TPM Vol. 32, No. S2, 2025
ISSN: 1972-6325
https://www.tpmap.org/

Open Access

MRNA- BASED CANCER VACCINES TARGETING TUMOR ASSOCIATED MACROPHAGES: REPROGRAMMING THE TUMOR MICROENVIRONMENT FOR ENHANCED IMMUNOTHERAPY

BONEY PRIYA P JOSE[2], AKSHAYA VISWANATHAN[1], NEHA BRAHMA[1], VIMAL S[1]*, DR. KISHORE KUMAR[3],
[1]DEPARTMENT OF BIOCHEMISTRY, SAVEETHA MEDICAL COLLEGE, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES, SAVEETHA UNIVERSITY, CHENNAI, TAMIL NADU, INDIA.
[2]DEPARTMENT OF DERMATOLOGY, VENEREOLOGY AND LEPROSY, SAVEETHA MEDICAL COLLEGE, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES, SAVEETHA UNIVERSITY, CHENNAI, TAMIL NADU, INDIA.
[3]VICE PRINCIPAL & PROFESSOR, DEPARTMENT OF ORTHODONTICS & DENTOFACIAL ORTHOPEDICS, SREE BALAJI DENTAL COLLEGE & HOSPITAL, CHENNAI, INDIA
CORRESPONDING AUTHOR *
DEPARTMENT OF BIOCHEMISTRY, SAVEETHA MEDICAL COLLEGE & HOSPITAL, SAVEETHA INSTITUTE OF MEDICAL AND TECHNICAL SCIENCES (SIMATS), THANDALAM, CHENNAI - 602105, TAMIL NADU, INDIA.

Abstract
Cancer immunotherapy is limited by the immunosuppressive tumor microenvironment (TME), largely shaped by tumor-associated macrophages (TAMs). mRNA-based vaccines offer a novel strategy to reprogram TAMs from a tumor-promoting M2 to a tumoricidal M1 phenotype. Delivered via targeted lipid nanoparticles, these vaccines enhance anti-tumor immunity and synergize with checkpoint inhibitors. This approach holds promise for converting “cold” tumors into “hot,” improving outcomes in resistant cancers.

Keywords: mRNA Vaccine, Tumor-Associated Macrophages, Macrophage Polarization, Tumor Microenvironment, Lipid Nanoparticles, Immunotherapy, Immune Reprogramming, Checkpoint Blockade

Cancer immunotherapy has emerged as a transformative approach in oncology, offering durable responses across various malignancies through strategies like immune checkpoint blockade (ICB), CAR-T cells, and cancer vaccines (1). Despite these advancements, a significant proportion of patients fail to benefit from current immunotherapeutic modalities, primarily due to the immunosuppressive tumor microenvironment (TME), which acts as a physical and functional barrier against immune cell infiltration and activation. Among the diverse cellular components of the TME, tumor-associated macrophages (TAMs) are particularly prominent, often comprising up to 50% of the tumor mass in solid tumors such as breast, lung, pancreatic, and ovarian cancers (2). These macrophages, predominantly polarized to an M2-like phenotype, actively support tumor progression by promoting angiogenesis, enhancing tumor cell invasion and metastasis, and suppressing adaptive immune responses through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, and the expression of immune checkpoint ligands like PD-L1 (3). Their immunosuppressive and pro-tumorigenic functions not only facilitate cancer progression but also mediate resistance to conventional immunotherapies. Thus, TAMs represent a compelling target for therapeutic intervention aimed at reprogramming the TME to favor anti-tumor immunity (4) (Figure 1). Preclinical studies have provided compelling evidence supporting the efficacy of this approach. In murine models of melanoma and breast cancer, LNP-formulated mRNA encoding IRF5 and IKKβ effectively reprogrammed TAMs, reduced tumor burden, and extended survival (5). These effects were associated with increased infiltration of cytotoxic $CD8^+$ T cells and elevated production of inflammatory mediators within the TME. Notably, combining these TAM-targeted mRNA vaccines with ICB agents such as anti-PD-1 or anti-CTLA-4 antibodies resulted in synergistic anti-tumor activity, overcoming resistance in immunologically “cold” tumors(6).

Furthermore, co-delivery strategies have been explored wherein mRNA vaccines simultaneously deliver TAM-reprogramming factors alongside tumor antigens, thereby priming both innate and adaptive arms of the immune system in a coordinated attack against cancer cells (7).

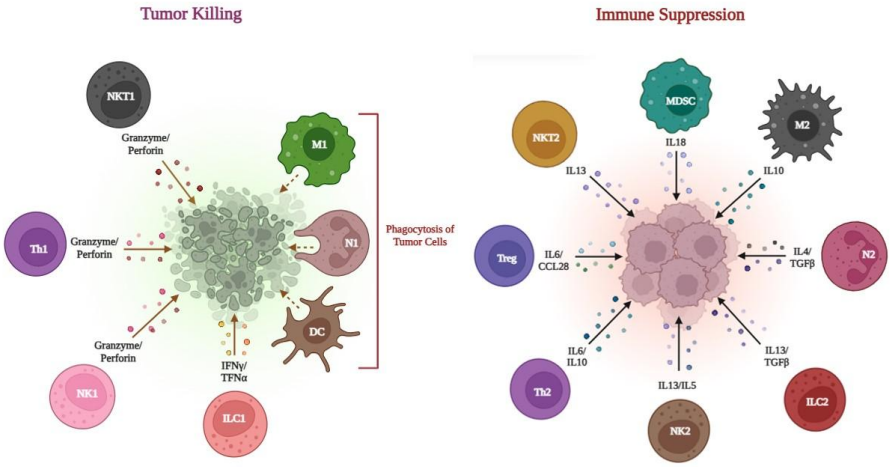
While these findings are promising, several challenges must be addressed to ensure clinical translation. First, achieving cell-type specificity is critical, as systemic reprogramming of macrophages may lead to off-target effects and unintended inflammation. This necessitates careful design of delivery systems and identification of TAM-specific surface markers for targeting (8). Second, TAMs are highly heterogeneous and dynamically adapt to environmental cues within different tumor types and stages. A deeper understanding of TAM subpopulations and their functional roles will be essential to tailor mRNA vaccines for maximal therapeutic benefit. Third, although mRNA vaccines are generally well-tolerated, repeated administration could elicit anti-vector immunity or off-target immune activation. Thus, strategies to minimize immunogenicity of the delivery vehicles and optimize dosing regimens will be important for maintaining efficacy and safety over multiple doses (9).

Additionally, the modular nature of mRNA synthesis allows for rapid customization of payloads, enabling the development of patient-specific formulations that incorporate tumor-specific antigens and immune-modulatory agents tailored to the individual's tumor immune landscape (9). This could be particularly valuable in combination settings, where mRNA vaccines serve as adjuvants to reprogram the TME and sensitize tumors to checkpoint blockade or other forms of immunotherapy. Importantly, mRNA vaccines may also play a role in overcoming resistance to existing therapies by reversing immune exclusion and reactivating immune surveillance mechanisms (10) (table 1).

The integration of single-cell sequencing, spatial transcriptomics, and in vivo imaging technologies will further refine our understanding of TAM dynamics and inform the rational design of mRNA therapeutics (11). Clinical trials are anticipated to explore the safety, pharmacodynamics, and immune correlates of TAM-targeted mRNA vaccines, either as monotherapy or in combination with ICIs, adoptive cell therapies, or conventional chemotherapy. Furthermore, the development of next-generation delivery vehicles capable of crossing biological barriers and achieving site-specific delivery will expand the applicability of mRNA vaccines beyond accessible tumors to include metastases and hematologic malignancies (12)(13).

In conclusion, mRNA-based cancer vaccines targeting tumor-associated macrophages represent a novel and transformative strategy to reprogram the immunosuppressive TME and enhance the efficacy of cancer immunotherapy. By leveraging the plasticity of TAMs and the versatility of mRNA technology, this approach offers the potential to convert immunologically “cold” tumors into “hot,” inflamed environments conducive to durable anti-tumor responses. As preclinical findings continue to translate into clinical applications, TAM-reprogramming mRNA vaccines may soon become a cornerstone in the next generation of immuno-oncology treatments.

Figure 1 the image shows the dual roles of immune cells in the tumor microenvironment, with tumor-killing cells releasing cytotoxic molecules or promoting phagocytosis and pro-inflammatory cytokines, and immunosuppressive cells releasing anti-inflammatory cytokines that support tumor immune evasion and progression. Tumor-killing cells, such as NK1, Th1, NKT1, ILC1, and DCs, act by releasing cytotoxic molecules.



Category	Details	Clinical Implications	References
Target Cells	Tumor-Associated Macrophages (TAMs), predominantly M2-like in solid tumors	Broad applicability across multiple tumor types with high TAM density	[2], [3]
Therapeutic Goal	Reprogram M2-like (tumor-promoting) TAMs to M1-like (tumoricidal) phenotype	Could restore immune surveillance and reduce immunotherapy resistance	[3], [4]
Delivery Vehicle	Lipid Nanoparticles (LNPs) for targeted delivery of mRNA payloads	Enables localized action and minimizes systemic toxicity	[5], [7]
mRNA Payloads	IRF5, IKKβ key regulators of inflammatory macrophage function	Induces effective macrophage repolarization to support anti-tumor response	[5]
Mechanism of Action	Promotes pro-inflammatory cytokines, enhances antigen presentation, recruits cytotoxic T cells	Amplifies innate and adaptive immune responses in the tumor microenvironment	[5], [6]
Synergistic Therapies	Immune checkpoint inhibitors, tumor antigens, chemotherapy, adoptive cell therapies	Enhances efficacy of existing therapies and may overcome resistance	[6], [10], [13]
Benefits of mRNA Approach	Rapid customization, transient expression, dual immune activation, non-integration	Ideal for personalized, timely, and flexible cancer treatment strategies	[7], [10], [13]
Challenges and Barriers	TAM heterogeneity, off-target effects, immune activation risk, marker specificity	Requires precise delivery strategies and patient stratification for efficacy and safety	[8], [9]
Strategies to Improve Specificity	TAM-targeted ligands, spatial omics, single-cell profiling	Improves targeting precision and reduces risk of immune-related adverse events	[9], [11]
Clinical Development Needs	In vivo tracking, pharmacodynamic biomarkers, combination regimen testing	Supports rational trial design and patient monitoring in clinical settings	[10], [11], [12]
Potential Impact	Converts “cold” tumors to “hot” tumors, reverses immune exclusion	Expands the pool of immunotherapy responders and improves durable response rates	[1], [6], [10]

Table 1 this table summarizes the key components, mechanisms, and therapeutic implications of mRNA-based cancer vaccines targeting tumor-associated macrophages (TAMs). It outlines molecular strategies for TAM reprogramming, delivery methods, clinical challenges, and potential synergies with existing immunotherapies. Clinical implications highlight how these innovations may enhance anti-tumor immunity and improve patient outcomes.

REFERENCES

1. Ghemrawi R, Abuamer L, Kremesh S, Hussien G, Ahmed R, Mousa W, et al. Revolutionizing Cancer Treatment: Recent Advances in Immunotherapy. Biomedicines. 2024 Sep 23;12(9):2158.
2. Sambi M, Bagheri L, Szewczuk MR. Current Challenges in Cancer Immunotherapy: Multimodal Approaches to Improve Efficacy and Patient Response Rates. Journal of Oncology. 2019 Feb 28;2019:1–12.
3. Wang S, Wang J, Chen Z, Luo J, Guo W, Sun L, et al. Targeting M2-like tumor-associated macrophages is a potential therapeutic approach to overcome antitumor drug resistance. npj Precis Onc. 2024 Feb 10;8(1):31.
4. Huang R, Kang T, Chen S. The role of tumor-associated macrophages in tumor immune evasion. J Cancer Res Clin Oncol. 2024 May 7;150(5):238.
5. Afzal A, Abbasi MH, Ahmad S, Sheikh N, Khawar MB. Current Trends in Messenger RNA Technology for Cancer Therapeutics. Biomater Res. 2025;29:0178.
6. Zhou Z, Zheng J, Lu Y, Mai Z, Lin Y, Lin P, et al. Optimizing CD8+ T cell-based immunotherapy via metabolic interventions: a comprehensive review of intrinsic and extrinsic modulators. Exp Hematol Oncol. 2024 Oct 22;13(1):103.
7. Malla R, Srilatha M, Farran B, Nagaraju GP. mRNA vaccines and their delivery strategies: A journey from infectious diseases to cancer. Molecular Therapy. 2024 Jan;32(1):13–31.

8. Karimova AF, Khalitova AR, Suezov R, Markov N, Mukhamedshina Y, Rizvanov AA, et al. Immunometabolism of tumor-associated macrophages: A therapeutic perspective. European Journal of Cancer. 2025 May;220:115332.
9. Sheykhhasan M, Ahmadieh-Yazdi A, Heidari R, Chamanara M, Akbari M, Poondla N, Yang P, Malih S, Manoochehri H, Tanzadehpanah H, Mahaki H. Revolutionizing cancer treatment: The power of dendritic cell-based vaccines in immunotherapy. Biomedicine & Pharmacotherapy. 2025 Mar 1;184:117858.
10. Gao Y, Yang L, Li Z, Peng X, Li H. mRNA vaccines in tumor targeted therapy: mechanism, clinical application, and development trends. Biomark Res. 2024 Aug 31;12(1):93.
11. Zhang W, Zhang X, Teng F, Yang Q, Wang J, Sun B, et al. Research progress and the prospect of using single-cell sequencing technology to explore the characteristics of the tumor microenvironment. Genes & Diseases. 2025 Jan;12(1):101239.
12. Han R, Wang Y, Lu L. Sensitizing the Efficiency of ICIs by Neoantigen mRNA Vaccines for HCC Treatment. Pharmaceutics. 2023 Dec 29;16(1):59.
13. Li Y, Wang M, Peng X, Yang Y, Chen Q, Liu J, et al. mRNA vaccine in cancer therapy: Current advance and future outlook. Clinical & Translational Med. 2023 Aug;13(8):e1384.