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Nanoparticle-Mediated T-Cell Drug Delivery: A Synergistic Approach for Enhanced Cancer Therapy

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ABSTRACT

Worldwide, cancer is a major cause of death, and solid tumors represent unique challenges for treatment success. Although T-cell-based immunotherapies have enjoyed some success in hematological malignancies with CAR T cells and T-cell receptor-engineered therapies, they have limited efficacy against solid tumors because of poor tumor infiltration, immunosuppressive tumor microenvironments (TME), and antigen heterogeneity. Nanomedicine provides an excellent opportunity to overcome these barriers by enhancing T-cell functionality and achieving targeted delivery of drugs. With controlled release, this type of drug delivery system provides an improved pharmacokinetic profile with selective tumor-targeted delivery while minimizing systemic toxicity. In addition, T-cell-conjugated nanoparticles can enhance immune cell infiltration, modulate TME, and improve the persistence and activity of adoptive T-cell therapies. Therefore, this review focuses on the recent advances of T-cell drug delivery by nanoparticles to optimize T-cell therapy by enhancing tumor penetration and relieving immune suppression while increasing therapeutic efficacy. A special focus is also given to their applications in treating CNS tumors, where standard therapy faces added challenges instituted by the blood-brain barrier. This would reciprocally present an opportunity to synergize nanotherapy-T-cell therapy combinations toward improving therapeutic gains in solid tumors while expanding the applicability of immunotherapy in oncology.

INTRODUCTION

According to recent statistics from the American Cancer Society (ACS), approximately 2 million new cancer cases were anticipated in the U.S. in 2022, with 600,000 associated deaths. Among these, lung cancer was particularly deadly, claiming nearly 350 lives daily. Despite ongoing advancements in cancer treatment, including surgery, radiation therapy, and chemotherapy, the disease remains a significant challenge. This persistence is largely due to key obstacles in effective disease management, such as drug toxicity, lack of treatment specificity, immune suppression within the tumor microenvironment (TME), and variations in disease response among patients.(1)

Over the past few decades, nanotechnology has gained increasing attention in medicine, particularly in diagnostics, therapy, and targeted cancer treatment. Nanoparticle (NP)-based drug delivery systems offer several advantages, including improved drug pharmacokinetics, enhanced tumor cell targeting, reduced side effects, and the ability to overcome drug resistance.(2,3)

T cell therapy has also emerged as a promising approach for cancer treatment. Both antigen-specific T cells and genetically modified chimeric antigen receptor (CAR) T cells have demonstrated clinical potential in treating various solid and hematologic malignancies in both adults and children. In the U.S., three CAR-T cell therapies—Kymriah, Yescarta, and Breyanzi—have been approved for treating B-cell leukemia and lymphoma. While these therapies have shown notable success in blood cancers, their effectiveness in treating solid tumors remains limited due to multiple inherent challenges.(4–6)

One major obstacle is the heterogeneity of tumor antigens, which means that T cells engineered to target a single antigen may be insufficient to eliminate tumors. Additionally, solid tumors exhibit abnormal vasculature, which can hinder T cell infiltration into the TME, thereby reducing treatment effectiveness. Furthermore, the immunosuppressive nature of the TME can inhibit T cell function, even when T cells successfully reach and recognize tumor cells. These challenges are even more pronounced in central nervous system (CNS) tumors, significantly limiting the therapeutic impact of T cell therapies.(7)

Nanotechnology has emerged as a promising tool for addressing these limitations. Due to their small size, high surface area-to-volume ratio, and ability to encapsulate therapeutic agents in a controlled manner, nanoparticles have been widely explored for cancer drug delivery. They can traverse complex anatomical barriers, such as the blood-brain barrier (BBB), making them valuable in imaging and targeted therapy for solid tumors. Numerous nanoparticle formulations have been evaluated in preclinical brain tumor models, demonstrating potential solutions to various treatment challenges.(8–10)

Recent research has begun to explore the role of nanotechnology in enhancing immunotherapy, particularly T cell-based approaches. However, there are still very few studies investigating how nanoparticles can improve T cell therapy for CNS tumors. This review aims to summarize recent advancements in nanoparticle-mediated T cell therapy and propose potential treatment strategies for CNS tumors. We discuss nanoparticle-based approaches to optimize adoptive T cell therapies, including nanoparticle conjugation to T cells to overcome TME

immunosuppression, nanoparticle-driven enhancement of T cell infiltration into tumors, in situ activation of T cells, and boosting T cell functionality. Finally, we examine how these strategies may be applied specifically to CNS-related cancers.(11–13)

Nanoparticle technology has also been used to develop artificial antigen-presenting cells, significantly improving antigen recognition in CAR-T cell therapy for solid tumors. For example, carbon nanotubes, due to their high surface area-to-volume ratio, have been shown to activate T cells effectively. These nanotubes can conjugate multiple antigen molecules, enhancing the efficiency of anti-CD3 antibody presentation to T cells. Additionally, they require significantly lower levels of IL-2 to achieve the same degree of T cell expansion.(14)

The spatial organization of CAR components plays a crucial role in overcoming therapeutic barriers and improving CAR-T cell efficacy. Integrating nanotechnology can help CAR-T cells navigate physical and biochemical obstacles, thereby enhancing their fu(15)nctionality. For instance, nanogels and liposomes can improve CAR-T cell delivery, ensuring precise targeting of tumor sites while reducing off-target effects. Furthermore, liposomes carrying an A2A receptor-specific antagonist can be attached to CAR-T cells, helping them counteract the immunosuppressive effects of adenosine within the TME. Additionally, protein nanogels loaded with an IL-15 superagonist (IL-15sa) and an anti-CD45 antibody can provide stimulatory signals while blocking inhibitory signals, thereby promoting CAR-T cell activation, persistence, and proliferation.(6,16)

T Cell Therapy in Cancer Treatment

Role of CD8+ Cytotoxic T Cells in Targeting Cancer

CD8+ cytotoxic T cells are essential components of the adaptive immune system and play a crucial role in the body's anticancer response. They serve as the foundation of cancer immunotherapy by directly eliminating tumor cells through cytotoxic mechanisms. Two primary immunotherapeutic strategies harnessing CD8+ T cells are immune checkpoint inhibitors (ICIs) and adoptive cell transfer (ACT).

ICIs work by blocking inhibitory immune receptors, thereby rejuvenating exhausted CD8+ T cells and enhancing their antitumor activity. Meanwhile, ACT—particularly CAR-T cell therapy—involves genetically modifying CD8+ T cells to express synthetic receptors, improving their ability to recognize and attack tumor cells. These advancements have significantly shaped the field of immuno-oncology, offering promising treatment options.

However, challenges remain. Not all patients experience long-term benefits, and adverse effects sometimes necessitate discontinuation of therapy. As a result, ongoing clinical trials are exploring next-generation immune checkpoint inhibitors, improved CAR-T cell therapies, and combination approaches to enhance efficacy while minimizing toxicity. A deeper understanding of these mechanisms will help shape the future of CD8+ T cell-based cancer immunotherapy.(17–19)

Engineered T Cells (CAR-T and TCR-T) and Their Limitations

Early adoptive immunotherapy involved transfusing tumor-responsive T cells (autologous or allogeneic) back into patients to target tumors. While effective, the limited number of tumor-infiltrating lymphocytes restricted its success. To overcome this, genetically engineered T cell therapies were developed, enhancing survival, migration, and tumor-targeting capabilities.

CAR-T cell therapy has emerged as a groundbreaking immunotherapeutic approach, particularly in acute B lymphocytic leukemia, and has been extensively studied for other cancers. CAR-T cells are genetically modified to express chimeric antigen receptors (CARs), enabling them to recognize tumor antigens independent of major histocompatibility complex (MHC) molecules. This specificity allows for direct tumor recognition and destruction while also providing immune memory, potentially leading to long-term treatment efficacy.(20–24)

Despite these successes, CAR-T therapy faces limitations:

- Restricted Targeting: It is primarily effective against surface antigens and cannot target intracellular oncogenic drivers.
- Immune-Related Toxicities: Cytokine release syndrome (CRS) and neurotoxicity are significant concerns.

TCR-T cell therapy is another engineered T cell approach that modifies T lymphocytes to recognize MHC-presented tumor antigens. Unlike CAR-T cells, which broadly target surface proteins, TCR-T cells can recognize intracellular antigens, expanding their potential applications. However, this therapy is constrained by:

- MHC Restriction: TCR-T cells require antigen presentation by specific MHC molecules, limiting their use across diverse patient populations.
- Immune Evasion: Some tumors downregulate MHC expression, reducing the efficacy of TCR-T therapies.

Despite these challenges, ongoing efforts aim to optimize engineered T cell therapies by broadening antigen targets, improving durability, and reducing adverse effects.

Recent advancements include nanoparticle-assisted imaging and stimulation of CAR-T cells. For instance, CAR-T cells labeled with iron oxide nanoparticles (25 nm spherical particles or 120 nm nanoworms) have been successfully imaged using MRI. Additionally, researchers have coated CAR-T cells with IL-12-loaded human serum albumin nanoparticles, which enhance chemokine production and boost T cell infiltration into tumors, creating a self-amplifying therapeutic loop.(25–30)

Challenges in T Cell-Based Cancer Therapy

Tumor Antigen Heterogeneity and T Cell Targeting

One major obstacle in T cell-based immunotherapy is the heterogeneity of tumor antigens, which means that T cells engineered to recognize a single antigen may not be sufficient for comprehensive tumor elimination. This limitation necessitates the development of strategies that broaden antigen recognition or combine multiple therapeutic modalities.

Impaired T Cell Infiltration

Solid tumors exhibit abnormal vasculature, which hinders T cell infiltration into the TME. Even when T cells reach tumor sites, immunosuppressive signals in the TME can inhibit their function. These challenges are particularly pronounced in CNS tumors, where the blood-brain barrier (BBB) further restricts therapeutic access.

Nanotechnology as a Tool for Enhancing T Cell Therapy

Nanotechnology has gained attention for its ability to encapsulate therapeutic agents, traverse biological barriers, and precisely target tumor cells. Due to their high surface area-to-volume ratio, nanoparticles (NPs) can be engineered to enhance T cell therapy in multiple ways.

Nanoparticle-Based Drug Delivery for Cancer Immunotherapy

NPs have been extensively explored for their role in cancer drug delivery, particularly in preclinical brain tumor models. By crossing the BBB, NPs can facilitate the delivery of imaging agents and therapeutics, overcoming one of the major limitations of CNS-targeted immunotherapies.(31–34)

Mechanisms of Synergy Between Nanoparticles and T Cell Therapy

Optimizing Adoptive T Cell Therapies with Nanoparticles

NPs can enhance adoptive T cell therapy (ACT) through various strategies:

Nanoparticle Conjugation to T Cells: Improves T cell persistence and trafficking to tumor sites.

Nanoparticle-Driven Enhancement of T Cell Infiltration: Modifies tumor vasculature and extracellular matrix to facilitate T cell penetration.

In Situ Activation of T Cells: Provides localized stimulation to enhance T cell cytotoxicity.

Boosting T Cell Functionality: Carries cytokines and stimulatory agents to maintain prolonged T cell activation.

Nanoparticle-Enabled CAR-T Cell Therapy

Nanoparticles have also been used to develop artificial antigen-presenting cells, significantly improving antigen recognition in chimeric antigen receptor (CAR)-T cell therapy. Carbon nanotubes, for instance, have been shown to enhance anti-CD3 antibody presentation to T cells while reducing IL-2 dependency for expansion. Additionally, protein nanogels loaded with IL-15 superagonists and anti-CD45 antibodies can promote CAR-T cell activation, persistence, and proliferation.(35)

Role of CD8+ Cytotoxic T Cells in Cancer Immunotherapy

CD8+ cytotoxic T cells are central to the adaptive immune system's anticancer response. Two major immunotherapeutic strategies leveraging CD8+ T cells include:
Immune Checkpoint Inhibitors (ICIs): Block inhibitory immune receptors to restore T cell activity.
Adoptive Cell Transfer (ACT): Genetically modifies T cells to enhance tumor recognition and destruction.
Despite promising outcomes, challenges remain, such as immune-related toxicities and limited patient responsiveness. Current research aims to develop next-generation ICIs, improved CAR-T cell therapies, and combination strategies to enhance efficacy while reducing adverse effects.(36)

Engineered T Cells: CAR-T and TCR-T Therapies

CAR-T Cell Therapy

CAR-T cell therapy has revolutionized immunotherapy, particularly for hematological malignancies like acute B lymphocytic leukemia. CAR-T cells recognize tumor antigens independently of MHC molecules, allowing direct tumor engagement. However, limitations include:
Restricted Targeting: Limited to surface antigens, excluding intracellular oncogenic drivers.
Immune-Related Toxicities: Risks such as cytokine release syndrome (CRS) and neurotoxicity.(37–40)

TCR-T Cell Therapy

TCR-T cells recognize intracellular antigens presented by MHC molecules, broadening their therapeutic potential. However, they face challenges like:
MHC Restriction: Requiring specific MHC molecules for antigen presentation, limiting patient applicability.
Immune Evasion: Some tumors downregulate MHC expression, reducing efficacy.(27,41)

Nanoparticle-Based Approaches in CAR-T and TCR-T Therapy

Recent advancements have introduced nanoparticle-assisted imaging and stimulation of CAR-T cells. Examples include:
Iron Oxide Nanoparticles: Enable MRI imaging of CAR-T cells for tracking within tumors.
IL-12-Loaded Nanoparticles: Enhance chemokine production, increasing T cell infiltration and forming a self-amplifying therapeutic loop.(11,42–44)
Clinical Translation and Future Directions
Despite promising preclinical results, many nanoparticle-based drug delivery systems (NDDSs) have yet to transition into clinical applications. Key challenges include:
Preclinical Models: Traditional subcutaneous tumor models fail to replicate human immune interactions. Genetically engineered mouse models may provide better insights.
Manufacturing and Scalability: NDDSs often require complex and costly production methods that hinder large-scale manufacturing.(8)

Active Tumor Homing and the Role of T Cells in Nanoparticle-Based Cancer Therapy

Active Tumor Homing

T cells naturally migrate into tumor tissues by recognizing tumor-specific antigens and chemokine signals within the tumor microenvironment. Unlike passive nanoparticle accumulation, which depends on the enhanced permeability and retention (EPR) effect, T cells actively navigate, infiltrate, and engage tumor tissues. This ability makes T cells an effective vehicle for targeted drug delivery in cancer therapy.(45)

Long Circulation Time

One of the main limitations of free nanoparticles is their rapid clearance by the immune system, reducing their circulation time and therapeutic efficacy. In contrast, T cells can circulate in the bloodstream for days to weeks, ensuring prolonged and sustained nanoparticle delivery to tumor sites.(33)

Ability to Penetrate Solid Tumors

Solid tumors are surrounded by a dense extracellular matrix and immunosuppressive barriers that limit drug penetration. However, T cells possess an intrinsic ability to migrate through these barriers, enhancing therapeutic delivery and improving treatment outcomes.(12,46)

Synergistic Potential with Immunotherapies

Nanoparticle-enhanced T cell therapy can be combined with various immunotherapeutic strategies, including:
Checkpoint inhibitors (e.g., anti-PD-1, anti-CTLA-4): To further enhance and prolong T cell activation.
CAR-T or ACT therapy: Nanoparticles can boost T cell function and anticancer activity in solid tumors.(1,10,47,48)
MECHANISM OF SYNERGY BETWEEN NANOPARTICLES AND T-CEL THERAPY Cancer immunotherapy advancements such as immune checkpoint blockade, adoptive T-cell therapy, cancer vaccines, oncolytic virotherapy, and cytokine-based treatments have opened the way for many innovative therapeutic strategies. Chemotherapeutic agents bring immune modulation through four mechanisms: inhibition of immune checkpoint expression, immunogenic cell death (ICD), enhancement of tumor killing T-cells, and reduction of immunosuppressive immune cells. These mechanisms not only improve the efficacy of CIT, but also offer opportunities to develop nanoparticle-mediated T-cell delivery drugs to augment therapy synergy.
Nanoparticle-based drug delivery systems (NDDSs) promise CIT with significant improvement changes in drug solubility, bioavailability, circulation time, oral administration, and pharmacokinetic behavior. More importantly, NDDSs can be designed for dual administration of chemotherapeutics and immunomodulatory agents, targeting precisely tumor cells and the immune microenvironment. Special structural designs like core-shell nanoparticles will also permit controlled drug release in optimal proportions to boost efficiency with T-cell modes, by allowing sustained T-cell activation and reducing tumor immune evasion.
Many NDDSs have been tested lately in bridging the gap from preclinical studies to clinical translation, although it is true that many NDDSs have failed to progress in clinical translation for one reason or the other. One of the reasons is the mismatch between tumor models employed in mice from those in humans, which has made it less reliable when predicting therapeutic outcomes. Traditional models used for preclinical studies fail to recreate the whole spectrum of immune interactions due to the complex nature of human tumor immunity. Much of current research employs subcutaneous tumor models that fail to mimic the immune dynamics seen in long-term established human tumors. Thus, genetically engineered mouse models that more accurately replicate the human disease state may represent a better platform for evaluating nanoparticle-enhanced T-cell therapies.(49)
From a commercialization and translational point of view, NDDSs need to be developed for T-cell drug delivery involving scalability, cost-effective solutions, and biocompatibility. NDDSs have been studied extensively in the scientific arena, yet most multidrug nanoparticle formulations are produced using methods that do not allow large-scale manufacturing considering the very small batch production usually resulting from high costs and equipment limitations and complexity of the process. Thus, the development of nanoparticle-delivery T-cell systems needs practical feasibility litmus to increase success rates in the application arena.
Combining treatments is critical when it comes to nanoparticle-enhanced T-cell therapy. Chemoimmunotherapy schemes generally integrate multiple agents, necessitating appropriate dose curtailments and synchronization of treatment regimens to reinforce their synergistic actions while minimizing unwanted adverse effects and resistance development. Some studies have indicated that a specific student will be able to find out the exact.(2,50)

Conclusion and Future Perspective:

Nanoparticle based T cell therapy is a game changing approach to cancer therapy, especially in solid tumors where T cell immunotherapy has major hurdles. This strategy substantially enhances T cell infiltration, persistence, and activity in the tumor microenvironment using the special abilities of nanoparticles to control the release of drugs, increase tumor targeting, and penetrate biological barriers.
Nanotechnology in conjunction with engineered T cell products, namely CAR-T and TCR-T cells, have synergistic potential solutions to challenges presented by antigen heterogeneity, immunosuppressive tumor microenvironments, and inadequate access to central nervous system (CNS) tumors. Although these nanoparticle-based platforms have shown promising preclinical efficacy, several challenges relating to scalability, cost-

effectiveness and biological compatibility need to be overcome to translate these platforms into the clinic.

The future efforts must be aimed at creation of smart, personalized, multifunctional nanoparticle-T cell platforms, along with novel preclinical models and production strategies. These breakthroughs could transform cancer immunotherapy by making it more effective and less toxic- eventually leading to more effective, convenient and personalized cancer treatment.

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