and the rapidly progressive nature of the disease. In addition to the difficulty in obtaining good quality T cell product for CAR-T cell manufacture in AML patients due to the heavy and intense treatments of AML patients who are candidates for CAR-T cell therapy.

Keywords: Acute Myeloid Leukemia; Chimeric antigen receptor; Antigen; Toxicity; Challenges

Abbreviations: AML: Acute Myeloid Leukemia; CAR: Chimeric Antigen Receptor; LSCs: Leukemic Stem Cells; HSCT: Hematopoietic Stem Cell Transplantation

Introduction

Acute myeloid leukemia (AML) is one of the most aggressive adults' hematological malignancies. From 10% to 40% of AML patients are primarily refractory to induction chemotherapy. About 50% of AML patients undergoing HSCT and 80% of the patients ineligible or waiting for HSCT will eventually relapse and die of the disease [1]. AML relapse seems to be associated with the selection of pre-existing drug-resistant clones rather than chemotherapy induced mutations. The number of LSC increases 9-90-fold upon AML relapse in comparison to the diagnostic specimens [2]. The treatment options for relapsed disease are limited and the median overall survival after the disease relapse is only months [1].

Chimeric antigen receptor (CAR)-T cell therapy is a type of cellular immunotherapy that redirects the cytotoxic activity of T lymphocytes toward specific antigens on cancer cells in a major histocompatibility complex-independent manner [3]. CAR-T cells is either derived from the patients' own T-lymphocytes engineered ex vivo (autologous CAR-T therapy) or from a donor's T-cells (allogeneic CAR-T therapy) [2]. CAR-T cell therapy has shown promising results in the treatment of several hematological malignancies, especially chemotherapy-refractory B cell malignancies, including acute lymphoblastic leukemia, B cell lymphoma and multiple myeloma. Comparable results in acute myeloid leukemia (AML) are highly needed [1]. A recent meta-analysis highlights a higher efficacy of CAR-T cell therapy in AML patients with previous hematopoietic cell transplantation and specific conditioning regimens. Further large-scale, randomized trials are essential to confirm this finding [4].

Challenges in the Use of CAR-T Cell Therapy in AML

The role of CAR-T cell therapy in AML is not as straight forward as in B-NHL [5]. Successful incorporation of CAR-T cell therapy in the treatment of AML patients is still dismal [1]. Beside the general limitations of CAR-T cell therapies e.g., cytokine release syndrome, neurotoxicity and durability of the response [1], CAR-T exploitation in AML is further challenged by absence of universal AML-specific antigen (the major limiting barrier for CAR-T cell

therapy application in AML), disease heterogeneity, the rapidly progressive nature of the disease [5], immunosuppressive tumor microenvironment induced by AML [6], and the interactions between LSCs and their microenvironment [7]. Furthermore, the fitness of the T-cell populations used in CAR engineering may be impacted by the heavy and intense treatments received by AML patients that are candidates for CAR-T cell therapy. This will challenge the successful manufacture of autologous CAR-T cells from AML patients [6].

Challenges and Strategies to Turn CAR-T Cells into a Tightly Controllable Therapeutic Tool in AML

Challenge 1: Absence of AML-specific antigen

LSC and HSC share similar immunophenotypic patterns (e.g., CD13, CD33, CD71, CD99, CD117, CD133, CD200, CD244) [2]. The presence of overlap in antigen expression between malignant and healthy HSCs and their myeloid and/or lymphoid progenitors make CAR-T cells unable to differentiate between normal and cancer cells. This will result in myeloablation [6]. The heterogeneity of AML combined with the propensity of leukemic cells to change the expression of their surface antigens with disease progression makes it difficult to identify the target antigen [8].

Promising strategy to overcome challenge 1: Identification of specific leukemic CAR target

The ideal target antigen for CAR-T cell is a molecule that is abundantly found on all subpopulations of cancer cells and is absent or minimally present in healthy tissues [8]. Neoantigens expressed on the vast majority of, if not all, AML cells will serve as optimal immunotherapeutic targets since they are unlikely to undergo antigen loss. The effect of hypoxia should be evaluated when selecting CAR-T cell targets to avoid antigen escape. The hypoxic environment can alter the surface phenotype of AML cells in vitro.

Attractive common myeloid antigens target for CAR-T cells

i. It is possible to redirect CAR-T cells to target intracellular neoepitopes presented by HLA complex on AML cells, as exemplified by CAR against NPM1c epitope-HLA-A2 complex. Additional candidate tumor-specific CAR antigens are FLT3-ITD, CD44v6, FLT3-Va and NOTCH2-Va [2].

ii. The discovery of de novo targets, the surfaceome, which are a set of proteins including surface receptor, adhesion molecules and transporters, among others expressed on the surface of primary AML patient samples. CD148, ITGA4, and integrin beta-7 are three identified promising targets. Integrin beta-7 was the most favorable among them, due to its absence or low expression in healthy hematopoietic tissues. CSF1R and CD86 antigen are two potential targets for CAR-T cell therapy with broad expression on AML blasts, and minimal toxicities toward healthy cells and tissues [7].

iii. The combinatorial antigen-targeting strategy against different AML targets. Combinations of CARs against different AML targets might be a promising solution for e.g. bicistronic CD123 and CD33 CAR-T cells which showed significant anti-tumor activity in artificially created cell lines (CD33+CD123-, CD33-CD123+) and in vivo [7].

iv. Employment of hypoxia-sensitive CAR-T cells, which are specifically activated in hypoxic sites (such as the AML-BM microenvironment) to avoid antigen escape and to avoid unwanted off-site toxicities. This approach could be investigated to eradicate residual LSC persisting in the hypoxic BM niche after chemotherapy [2].

Challenge 2: Interactions between LSCs and their microenvironment

The interactions between LSCs and their microenvironment are reciprocal. The niche cells foster LSC growth and LSCs can alter their microenvironment. LSCs secrete pro-angiogenic VEGF and interleukins which stimulate angiogenesis to provide additional nutrients, oxygen, and growth factors and to promote proliferation. AML cells promote the expression of immunomodulatory factors including transforming growth factor β (TGF β), arginase II, prostaglandin E2 (PGE2), programmed death receptor (PD-1), lymphocyte activation gene 3 (LAG3), cytotoxic T lymphocyte-associated protein 4 (CTLA-4), and T cell immunoglobulin and mucin-containing-3 (TIM3) on T cells that impair cytotoxic T lymphocyte (CTL) activation in the tumor microenvironment [7]. Furthermore, leukemia cells can modulate the NK cell receptor repertoire and inhibit NK cell activity [7]. AML cells can preferentially downregulate the expression of major histocompatibility complexes (MHC) and natural killer group 2 member D (NKG2D) ligands, which are required for immune recognition by T- and NK-cells respectively [2].

Promising strategy to overcome the negative effects of microenvironment

i. Combining CAR-T cells and immune checkpoint blockage (PD-1, CTLA-4, etc.) to improve T cell persistence and anti-tumor efficacy [7].

ii. Eliminating the expression of immune checkpoint proteins, by gene editing approach to enhance anti-tumor immunity [7].

iii. Targeting immunosuppressive cells such as Tregs (with anti-CD25 antibodies) and MDSCs (anti-Gr-1 antibodies) in the tumor microenvironment [7].

iv. Generating cytokine-induced memory-like (CIML) NK cell therapy by their pre-activation in vitro with IL-12, IL-15, and IL-18. It showed promising responses in a phase I trial in relapsed/refractory AML. Despite several manipulations for longer persistence of NK cells, the response to NK cell infusions varies without long-term remissions [7].

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Challenge 3: intense AML treatments

The heavy and intense treatments of AML patients who are candidates for CAR-T cell therapy may make it harder to obtain good quality T cell product for CAR-T cell manufacture.

Promising strategy to overcome challenge 3:

Selecting chemo-refractory patients relatively early in their treatment course based on accepted prognostic markers [6].

Challenge 4: on-target/off-tumor CAR-T cell therapy side effects.

Promising strategies: Promising strategies to overcome challenge 4 include biodegradable CARs, suicide-switch containing CARs, logic-gated CAR-T cells, inducible CARs and two-component modular CARs.

Biodegradable CAR-T cells: Biodegradable CAR-T cells refer to T cells that express the CAR transiently. mRNA encoding the CAR is inserted transiently via, nanoparticles, electroporation, or photoporation [5].

Suicide switch CAR-T cells: Suicide switch CAR-T cells refer to the introduction of a genetically engineered small molecule or antibody that triggers apoptosis of the introduced CAR-T cell in case of unexpected toxicities [5].

Logic-gated CAR-T cells: Logic-gated CAR-T cells Target multiple antigens in order to exert their cytotoxic effect. Specifically, "AND-gated" dual CAR-T cells exert their anti-tumor effects when at least two markers are expressed on the target cells. Conversely, "NOT-gated" CAR-T cells exert their effects when one marker is expressed and the second one is absent [4]. Not gating may reduce the likelihood of leakiness out of the tumor microenvironment to prevent toxicity [5].

Inducible CAR-T cells: Administration of specific molecules to trigger the expression or functional assembly of the CAR to increase their tumor selectivity [5].

MODULAR, switchable CAR-T cells: CAR is not targeted at the tumor antigen itself; instead it is directed at an adaptor or switch element. This adaptor serves as the targeting element binding to the tumor antigen. Adaptors turn on CARs and enables targeting of multiple tumor associated antigens with one receptor [5]. The optimal construct is preferably modular. Initial results are limited and suggest that toxicity can be mitigated and CAR activity is maintained by the use of modular CAR concepts that allows for 'ON' and 'OFF' switching [5]. There is a risk of lasting toxicity with non-switchable CARs [5].

Conclusion

The quiescent and immune-evasive nature of LSC makes them critical players in therapy escape and disease relapse. CAR-T cells represent a promising option in relapsed AML. It can effectively target LSCs irrespective of their quiescent status or their immune visibility by mediating MHC-independent tumor recognition. Effective targeting of LSC is vital for curative treatments of AML.

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