Targeting macrophages: A new frontier in cancer immunotherapy with CAR-NK cells

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Received: March 1, 2026; Accepted: April 20, 2026; Published Online: April 23, 2026; https://doi.org/10.59717/j.xinn-oncol.2026.100008

Citation: Dai X. and Wang D. (2026). Targeting macrophages: A new frontier in cancer immunotherapy with CAR-NK cells. *The Innovation Oncology* **1**:100008.

Cancer immunotherapy has seen significant success in treating hematological malignancies; however, its effectiveness in solid tumors is often hindered by the immunosuppressive tumor microenvironment (TME) and therapeutic resistance. Tumor-associated macrophages (TAMs) represent one of the most abundant immune cells in solid tumors, play a crucial role in mediating immunosuppression, and are therefore important targets for next-generation immunotherapy. However, traditional strategies targeting TAMs tend to lack specificity and provide limited clinical benefits. Natural killer (NK) cells are ideal candidates for chimeric antigen receptor (CAR) engineering because they exhibit strong anti-tumor activity without needing prior sensitization. CAR-NK cells have advantages over CAR-T cells, including superior safety, better tumor infiltration, and greater scalability. Moreover, they can work in synergy with agents targeting myeloid cells. Here, we explore the potential of combining CAR-NK cell therapy with TAM targeting by focusing on surface markers such as triggering receptors expressed on myeloid cells 2 (TREM2) and folate receptor 2 (FOLR2). This approach aims to deplete pro-tumor TAMs and reprogram the TME. By alleviating immunosuppression and enhancing anti-tumor immunity, this integrated strategy overcomes the limitations of current treatments and represents a promising advancement in solid tumor immunotherapy.

Cancer immunotherapy has transformed the treatment landscape over the past decade. Immune checkpoint blockade (ICB) and CAR-T cell therapy have shown significant success in treating hematological malignancies.[1] However, these therapies encounter substantial limitations when applied to solid tumors. This is largely due to the complex TME and antigen heterogeneity that lead to low overall response rates. Primary and acquired resistance further complicate their efficacy, as the immunosuppressive TME—dominated by TAMs—creates barriers that hinder antitumor immune responses.[2] While targeting TAMs presents a promising opportunity, traditional strategies, such as colony-stimulating factor-1 receptor (CSF1R) inhibition, have yielded limited clinical benefits due to their limited specificity and potential off-target effects.[2,3] This underscores the need for more precise and flexible therapeutic approaches.

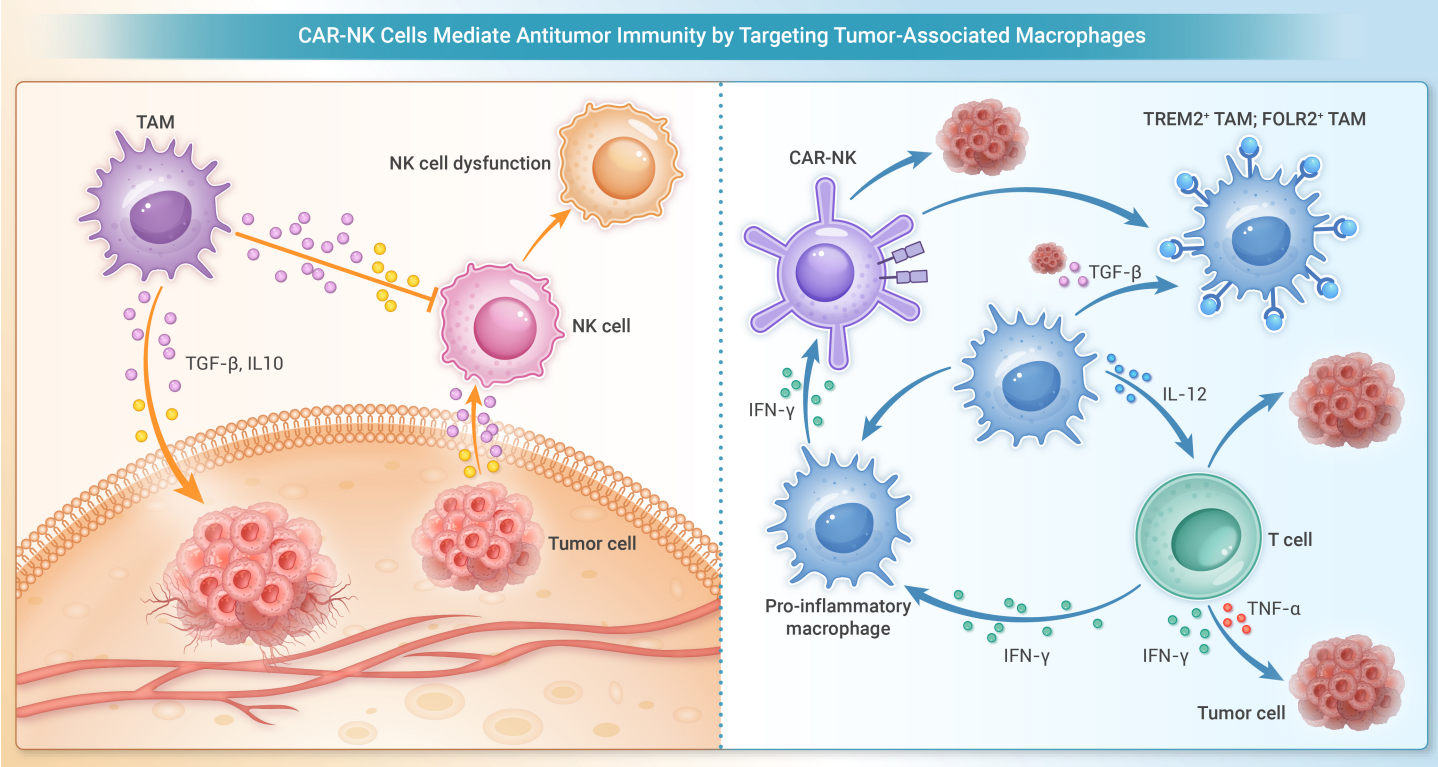

Figure 1. CAR-NK cells mediate antitumor immunity by targeting tumor-associated macrophages Schematic diagram illustrating the antitumor mechanism of CAR-NK cells targeting triggering receptors expressed on myeloid cells 2 (TREM2)$^+$ or folate receptor 2 (FOLR2)$^+$ tumor-associated macrophages (TAMs). In the tumor microenvironment, TAMs and tumor cells secrete immunosuppressive cytokines, such as transforming growth factor beta (TGF-β) and interleukin (IL)-10, leading to NK cell dysfunction. Pro-inflammatory macrophages secrete IL-12 and promote the activation of T cells, enhancing antitumor immunity and the production of interferon-γ (IFN-γ), as well as tumor necrosis factor-α (TNF-α). Engineered CAR-NK cells can directly kill tumor cells. In addition, CAR-NK cells could recognize and eliminate TREM2$^+$ or FOLR2$^+$ TAMs. Additionally, TGF-β produced by tumor cells in the tumor microenvironment drives the conversion of pro-inflammatory macrophages into TAMs. IL-12, released in the process, also participates in the amplification of pro-inflammatory responses and antitumor effects.

TAMs are the most abundant immune cell population in solid tumors and display remarkable functional plasticity, allowing them to either promote tumor progression or facilitate tumor elimination. This dual capability stems from TAM heterogeneity, which is influenced by their developmental origins (tissue-resident versus bone marrow-derived), transcriptional profiles, and microenvironmental signals. Pro-tumor TAMs promote immunosuppression by expressing immune checkpoints (such as programmed death ligand 1 [PD-L1] and TREM2), secreting tolerogenic cytokines (like transforming growth factor beta [TGF-β] and IL-10), and remodeling the extracellular matrix to support angiogenesis and metastasis (Figure 1). In contrast, antitumor TAMs can directly kill cancer cells through phagocytosis or the production of reactive oxygen species (ROS), as well as enhance adaptive immunity by presenting antigens and recruiting T cells and natural killer (NK) cells. A recent review in *Cancer Cell* by Sun et al. emphasizes that TAMs are not only obstacles to immunotherapy but also untapped targets.[2] Strategies to reprogram or activate TAMs could unleash their tumoricidal potential while alleviating immunosuppression,[2] making TAMs a central focus for next-generation cancer immunotherapy and providing a complementary approach to T cell-based approaches.

NK cells play a crucial role in tumor immune surveillance and antitumor responses, distinguished by their ability to recognize and eliminate cancer cells without prior antigen sensitization.[4] Unlike T cells, NK cells target "missing-self" or "stress-induced" antigens, making them effective against major histocompatibility complex (MHC)-deficient tumors that evade CAR-T therapy. However, NK cells often become functionally exhausted within the TME, where TAMs contribute to their dysfunction through the secretion of immunosuppressive cytokines and the expression of inhibitory ligands. While CAR-T therapy has revolutionized the treatment of hematological cancers, its limitations in solid tumors—such as poor tumor infiltration, antigen escape, and severe toxicities like cytokine release syndrome and neurotoxicity—underscore the need for alternative cell therapies. CAR-NK cells address these shortcomings by combining NK cells' natural antitumor properties with the specificity of CAR engineering. The advantages of CAR-NK cells include reduced off-target toxicity (due to the absence of alloreactivity), enhanced ability to infiltrate solid tumors, and the potential for "off-the-shelf" manufacturing from donor cells or induced pluripotent stem cells (iPSCs). Moreover, CAR-NK cells can synergize with other immunotherapies by producing proinflammatory cytokines (such as interferon-γ [IFN-γ] and tumor necrosis factor-α [TNF-α]) that activate antitumor TAMs and enhance T cell responses.[5] These features position CAR-NK cells as ideal candidates for targeting TAMs and overcoming the limitations of current immunotherapies.

The convergence of CAR-NK cell technology and TAM targeting represents a transformative strategy for cancer immunotherapy. CAR-NK cells can be engineered to specifically recognize pro-tumor TAM subsets via surface markers such as TREM2 or FOLR2—molecules identified in Sun et al.'s review as defining immunosuppressive TAM populations.[2] Preclinical studies have indicated that anti-TREM2 or anti-FOLR2 CAR-T cells can deplete pro-tumor TAMs and reprogram the TME,[2] but CAR-NK cells may offer superior safety and versatility in this application. Engineering CAR-NK cells to target TAM-specific antigens can enable the precise depletion of immunosuppressive subsets while preserving antitumor TAMs and other immune cells. However, TREM2 and FOLR2 are also expressed by resident macrophages in certain healthy tissues, which may raise concerns about off-target or off-tumor toxicity in clinical translation. In future clinical applications, combination regimens, dose optimization, and tissue-specific delivery systems could further reduce potential off-tumor effects and enhance the safety of targeting $TREM2^+$ or $FOLR2^+$ macrophages. Additionally, CAR-NK cells can be engineered to express cytokines (such as IL-12 and IL-15) that enhance their persistence and capability to reprogram residual TAMs toward an antitumor phenotype. For instance, IL-12-expressing CAR-T or CAR-NK cells could not only kill pro-tumor TAMs but also induce the enrichment of C-X-C motif chemokine ligand 9 $(CXCL9)^+$ TAMs, which in turn recruit and activate T cells to amplify antitumor immunity. This "kill-and-reprogram" strategy addresses the key challenge of TAM targeting: eliminating immunosuppressive populations while harnessing the tumoricidal potential of the remaining macrophages. Furthermore, pro-inflammatory macrophages produce IL-12, which promotes the development of helper T cell 1 (Th1) responses and acts as a potent inducer of IFN-γ production by T cells and NK cells (Figure 1).

Furthermore, CAR-NK cells can work in synergy with therapies aimed at targeting tumor-associated macrophages (TAMs), such as "don't-eat-me" pathway inhibitors (like anti-CD47) or myeloid cell engagers. By depleting pro-tumor TAMs, CAR-NK cells help reduce sources of immunosuppression, thereby enhancing the effectiveness of these therapies. Conversely, the effectorization of TAMs by anti-CD47 antibodies can boost the functionality of CAR-NK cells by mitigating exhaustion caused by the TME. A review by Sun et al. emphasizes that successful targeting of TAMs necessitates precise delivery and combination strategies.[2] CAR-NK cells can meet this need by providing tumor-localized, cell-autonomous activity. The clinical application of CAR-NK cells targeting TAMs is further supported by ongoing trials involving CAR-NK therapy for solid tumors, with preliminary data showing promising safety profiles and indications of tumor regression.

In conclusion, targeting TAMs with CAR-NK cells represents a pioneering approach to overcoming the limitations of current cancer immunotherapy. The functional plasticity of TAMs offers a unique opportunity to both alleviate immunosuppression and stimulate antitumor immunity. CAR-NK cells combine the specificity of chimeric antigen receptors (CARs) with the natural antitumor capabilities of NK cells, creating a safe, scalable, and effective platform for targeting TAMs. By engineering CAR-NK cells to recognize pro-tumor TAM subsets and equipping them with cytokines to reprogram the TME, we can develop a synergistic antitumor response that addresses not only cancer cells but also their supportive microenvironment. As advancements in single-cell omics and bioengineering progress, the ability to accurately target TAM subsets and optimize CAR-NK cell functionality will enhance the translational potential of this strategy. Ultimately, CAR-NK cells targeting TAMs are well-positioned to become a cornerstone of next-generation cancer immunotherapy, providing new hope for patients with solid tumors that are resistant to current treatments.

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FUNDING AND ACKNOWLEDGMENTS

This work was supported by the Natural Science Foundation of China (# 82370217), Anhui Provincial Department of Education Scientific Research Project (# 2022AH030128), Anhui Provincial Natural Science Foundation (# 2308085Y46), the Research Fund for the Key Laboratory of Anhui Province (KFKT202403), USTC Research Funds of the Double First-Class Initiative (# YD9110002019), and USTC Key Youth Innovation Fund (# WK9100000091). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript

AUTHOR CONTRIBUTIONS

D.W. conceived and designed the analysis; X.D. wrote the paper. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.