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Commentary

Modelling CAR-T therapy in humanized mice

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In the current issue of *EBioMedicine*, Jin et al. demonstrated a humanized mouse (hu-mouse) model in which a functional human immune system was established and genetically-matched (autologous) to primary acute B-lymphoblastic leukemia (B-ALL) in severe immunodeficient NSG mice [1]. Using this hu-mouse model, the authors generated CD19-targeted chimeric antigen receptor (CAR) T cells from human autologous mature T cells and tested the efficacy of CAR-T therapy against primary B-ALL.

Anti-CD19 CAR-T therapy has made a significant impact on the clinical prognosis of patients with relapsed or refractory B-cell lymphoma [2,3]. Based on results of the ZUMA-1 trial and subsequently the JULIET trial [4,5], the US Food and Drug Administration and the European Medicines Agency approved two anti-CD19 CAR-T products, with a CD28 or 4-1BB co-stimulatory domain, to treat pediatric or young adult B-cell precursor B-ALL in 2017, and then adults with relapsed or refractory diffuse large B-cell lymphoma in early 2018.

Although these landmark clinical trials showed that anti-CD19 CAR-T therapy induced a consistent and durable response against B-cell malignances, approximately half of the patients in these studies failed to respond or acquired resistance [4,5]. Among the suspected mechanisms of resistance to therapy, two convincing models proposed involve loss of CD19 and/or gain of expression of PD-L1. Furthermore, toxicities and side effects are also associated with CAR-T therapy, including cytokine release syndrome (CRS), neurologic toxicity and B-cell aplasia, which also limit the therapeutic potential [6]. Therefore understanding the mechanisms by which resistance occurs and toxicities/side effects develop are highly warranted to further potentiate the success of anti-CD19 CAR-T therapy for treatment of B-cell malignances.

Given that clinical trials have their own limitations to restrain in depth mechanistic studies in patients, the antitumor activity of CAR-engineered human T cells are primarily evaluated through *in vitro* assays or in immunodeficient mice engrafted with only human tumor cell lines. Although other studies using mouse models can reveal mechanistic insight in depth, these studies test murine CAR-T constructs on mouse T cells in response to mouse tumors. More recently, patient-derived xenograft (PDX) models have been created by grafting patient-derived cancer cells in immunodeficient mice. PDX models make it possible to directly assess human immune responses to human primary cancer cells, which recapitulate the clinical scenario with human cancers and immunotherapy [7]. A PDX model was also used in evaluating the therapeutic efficacy of CAR T cells in human B-ALL. However, PDX models are typically established in immunodeficient mice and most of them involve allogeneic and/or xenogeneic immune responses that are obviously different from cancer patients.

A group of investigators led by Yang and Sykes have made substantial effort to create humanized mouse models in which immunodeficient mice are fully reconstituted with human hematopoietic and immune systems [8]. Using these humanized mice, the Yang group has established numerous models that simulate human diseases or conditions, including a spontaneous human B-ALL model [9]. The current work by the same group utilized this human B-ALL model to evaluate the efficacy of anti-CD19 CAR-T therapy [1]. There are several unique features in this model over previously published models: 1) the recipient hu-mice have a functional human hematopoietic and immune system; 2) autologous primary B-ALL is driven by a patient-derived fusion MLL-AF9 oncogene; 3) anti-CD19 CAR-expressing human T cells are also derived by mature human T cells from the same individual; 4) the human mature T cells as a source of CAR T cells are developed in the human thymus engrafted in murine host. These features offer many advantages of this unique model including permitting the evaluation of antitumor responses in immunocompetent hosts, testing human CAR-T constructs against human primary malignance, and avoiding allogeneic responses and anti-mouse xeno-antigens. These advantages make this model highly valuable for mechanistic and preclinical studies of anti-CD19 CAR T-cell immunotherapy. In fact, the current study demonstrates the efficacy of anti-CD19 CAR-T therapy, positive correlation of CAR-T survival and expansion with B-ALL regression, and causative relationship between proinflammatory cytokines and CRS. Given this proof-of-principle study, such hu-mouse models can be established to evaluate efficacy of various CAR-T cells in the treatment of relevant hematologic malignances and to study underlying mechanisms of resistance and toxicity.

While presenting many advantages, this hu-mouse model is not identical to a human host. It is obvious that non-hematopoietic tissues are mouse origin that may interfere anti-tumor responses, although the concern is mitigated in the situation of hematologic malignances. A specific limitation in evaluating CAR-T therapy using this hu-mouse model may lay in toxicity studies, as IL-6 was below the detectable

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level in mouse sera [1] similar to another published study using non-humanized NSG mice [10]. The results are in sharp contrast to those from clinical trials where IL-6 has been shown to be a primary driving force for CRS. As discussed by the authors, using human cytokine-transgenic SGM3 mice that produce human SCF, GM-CSF and IL-3 might correct the defect, which remains to be investigated and confirmed. Technically, one should keep in mind that the procedure to establish such a hu-mouse model is rather convoluted. In conclusion, Jin et al. provide a preclinical mouse model that represents a close recapitulation of the human host in evaluating CAR-T therapy against hematologic malignancies to compensate the limitation of clinical trials. However, such a hu-mouse model is not identical to the human host and thus certain limitations remain.

Disclosure

The authors declare no conflicts of interest.

References

[1] Jin CH, Xia J, Rafiq S, Huang X, Hu Z, Zhou X, et al. Modeling anti-CD19 CAR T cell therapy in humanized mice with human immunity and autologous leukemia. EBioMedicine 2019;20(1):2–3.

[2] Schuster SJ. CD19-directed CAR T cells gain traction. Lancet Oncol 2018 Jan;30(1):2–3 PubMed PMID: 30518503.

[3] Havard R, Stephens DM. Anti-CD19 chimeric antigen receptor T cell therapies: harnessing the power of the immune system to fight diffuse large b cell lymphoma. Curr Hematol Malig Rep 2018 Dec;13(6):534–42 (PubMed PMID: 30362020).

[4] Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-Cell therapy in refractory large b-cell lymphoma. N Engl J Med 2017 Dec 28;377(26):2531–44 (PubMed PMID: 29226797. Pubmed Central PMCID: 5882485).

[5] Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, JP McGuirk, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large b-cell lymphoma. N Engl J Med 2019 Jan 3;380(1):45–56 (PubMed PMID: 30501490).

[6] Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, et al. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. Nat Rev Clin Oncol 2017 Sep 15;17(10):632 (PubMed PMID: 30082906).

[7] Byrne AT, Alferez DG, Amant F, Annibali D, Arribas J, Biankin AV, et al. Interrogating open issues in cancer medicine with patient-derived xenografts. Nat Rev Cancer 2017 Sep 15;17(10):632 (PubMed PMID: 28912576).

[8] Kalscheuer H, Danzl N, Onoe T, Faust T, Winchester R, Goland R, et al. A model for personalized in vivo analysis of human immune responsiveness. Sci Transl Med 2012 Mar 14;4(125):125ra30 (PubMed PMID: 22422991. Pubmed Central PMCID: 3697150).

[9] Xia J, Hu Z, Yoshihara S, Li Y, Jin CH, Tan S, et al. Modeling human leukemia immunotherapy in humanized mice. EBioMedicine 2016 Aug;10:101–8 (PubMed PMID: 27394641. Pubmed Central PMCID: 5006579).

[10] Singh N, Hofmann TJ, Gershenson Z, Levine BL, Grupp SA, Teachey DT, et al. Monocyte lineage-derived IL-6 does not affect chimeric antigen receptor T-cell function. Cytotherapy 2017 Jul;19(7):867–80 (PubMed PMID: 28506444).