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Perspective

Tumor-Associated Macrophage Reprogramming *via* Targeted Lipid Nanoparticles for Enhanced Cancer Immunotherapy

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DESCRIPTION

Tumor-Associated Macrophages (TAMs) represent a substantial component of the tumor microenvironment, often accounting for 30%-50% of the cellular mass in solid tumors. Typically polarized toward an immunosuppressive, pro-tumoral M2-like phenotype, these cells contribute significantly to therapeutic resistance and disease progression. We have developed specialized Lipid Nanoparticles (LNPs) designed to selectively target and repolarize TAMs toward a pro-inflammatory, anti-tumoral M1-like phenotype, thereby converting these cellular liabilities into therapeutic assets. These LNPs, approximately 85 nm in diameter, incorporate specific targeting ligands and immunomodulatory payloads that work synergistically to reshape the tumor immune landscape.

The LNP formulation consists of an ionizable amino lipid with optimized pKa values that facilitate selective uptake in the mildly acidic tumor microenvironment, combined with phospholipids and cholesterol in ratios that ensure stability during circulation while enabling efficient intracellular delivery following endocytosis. Surface functionalization with mannose and galactose moieties facilitates specific binding to C-type lectin receptors highly expressed on TAMs, particularly the mannose receptor (CD206) associated with the M2-like phenotype. The therapeutic payload consists of a combination of CpG oligonucleotides to activate Toll-Like Receptor 9 (TLR9) and small molecule inhibitors of Colony-Stimulating Factor 1 Receptor (CSF1R), creating complementary mechanisms to both block signals maintaining the M2-like state and actively promote M1-like polarization.

In vitro characterization using macrophages polarized under tumor-conditioned media demonstrated efficient reprogramming capability, with approximately 78% of treated cells shifting from CD206high/CD80low to CD206low/CD80high expression profiles within 48 hours of treatment. Transcriptomic analysis revealed comprehensive phenotypic conversion with upregulation of pro-inflammatory cytokines (IL-12, TNFα) and downregulation of immunosuppressive factors (IL-10, TGF-β, arginase-1). Functional assays demonstrated restoration of phagocytic activity against tumor cells and enhanced antigen presentation capacity, with significantly increased T cell stimulatory potential as measured by mixed lymphocyte reaction assays.

In vivo evaluation utilized multiple tumor models including B16F10 melanoma and E0771 triple-negative breast cancer, both characterized by substantial macrophage infiltration. Biodistribution studies using fluorescently labeled LNPs confirmed preferential accumulation in $CD11b^{+}F4/80^{+}$ TAMs, with approximately 65% of these cells showing successful uptake within 24 hours of intravenous administration. Flow cytometric analysis of tumor infiltrating leukocytes following three weekly treatments revealed significant TAM repolarization, with M1 ratios shifting from approximately 0.3 in control tumors to 2.7 in treated tumors. This shift correlated with dramatic increases in $CD8^{+}$ T cell infiltration and activity, with approximately 3.5-fold higher granzyme B^{+} effector T cells compared to control tumors.

Therapeutic efficacy studies demonstrated significant tumor growth inhibition as monotherapy (approximately 67% reduction in tumor volume compared to controls), with even more dramatic effects when combined with immune checkpoint inhibitors targeting the PD-1/PD-L1 axis. This combination therapy resulted in complete responses in approximately 45% of treated animals, with evidence of immunological memory as demonstrated by rejection of tumor re-challenge. Analysis of distant, untreated tumors in dual-tumor models showed evidence of systemic anti-tumor immunity, suggesting potential for addressing metastatic disease. Mechanistic studies confirmed the central role of repolarized macrophages, as depletion of these cells substantially reduced therapeutic efficacy.

CONCLUSION

Safety assessment revealed no evidence of systemic inflammatory activation, with serum cytokine levels remaining within normal ranges throughout the treatment period. Histopathological

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examination of major organs showed no significant toxicity, and comprehensive blood chemistry and hematological analyses remained within normal parameters. These TAM-repolarizing lipid nanoparticles represent a promising approach for cancer immunotherapy, potentially converting immunosuppressive components of the tumor microenvironment into active participants in anti-tumor immunity while complementing existing immunotherapeutic strategies.