

Nanomaterial Enhanced Photothermal Therapy Combined With Checkpoint Inhibitors in Melanoma

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DESCRIPTION

Melanoma is one of the most aggressive forms of skin cancer, originating from melanocytes and characterized by high metastatic potential and resistance to conventional therapies in advanced stages. Traditional treatments such as surgical excision, chemotherapy, and radiation therapy provide benefit in early stage disease but are often insufficient in controlling metastatic progression. The emergence of immunotherapy, particularly immune checkpoint inhibition, has revolutionized melanoma treatment by reactivating cytotoxic T cells against tumor cells. Despite this progress, a significant proportion of patients either fail to respond or develop resistance due to the immunosuppressive tumor microenvironment. Recent advances in nanotechnology have enabled the development of nanomaterial enhanced photothermal therapy, offering a novel strategy to potentiate immune responses and improve outcomes when combined with checkpoint inhibitors.

Photothermal therapy relies on the conversion of near infrared light energy into localized heat to induce tumor cell death. Nanomaterials, including gold nanoparticles, carbon based materials, and semiconductor nanostructures, have been engineered to efficiently absorb near infrared light and convert it into heat, enabling precise tumor ablation with minimal damage to surrounding normal tissue. The physical destruction of tumor cells by localized hyperthermia not only reduces tumor burden but also releases tumor associated antigens and damage associated molecular patterns into the tumor microenvironment. These signals can prime dendritic cells and enhance antigen presentation, promoting activation of cytotoxic T cells and other immune effector mechanisms.

Checkpoint inhibitors target regulatory pathways in T cells, such as programmed cell death protein one and cytotoxic T lymphocyte associated protein four, that tumors exploit to evade immune surveillance. By blocking these inhibitory signals, checkpoint inhibitors restore T cell function and facilitate recognition and destruction of tumor cells. Combining photothermal therapy with checkpoint inhibitors has the potential to synergistically enhance antitumor immunity.

Photothermal therapy generates an inflammatory environment and releases tumor antigens, providing the necessary signals for T cell priming, while checkpoint inhibitors prevent T cell exhaustion and allow sustained cytotoxic activity against melanoma cells.

Preclinical studies in murine models of melanoma have demonstrated that nanomaterial enhanced photothermal therapy alone can induce significant tumor regression, but residual tumor cells and distant metastases often persist. When combined with checkpoint inhibition, the therapy not only achieves more complete primary tumor elimination but also promotes systemic immune responses capable of targeting metastatic lesions. This combination strategy is particularly effective in converting "cold" tumors, which are poorly infiltrated by immune cells, into "hot" tumors characterized by abundant cytotoxic T cell infiltration and heightened inflammatory activity.

The design and engineering of nanomaterials are critical to the success of photothermal therapy. Key parameters include absorption spectrum, particle size, shape, surface chemistry, and biocompatibility. Gold nanorods, nanoshells, and nanostars have been extensively studied due to their tunable optical properties and stability under near infrared irradiation. Surface modification with polyethylene glycol and tumor targeting ligands improves circulation time, reduces off target accumulation, and enhances selective uptake by melanoma cells. Carbon based nanomaterials, including graphene oxide and carbon nanotubes, offer high photothermal conversion efficiency and the potential for multifunctional applications such as drug delivery or imaging. Optimizing these properties ensures effective heat generation at the tumor site while minimizing systemic toxicity.

The immune modulatory effects of photothermal therapy extend beyond antigen release. Hyperthermia induces expression of heat shock proteins, inflammatory cytokines, and chemokines that recruit dendritic cells, macrophages, and natural killer cells into the tumor microenvironment. This immune activation complements the action of checkpoint inhibitors, which sustain T cell mediated cytotoxicity and prevent inhibitory signaling

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pathways from limiting antitumor responses. Additionally, photothermal therapy can disrupt tumor vasculature and reduce hypoxic regions, further enhancing immune infiltration and therapeutic efficacy.

Several challenges remain in translating this combination approach to clinical practice. Controlling the precise temperature and spatial distribution of heat is essential to avoid damage to surrounding healthy tissue. Overheating can induce necrotic cell death that may generate immunosuppressive signals, whereas insufficient heating may fail to release tumor antigens effectively. Careful calibration of laser parameters, nanomaterial dosage, and administration route is required to achieve optimal outcomes. Furthermore, immune related adverse events associated with checkpoint inhibitors, such as colitis, pneumonitis, and dermatologic toxicity, must be monitored closely, particularly when combined with inflammatory effects induced by photothermal therapy.

Early phase clinical trials exploring nanomaterial mediated photothermal therapy combined with checkpoint inhibitors in melanoma are underway. Preliminary results indicate that this approach is feasible and can induce both local tumor regression and systemic immune responses. Biomarker analysis, including measurement of tumor infiltrating lymphocytes, cytokine profiles, and circulating tumor DNA, provides insight into mechanisms of response and potential predictors of therapeutic efficacy. Personalized treatment strategies that consider tumor antigenicity, immune profile, and nanomaterial pharmacokinetics may further enhance outcomes and reduce toxicity.

The integration of imaging modalities, such as photoacoustic imaging and magnetic resonance imaging, with nanomaterial enhanced photothermal therapy allows real time monitoring of nanoparticle accumulation, temperature distribution, and

tumor response. This approach enables precision treatment planning and adjustment, ensuring that the therapy effectively targets tumor tissue while sparing healthy structures. Imaging guidance also facilitates combination with checkpoint inhibitors by providing temporal and spatial data on immune activation and tumor regression.

Future directions in this field include the development of multifunctional nanomaterials capable of simultaneous photothermal therapy, targeted drug delivery, and immune modulation. Incorporation of immune stimulatory agents, such as toll like receptor agonists or cytokines, into nanomaterials may further amplify antitumor immunity and enhance synergy with checkpoint inhibitors. Exploration of combination strategies with other immunotherapies, such as adoptive cell transfer or cancer vaccines, may also provide additional benefit in overcoming immune escape mechanisms in melanoma.

CONCLUSION

Nanomaterial enhanced photothermal therapy combined with checkpoint inhibitors represents a promising strategy to improve outcomes in melanoma. By integrating precise tumor ablation with systemic immune activation, this approach addresses both local tumor control and distant metastases. Preclinical and early clinical data highlight the potential of this combination to convert poorly immunogenic tumors into immunologically active lesions, providing durable responses and enhanced survival. Continued research in nanomaterial engineering, immune biology, and clinical translation is essential to optimize safety, efficacy, and accessibility. As the understanding of tumor immunology and nanotechnology advances, this integrated therapeutic approach has the potential to become a standard component of melanoma treatment, offering hope for patients with advanced or treatment resistant disease.