Available Online: 4 November 2026 DOI: 10.54254/3029-0821/2026.38622

Advances, challenges, and future perspectives of nanocarriers in cancer immunotherapy

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Abstract. Cancer treatment has always been an important topic in medical research. In recent years, cancer immunotherapy has received growing attention because it helps the body's immune system recognize and fight cancer cells. However, current immunotherapy still has several limitations. Some tumors respond poorly to treatment, and certain therapies can cause serious side effects. Nanocarriers are nanoscale drug delivery systems that can carry drugs used in cancer immunotherapy. This paper reviews how cancer immunotherapy works, explains its main limitations, and discusses how different types of nanocarriers may improve treatment. It also examines the challenges that prevent these technologies from being widely used in hospitals. Based on the studies reviewed, nanocarriers can protect certain drugs from breaking down too quickly and may improve drug delivery to tumor tissues. Some nanocarrier systems can also change the Tumor Microenvironment (TME), making it easier for immune cells to attack cancer cells. This may help turn some "cold tumors," which have limited immune cell activity, into "hot tumors" that respond better to immunotherapy. However, problems such as rapid nanoparticle clearance, complicated manufacturing, and uncertain long-term safety still limit their clinical use.

Keywords: nanocarriers, tumor immunotherapy, tumor microenvironment, drug delivery

1. Introduction

Cancer is one of the major threats to human health. Traditional cancer treatments mainly include surgery, chemotherapy, and radiation therapy. Although these methods have helped many patients, they still have limitations. Surgery may not remove every cancer cell, especially when cancer has spread to other parts of the body. Chemotherapy and radiation therapy can also damage healthy cells while treating tumors [1].

Cancer immunotherapy works differently from traditional treatments. Instead of only attacking cancer cells directly, it helps the body's immune system recognize and destroy them. Scientists have developed several types of immunotherapy, including cancer vaccines and immune checkpoint inhibitors. However, these treatments do not work equally well for every patient or every type of cancer.

One major challenge is drug delivery. Some immunotherapy drugs break down quickly after entering the body, while others may not reach tumors in sufficient amounts. In addition, certain treatments can affect healthy organs and cause unwanted immune reactions [2]. To address these problems, researchers have started studying nanocarriers. These are extremely small drug delivery systems that can transport therapeutic

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molecules through the body. By carrying immunotherapy drugs, nanocarriers may help protect the drugs and improve their delivery to tumor tissues.

This paper reviews the current applications of nanocarriers in cancer immunotherapy, their advantages, and the challenges that still need to be solved. The purpose of this literature review is to provide a clearer understanding of how nanotechnology may improve cancer treatment. By examining existing research, this paper also identifies important problems and possible directions for future studies.

2. Current status and limitations of cancer immunotherapy

2.1. Basic principles of cancer immunotherapy

The human immune system plays an important role in protecting the body from abnormal cells, including some cells that may become cancerous. Dendritic cells are immune cells that capture tumor antigens and present them to T cells. Tumor antigens are molecules that the immune system can recognize as targets. After receiving these signals and becoming activated, certain T cells, especially cytotoxic T cells, can recognize and destroy cancer cells [3].

However, cancer cells can develop ways to escape the immune system. For example, tumors may release substances that weaken immune responses or attract immune cells that suppress T-cell activity. These processes create an immunosuppressive Tumor Microenvironment (TME). The TME includes cancer cells, immune cells, blood vessels, and other surrounding tissues. When this environment suppresses immune activity, cancer cells can survive and continue growing [3]. Cancer immunotherapy aims to overcome these immune escape mechanisms and help the immune system attack tumors more effectively [4].

2.2. Common types of cancer immunotherapy

There are several major types of cancer immunotherapy. The first type is cancer vaccines. Therapeutic cancer vaccines introduce tumor antigens or instructions for producing these antigens into the body. Their goal is to help the immune system recognize cancer cells and develop a stronger antitumor response. The second type is Immune Checkpoint Inhibitors (ICIs). Immune checkpoints are proteins that help control immune responses and prevent excessive immune activity. However, cancer cells can use these pathways to avoid being attacked. Checkpoint inhibitors block certain inhibitory signals, such as PD-1/PD-L1 interactions, allowing T cells to attack cancer cells more effectively. The third type is immune modulators. These treatments change immune activity or the tumor microenvironment to improve the body's ability to fight cancer [1]. Another important approach is adoptive cell therapy, which uses immune cells collected from a patient or donor. These cells may be expanded or modified in a laboratory before being given to the patient. CAR T-cell therapy is one example of this approach [5].

2.3. Limitations of conventional immunotherapy

Although immunotherapy has improved cancer treatment, several challenges remain. One major problem is that some tumors respond poorly to immunotherapy. These tumors are often called "cold tumors" because they contain few active tumor-fighting T cells or have weak immune activity. As a result, treatments such as immune checkpoint inhibitors may be less effective [2]. Another problem is the risk of side effects. When immunotherapy drugs are delivered throughout the body, they can affect healthy tissues. For example, immune checkpoint inhibitors may cause the immune system to attack normal organs, leading to immune-related adverse events [1]. Drug stability is also a challenge. Some immunotherapy drugs, especially certain proteins

and nucleic acid-based treatments, can be broken down by enzymes or cleared from the bloodstream before reaching their targets. In addition, solid tumors often have dense tissue structures and high interstitial fluid pressure. These conditions can make it difficult for therapeutic drugs to move from blood vessels into deeper parts of the tumor [6]. Because of these limitations, researchers are exploring new drug delivery systems that may improve the effectiveness and safety of cancer immunotherapy.

3. Advantages of nanocarriers in cancer immunotherapy

Several types of nanocarriers have been studied for cancer treatment, including liposomes, polymeric nanoparticles, albumin-based nanocarriers, and inorganic nanoparticles [1].

One important advantage of nanocarriers is their ability to protect therapeutic molecules. Some immunotherapy drugs are unstable in the bloodstream and can be broken down before reaching their targets. Encapsulating these drugs in nanocarriers may protect them from degradation and improve their stability [2]. Nanocarriers may also improve drug delivery to tumors. Some nanoparticles can accumulate in tumor tissues through the Enhanced Permeability and Retention (EPR) effect. This effect occurs because certain tumors have abnormal blood vessels that allow nanoparticles to enter more easily, while poor lymphatic drainage may slow their removal. However, the EPR effect varies greatly between tumors and patients. Therefore, it does not guarantee that nanoparticles will successfully reach every tumor [7].

Another advantage is that nanocarriers can carry multiple therapeutic agents at the same time. For example, a nanocarrier may deliver both an immune-stimulating drug and a chemotherapy drug. This approach may allow different treatments to work together and improve antitumor activity [3]. Some nanocarriers can also help change the tumor microenvironment. By reducing immunosuppressive signals or increasing immune cell activity, they may help turn certain cold tumors into hot tumors. Hot tumors generally have more active immune responses and may respond better to some forms of immunotherapy [3]. Researchers have also developed stimuli-responsive nanocarriers. These systems are designed to release drugs under specific conditions, such as changes in pH or temperature. For example, pH-responsive nanocarriers may release their drugs more easily in the relatively acidic environment found in many tumors [8]. Together, these features make nanocarriers promising tools for improving cancer immunotherapy, although their effectiveness depends on the materials used and the characteristics of the tumor.

4. Applications of nanocarriers in cancer immunotherapy

4.1. Delivery of cancer vaccines

Cancer vaccines aim to train the immune system to recognize and attack tumor cells. However, when tumor antigens are injected directly into the body, they may be broken down or cleared before immune cells can effectively capture them. Nanocarriers may help solve this problem by protecting tumor antigens and improving their delivery to immune cells. Some nanocarriers can carry both tumor antigens and adjuvants, which are substances that strengthen immune responses. These materials can be transported to lymph nodes, where dendritic cells take up the antigens and present them to T cells. This process can improve T-cell activation and may help the immune system develop long-term memory against tumor antigens [1]. Studies in animal models have shown that certain nanovaccines can produce stronger antitumor immune responses than vaccines containing free antigens. However, these results do not necessarily mean that the same benefits will occur in humans [1]. Albumin-based nanocarriers are one example of this approach. Albumin is a protein

naturally found in blood. Some albumin-based delivery systems can take advantage of lymphatic transport pathways to improve the delivery of vaccine components to lymph nodes [1].

4.2. Delivery of immune checkpoint inhibitors

Immune checkpoint inhibitors help T cells attack cancer cells by blocking signals that normally reduce immune activity. However, these drugs may cause side effects when they affect immune responses throughout the body. Researchers are studying nanocarriers as a way to improve the delivery of checkpoint inhibitors to tumor tissues. For example, liposomes and polymeric nanoparticles can be designed to carry or release certain checkpoint-blocking agents near tumors. This approach may increase local drug exposure while reducing unnecessary exposure in healthy tissues [2]. Nanocarrier-based checkpoint inhibition can also be combined with other treatments, such as chemotherapy or photothermal therapy. Photothermal therapy uses materials that absorb light and convert it into heat. Under controlled conditions, this heat can damage tumor cells and may support additional immune responses. Combining these approaches may improve treatment outcomes, although more clinical research is needed to confirm their safety and effectiveness [2]. Liposomes are among the most established nanocarrier systems in drug delivery. Their structure makes them useful for carrying different types of therapeutic molecules, including some agents being investigated for cancer immunotherapy [1].

4.3. Delivery of tumor microenvironment modulators

The tumor microenvironment can strongly affect how well cancer immunotherapy works. In many tumors, immune cells are present but cannot function effectively because the surrounding environment suppresses their activity. Nanocarriers can be used to deliver drugs that change this environment and support stronger antitumor immune responses [3]. For example, some inorganic nanoparticles, including gold nanoparticles, can carry therapeutic drugs and also produce heat when exposed to specific wavelengths of light. This process is known as the photothermal effect. The heat generated by these nanoparticles can damage tumor cells. In some cases, the resulting cell damage may release tumor antigens and danger signals that help activate immune responses [3]. Other nanocarrier systems are designed to reduce the activity of immunosuppressive cells. Two important examples are regulatory T cells (Tregs) and M2-like Tumor-Associated Macrophages (TAMs). Regulatory T cells normally help prevent excessive immune responses, but they can also suppress antitumor immunity. M2-like macrophages may support tumor growth and reduce immune activity in certain tumor environments. By changing the activity of these cells, some nanocarrier-based treatments may help create a tumor microenvironment that supports stronger immune responses [3].

5. Current challenges

Although nanocarriers have shown promising results in laboratory and animal studies, several problems still limit their clinical applications. One major challenge is how nanoparticles behave after entering the human body. Nanoparticles may be recognized by the immune system and removed before reaching tumors. Many are taken up by cells in the liver and spleen, which are involved in filtering and clearing foreign materials from the bloodstream [1]. As a result, only a small portion of the administered nanoparticles may reach the intended tumor site.

Another problem is tumor heterogeneity, which means that tumors can differ in their biological characteristics. For example, tumors may have different blood vessel structures, tissue densities, and immune environments. These differences can affect how well nanoparticles enter and accumulate in tumor tissues [1].

The EPR effect is also highly variable. Although it has been observed in many animal tumor models, its effectiveness in human tumors is less consistent. This makes passive nanoparticle targeting difficult to predict [7].

Manufacturing is another important challenge. Some multifunctional nanocarriers require several complicated preparation steps. Producing these materials on a large scale while maintaining consistent particle size, drug loading, and product quality can be difficult. These requirements may increase manufacturing costs and slow the development of clinical products [2].

Long-term safety is also a concern. Certain inorganic nanoparticles may remain in the body for extended periods, depending on their composition, size, and surface properties. Researchers still need to better understand how these materials are broken down, removed, or stored in different organs. Their possible long-term toxicity must also be carefully evaluated [3].

Finally, many studies showing strong treatment effects have been performed in mice. However, mouse tumors and human tumors differ in several important ways, including their immune systems, blood vessel structures, and biological complexity. Because of these differences, treatments that work well in mice may not produce the same results in human patients [1]. More clinical studies are needed to determine which nanocarrier systems are safe and effective enough for regular medical use.

6. Conclusion

Nanocarriers have the potential to improve cancer immunotherapy by addressing several problems found in conventional drug delivery. Different types of nanocarriers, including liposomes, polymeric nanoparticles, albumin-based systems, and inorganic nanoparticles, offer different advantages. They may protect therapeutic drugs from degradation, improve drug delivery, and allow multiple treatments to be combined in one system. Some nanocarriers may also help change the tumor microenvironment and increase antitumor immune activity. However, important challenges remain. These include rapid clearance from the body, differences between patients, complicated manufacturing processes, and uncertain long-term safety. This paper mainly reviews existing studies and does not provide a detailed comparison of large clinical trials or the performance of different nanocarrier materials. In future research, scientists should focus on developing nanocarriers that are safer, biodegradable, and easier to produce. Personalized nanovaccines may also become an important direction. By designing treatments based on the characteristics of individual tumors, researchers may be able to improve immune responses in different patients. Another possible direction is combining nanocarrier-based immunotherapy with treatments such as radiation therapy and photothermal therapy. However, more human clinical trials are necessary to determine whether these approaches can provide meaningful benefits to patients. Overall, nanocarriers offer promising opportunities for cancer immunotherapy, but further research is needed before many of these technologies can be widely used in clinical practice.

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