J Exp Pathol. 2026;7(1):10–11.

Journal of Experimental Pathology Editorial

Tumor Microenvironment and CAR-T cell Therapy: Challenges, Breakthroughs, and Future Perspectives

Chenhe Hu[1], Ying Xue[1], Shishuo Sun[1,*]

[1]Cancer Institute, Cellular Therapeutics School of Medicine, Xuzhou Medical University, Xuzhou, Jiangsu, P.R. China

[*]Correspondence should be addressed to Shishuo Sun, sssun@xzhmu.edu.cn

Received date: February 01, 2026, **Accepted date:** February 09, 2026

Citation: Hu C, Xue Y, Sun S, Tumor Microenvironment and CAR-T cell Therapy: Challenges, Breakthroughs, and Future Perspectives. J Exp Pathol. 2026;7(1):10–11.

Introduction

Chimeric antigen receptor (CAR) T cell therapy has achieved unprecedented success in hematologic malignancies, yet its application in solid tumors remains fraught with challenges. Key barriers include antigen heterogeneity, limited tumor infiltration, and most critically, the profoundly immunosuppressive tumor microenvironment (TME). This editorial synthesizes current research to detail the multifaceted suppressive effects of the TME on CAR-T cells, reviews innovative strategies being developed to overcome these barriers, and discusses the future trajectory of CAR-T therapy for solid tumors.

Suppressive Effects of the Tumor Microenvironment on CAR-T cell Therapy

The TME presents a composite barrier to CAR-T cell efficacy, integrating physical, immunological, and metabolic obstacles [1]. Physically, solid tumors are characterized by a dense extracellular matrix (ECM) and aberrant vasculature, which severely impede CAR-T cell infiltration. Cancer-associated fibroblasts (CAFs) secrete components like collagen and hyaluronic acid, creating a rigid stromal network that blocks access to the tumor core, while abnormal blood vessels hinder both nutrient delivery and immune cell extravasation [2,3].

Immunologically, the TME is enriched with suppressive cells and cytokines that drive CAR-T cell exhaustion and dysfunction. Regulatory T cells (Tregs), which accumulate in the TME, inhibit cytotoxic $CD8^+$ T cell function via direct contact, secretion of inhibitory cytokines (e.g., IL-10, TGF-β), or granzyme/perforin-mediated lysis [4]. Similarly, tumor-associated macrophages (TAMs) predominantly adopt a pro-tumor M2 phenotype. These M2 TAMs secrete immunosuppressive factors (e.g., IL-10, TGF-β, Arg1), recruit Tregs, and actively suppress T cell-mediated immunity, thereby promoting tumor progression [5]. Critically, these mechanisms that suppress endogenous T cells are equally effective against engineered CAR-T cells, severely constraining their effector functions.

Breakthroughs in Overcoming TME-Mediated Suppression

To enhance tumor infiltration, strategies targeting the tumor vasculature have been explored. Vascular abnormalities, often driven by VEGF overexpression, directly hinder CAR-T cell extravasation [1]. Consequently, VEGF blockade has emerged as a promising approach. Animal studies show that anti-VEGF strategies can increase tumor-infiltrating T cells and improve survival [6]. Building on this, the development of CAR-T cells targeting VEGFR1 and VEGFR2 has demonstrated potent anti-tumor and anti-angiogenic effects in preclinical models [7–9]. However, clinical translation has been challenging, as evidenced by a trial of VEGFR2-targeted CAR-T cells where only 1 of 24 patients achieved a partial response (NCT01218867), highlighting the need for more optimized strategies.

Combination therapies represent another avenue to modulate the TME. For instance, combining CAR-T cells with FLASH radiotherapy (ultrahigh-dose-rate delivery at ≥40 Gy/s) has shown superior synergistic efficacy in a medulloblastoma model. Research indicates that FLASH RT reprograms the TME by downregulating pro-tumor oxidative pathways, shifting macrophages from an M2 to an M1 phenotype, and sensitizing tumor cells to GD2 CAR-T cells, thereby achieving potent therapeutic effects while sparing normal tissue [10].

To directly counteract TME-induced dysfunction, "armored" CAR-T cells engineered to overexpress cytokines have been developed. For example, HER2-targeted CAR-T cells engineered to express IL-10 (IL-10 HER2 CAR-T) showed improved mitochondrial fitness (via enhanced OXPHOS), reduced exhaustion, and a stem-like memory phenotype, leading to enhanced tumor killing in models where conventional CAR-T cells failed [11]. This strategy, termed TRUCK (T cells redirected for universal cytokine-mediated killing), is a significant engineering approach, with similar efforts focusing on cytokines like IL-2, IL-7, and IL-15 [12].

A major challenge for armored CAR-T cells is systemic toxicity from constitutive transgene expression. An innovative solution involves using CRISPR knock-in to place cytokine genes (e.g., IL-12) under the control of endogenous, tumor-restricted promoters (e.g., NR4A2, RGS16). These promoters are activated primarily upon antigen stimulation at the tumor site. This approach enables localized cytokine delivery, which drives potent anti-tumor immunity and epitope spreading while avoiding systemic toxicity, as demonstrated in preclinical models [13].

Perspectives

The immunosuppressive TME remains a formidable barrier, but the strategies outlined here, ranging from vascular normalization and combination therapies to intelligently engineered CAR-T cells represent a concerted assault on this "peak." The field is moving beyond simply overcoming suppression towards actively reprogramming the TME into a permissive state. Future success will likely hinge on the precise spatial and temporal control of therapeutic payloads, the development of more predictive preclinical models, and the design of smarter clinical trials that prioritize biomarker-driven patient selection. While the gap between hematologic and solid tumor efficacy is still significant, the convergence of immunology, gene editing, and bioengineering continues to fuel tangible progress, bringing renewed hope for patients with solid tumors.

References

1. Rodriguez-Garcia A, Palazon A, Noguera-Ortega E, Powell DJ Jr, Guedan S. CAR-T Cells Hit the Tumor Microenvironment: Strategies to Overcome Tumor Escape. Front Immunol. 2020 Jun 17;11:1109.

2. Salmon H, Franciszkiewicz K, Damotte D, Dieu-Nosjean MC, Validire P, Trautmann A, et al. Matrix architecture defines the preferential localization and migration of T cells into the stroma of human lung tumors. J Clin Invest. 2012 Mar;122(3):899–910.

3. Kuczek DE, Larsen AMH, Thorseth ML, Carretta M, Kalvisa A, Siersbæk MS, et al. Collagen density regulates the activity of tumor-infiltrating T cells. J Immunother Cancer. 2019 Mar 12;7(1):68.

4. Togashi Y, Shitara K, Nishikawa H. Regulatory T cells in cancer immunosuppression - implications for anticancer therapy. Nat Rev Clin Oncol. 2019 Jun;16(6):356–71.

5. Peranzoni E, Lemoine J, Vimeux L, Feuillet V, Barrin S, Kantari-Mimoun C, et al. Macrophages impede CD8 T cells from reaching tumor cells and limit the efficacy of anti-PD-1 treatment. Proc Natl Acad Sci U S A. 2018 Apr 24;115(17):E4041–50.

6. Li B, Lalani AS, Harding TC, Luan B, Koprivnikar K, Huan Tu G, et al. Vascular endothelial growth factor blockade reduces intratumoral regulatory T cells and enhances the efficacy of a GM-CSF-secreting cancer immunotherapy. Clin Cancer Res. 2006 Nov 15;12(22):6808–16.

7. Chinnasamy D, Yu Z, Theoret MR, Zhao Y, Shrimali RK, Morgan RA, et al. Gene therapy using genetically modified lymphocytes targeting VEGFR-2 inhibits the growth of vascularized syngenic tumors in mice. J Clin Invest. 2010 Nov;120(11):3953–68.

8. Wang W, Ma Y, Li J, Shi HS, Wang LQ, Guo FC, et al. Specificity redirection by CAR with human VEGFR-1 affinity endows T lymphocytes with tumor-killing ability and anti-angiogenic potency. Gene Ther. 2013 Oct;20(10):970–8.

9. Niederman TM, Ghogawala Z, Carter BS, Tompkins HS, Russell MM, Mulligan RC. Antitumor activity of cytotoxic T lymphocytes engineered to target vascular endothelial growth factor receptors. Proc Natl Acad Sci U S A. 2002 May 14;99(10):7009–14.

10. Ni H, Reitman ZJ, Zou W, Akhtar MN, Paul R, Huang M, et al. FLASH radiation reprograms lipid metabolism and macrophage immunity and sensitizes medulloblastoma to CAR-T cell therapy. Nat Cancer. 2025 Mar;6(3):460–73.

11. Zhao Y, Chen J, Andreatta M, Feng B, Xie YQ, Wenes M, et al. IL-10-expressing CAR T cells resist dysfunction and mediate durable clearance of solid tumors and metastases. Nat Biotechnol. 2024 Nov;42(11):1693–04.

12. Tang L, Pan S, Wei X, Xu X, Wei Q. Arming CAR-T cells with cytokines and more: Innovations in the fourth-generation CAR-T development. Mol Ther. 2023 Nov 1;31(11):3146–62.

13. Chen AXY, Yap KM, Kim JS, Sek K, Huang YK, Dunbar PA, et al. Rewiring endogenous genes in CAR T cells for tumour-restricted payload delivery. Nature. 2025 Aug;644(8075):241–51.