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Commentary

Synthetic Bacterial Nanocells for Targeted Immunotherapy of Solid Tumors

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DESCRIPTION

Immunotherapy has revolutionized cancer treatment; however, solid tumors often present significant challenges due to their immunosuppressive microenvironment and physical barriers limiting therapeutic access. We have developed Synthetic Bacterial Nanocells (SBNs) that combine the tumor-penetrating capabilities of bacterial pathogens with precisely engineered immunomodulatory functions while eliminating risks associated with live bacterial therapies. These cell-free nanocells, approximately 400 nm in diameter, were fabricated through sequential isolation and reconstruction of bacterial membrane components from detoxified Salmonella typhimurium, incorporating recombinant surface proteins that facilitate tumor targeting and immune stimulation.

The SBN architecture consists of a unilamellar vesicle comprised of bacterial phospholipids and membrane proteins, stabilized through controlled sonication and extrusion processes. Key pathogen-associated molecular patterns, including lipopolysaccharide and flagellin proteins, were retained in modified forms to elicit immune activation while minimizing systemic toxicity. Surface functionalization included recombinant adhesins targeting tumor-associated glycosylation patterns, enabling preferential binding to malignant cells. The internal compartment was loaded with synergistic immunostimulatory payloads, including cyclic dinucleotide STING agonists and siRNA targeting Indoleamine 2,3-Dioxygenase 1 (IDO1), a critical metabolic checkpoint in the tumor microenvironment. This combination was designed to simultaneously activate innate immune pathways while countering immunosuppressive mechanisms.

In vitro characterization demonstrated specific binding to multiple cancer cell lines with approximately 6-fold higher affinity for malignant versus normal epithelial cells. Co-culture studies with human peripheral blood mononuclear cells revealed robust activation of dendritic cells following SBN exposure, with significant upregulation of costimulatory molecules (CD80, CD86) and proinflammatory cytokine production. Transcriptional profiling of treated dendritic cells confirmed activation signatures associated with type I interferon responses and enhanced antigen presentation capability. Furthermore, SBN treatment effectively reprogrammed tumor-associated macrophages from immunosuppressive M2-like phenotypes toward proinflammatory M1-like states, as evidenced by altered cytokine profiles and surface marker expression.

In vivo biodistribution studies using fluorescently labeled SBNs in multiple tumor models demonstrated preferential accumulation in malignant tissue, with tumor-to-liver ratios approximately 5-fold higher than conventional liposomal formulations at 48 hours post-administration. Intratumoral distribution analysis revealed extensive penetration into hypoxic regions typically resistant to therapeutic access. Treatment of established B16F10 melanoma tumors in immunocompetent mice resulted in significant tumor growth inhibition (78% reduction in tumor volume compared to controls), with 3 of 10 animals achieving complete responses. Combination with anti-PD-1 checkpoint blockade further enhanced efficacy, with complete response rates increasing to 60% and evidence of immunological memory demonstrated through rejection of tumor rechallenge.

CONCLUSION

Immunophenotyping of treated tumors revealed dramatic remodeling of the microenvironment, characterized by increased $CD8^+$ T cell infiltration, elevated $CD8^+$/Treg ratios, and reduced myeloid-derived suppressor cell populations. Transcriptomic analysis of treated tumors demonstrated upregulation of interferon-stimulated genes and cytotoxic effector molecules, consistent with conversion from "cold" to "hot" tumor immune phenotypes. Importantly, systemic inflammatory markers remained within normal ranges throughout treatment, with no evidence of cytokine storm or significant off-target inflammation in major organs. These synthetic bacterial nanocells represent a promising platform for targeted cancer immunotherapy, combining the evolutionary-optimized tissue penetration capabilities of bacterial pathogens with precisely engineered immunomodulatory functions while eliminating safety concerns associated with live bacterial therapies.

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