Combined nanotechnology with monoclonal antibody drugs for cancer immunotherapy

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Abstract. Cancer, a genetic disease characterized by uncontrolled cell growth and spread, remains a major global health challenge, with its complexity lying in the myriad ways it can manifest and resist treatment. It is marked by the accumulation of mutations that lead to genomic instability, contributing to its lethality and the difficulty in treatment. Epidemiologically, cancer constitutes a significant burden worldwide, being a leading cause of death. The International Agency for Research on Cancer projects a relentless increase in cancer incidence and mortality, underscoring the urgent need for more effective treatment modalities. Among the therapeutic strategies, immunotherapy, especially monoclonal antibodies (mAbs), has emerged as a revolutionary approach, exploiting the immune system's inherent ability to combat cancer. This review also elucidates the mechanisms through which mAbs target cancer cells. The core of the article highlights the innovative merger of mAbs with nanotechnology, showcasing how this combination aims to surmount the limitations of current therapies by improving drug delivery, reducing side effects, and enhancing treatment efficacy. By leveraging nanocarriers like gold and albumin nanoparticles, this integrated approach holds promise for more personalized, effective, and safer cancer treatments, marking a significant stride towards better patient outcomes in the ongoing battle against cancer. This review article provides an exploration into the evolving landscape of cancer treatment, focusing on the advancements in monoclonal antibody (mAb) therapies and their synergistic integration with nanotechnology.

Keywords: Cancer; monoclonal antibody; nanotechnology.

1. Introduction

Cancer is a genomic disease in which genome instability leads to the accumulation of mutation points, ultimately leading to structural alterations. It is assumed that the structure of somatic tissue can inhibit the rate of somatic cell evolution, and the evolution-limiting tissue structure of cancer cells is broken down, which leads to the rapid generation and unrestricted growth of abnormal cells [1]. After heart disease, cancer ranks as the leading cause of death globally among adults and children, with the International Agency for Research on Cancer (IARC) showing about 20 million new cases and 9.7 million fatalities in 2022 [2]. Worldwide, about one in five people has had or currently suffers from cancer [2]. In the past decade, as the world's population has continued to increase, the number of cancer cases has also increased significantly, and with the outbreak of COVID-19, cancer mortality has also been affected and increased [3]. Cancer has always been a major health problem worldwide.

Treatment methods vary for different types of cancer. For cancers that are localized and have not spread, surgery and radiation therapy are effective. However, their effectiveness diminishes when cancer metastasizes, making systemic treatments like chemotherapy, hormonal therapies, and biological therapies the preferable options for advanced stages. Immunotherapy, as a targeted biological therapy, is a pillar strategy in cancer treatment. Unlike other drug treatments that directly kill cancer cells, immunotherapy utilizes drugs that act on the immune system to activate or promote the body's immune response and kill tumor cells through natural mechanisms [4]. This artificially promoted immune response is specific, which means that it can specifically target non-self antigens. Based on this principle, different types of immunotherapies have been developed, and some have entered the clinical stage or been used. The key types of immunotherapy encompass cytokines, cancer vaccines, monoclonal antibodies (MABs), checkpoint inhibitors, and CAR T-cell therapy, etc. [5].

The advent of cancer immunotherapy has marked a new era in the fight against cancer, and in this revolution, monoclonal antibodies (mAbs) playing an important role. The landscape of cancer

treatment was revolutionized with the approval of the first monoclonal antibody by the US FDA in 1986, which has since been approved for cancer treatments. The integration of nanotechnology with monoclonal antibody-based therapies is one of the latest advancements in cancer treatment. Conjugating nanoparticles with monoclonal antibodies forms targeted drug delivery systems that enhance the effectiveness and reduce the toxicity of cancer treatments by directly targeting tumor cells and sparing healthy ones [6].

This review elucidates the intricacies of monoclonal antibody therapy and focuses on the mechanisms by which these antibodies exert their effects against cancer cells. The innovative integration of nanotechnology with monoclonal antibody drugs is explored, addressing the challenges and limitations currently faced in monoclonal antibody therapies. This review aims to summarize the state-of-the-art in monoclonal antibody treatments and nanotechnology applications, shedding light on future directions that could surmount existing limitations.

2. The mechanism of monoclonal antibodies

The direct mechanism by which mAbs induce tumor cell apoptosis is by blocking growth factor receptors, inhibiting signaling pathways that are essential for tumor growth and survival. Immune checkpoints are regulatory pathways in the immune system that either stimulate or inhibit its responses [7]. Certain cancer cells exploit these checkpoints to protect themselves from the immune system. MAbs can block these immune checkpoints competitively, preventing cancer cells from using them to evade the immune system [7]. For example, pembrolizumab (Keytruda) binds to the PD-1 receptor on T cells, blocking its interaction with PD-L1 on tumor cells, thus enhancing the immune response against cancer [8].

The indirect actions of mAbs involve the recruitment and activation of various components of the host's immune system: NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC), macrophage-mediated antibody-dependent cellular phagocytosis (ADCP), and activation of the complement-dependent cytotoxicity (CDC) [7]. For example:

ADCC: Rituximab (Rituxan) targets CD20 on B cells, leading to natural killer (NK) cell recruitment and subsequent destruction of these B cells in conditions like non-Hodgkin lymphoma [9].

ADCP: Trastuzumab (Herceptin) binds to HER2 on breast cancer cells, flagging them for destruction through phagocytosis by macrophages [10].

CDC: Alemtuzumab (Campath) targets CD52 on lymphocytes, activating the complement system which leads to cell lysis and depletion of these cells, used in the treatment of chronic lymphocytic leukemia [11].

3. Combined nanotechnology with monoclonal antibody drugs

Despite there are significant therapeutic benefits of mAbs, there are efficiency and safety concerns associated with their use. The variability in response rates among different patient populations often limits the effectiveness of monoclonal antibodies (mAbs), complicating the prediction of patient outcomes [12]. Furthermore, it is hard for mAbs to effectively deliver to solid tumors, as the dense microenvironments of these tumors are complicated, which may impede the antibodies reach and act upon their intended targets [12].

Safety concerns also play a critical role in the limitations of mAbs. There are potential adverse reactions of mAbs, such as the potential for autoimmune side effects, where the body's immune system attacks its own tissues, which lead to cytokine release syndrome and vascular leak syndrome [13]. These adverse effects, ranging from severe hypotension and fever to renal dysfunction, which means it is important to develop delivery mechanisms that can mitigate these risks [13].

This has led to an increased emphasis on developing novel delivery technologies to overcome these limitations. Innovations in delivery technologies, including nanoparticles, scaffolds, and cell-

based platforms, could improve the precision and safety of immunotherapies, enhancing the targeting of tumor and immune cells while minimizing unintended effects [14]. Nanotechnology is revolutionizing the medical field, particularly in the domain of drug delivery and therapeutic applications. Its unique advantage lies in the ability to engineer materials at the molecular level, enabling the creation of nanocarriers that can navigate the body's complex environments to deliver drugs more efficiently and with fewer side effects. In medical applications, nanotechnology offers the potential to bypass biological barriers, target specific cells or tissues, and release therapeutic agents in a controlled manner [15]. This precision not only enhances the effectiveness of treatments but also significantly reduces the risk of adverse effects. Additionally, the significant drug-loading capacity of nanoparticles due to their high surface area to volume ratio boosts the therapeutic index of drugs. These capabilities make nanotechnology play a pivotal role in advancing personalized medicine by allowing treatments to be specifically designed according to a patient's genetic profile, thus enhancing treatment safety and effectiveness [16].

Currently, the development and application of various nanocarriers have emerged as a promising strategy. For instance, gold nanoparticles (GNPs) have demonstrated significant potential in the realm of cancer therapy due to their unique physicochemical properties. These properties allow GNPs to act as efficient drug delivery systems, angiogenesis modulators, or heat-activated therapeutic agents, providing a promising avenue for developing targeted and less toxic cancer treatments [17]. Despite the promise, challenges such as synthesis variability, potential for aggregation, and visualization difficulties highlight the need for further research to fully harness GNPs' therapeutic potential [18].

Albumin nanoparticles are another innovative nanotechnology in medicine. Albumin, a natural protein, is an excellent material for creating drug carriers, thanks to its biodegradability, biocompatibility, non-toxicity, and minimal immunogenicity. These nanoparticles can bind a wide range of drugs, offering a versatile platform for medication delivery [19]. The production of nanoparticles involves techniques like nano-spray drying, desolation, emulsification, thermal gelation, and self-assembly, resulting in particles with specific sizes, surface charges, and shapes. Their applications extend to both diagnostic and therapeutic uses [20].

Similarly, dendrimers and nanogels represent two other types of nanocarriers with distinct advantages. Dendrimers, with their highly branched, tree-like structures, provide a high degree of control over size and shape, enabling precise drug encapsulation and release[21]. Nanogels, hydrogel particles at the nanoscale, offer responsive release mechanisms that can be triggered by environmental stimuli, ensuring drugs are released at the right time and place in the body[22]. These features make dendrimers and nanogels especially useful for delivering therapeutic agents with high precision and minimal side effects. Table 1 categorizes and discusses these carriers in a structured manner.

Table 1. Nanocarriers for drug delivery related to antibody drugs

Nanocarrier	Advantages	Own Drug Effects	Examples
Gold Nanoparticles (GNPs)	High biocompatibility, versatility in size and shape, modifiable optical properties, high drug loading capacity, non-cytotoxic, accumulate in cancerous tissues [18]	Enhance radiation therapy effects, anti-angiogenic effects, promote osteogenesis, inhibit osteoclast production, reduce inflammation [18]	The conjugation of gold nanospheres with Rituximab demonstrates the potential to enhance the complement-dependent cytotoxicity of anti-CD20 monoclonal antibody-based drugs [23]
Albumin Nanoparticles	High stability, increased permeability at inflammation sites, natural biodegradation, no toxic effect, active targeting via SPARC overexpression [19]	Prolong drug action, improve pharmacokinetic properties and efficacy [19]	Fusion of HSA with IL-1Ra, showing extended joint accumulation, excellent targeting, and significant therapeutic effects in Rheumatoid arthritis [20]
Dendrimers	Uniformity, high biocompatibility, and a well-defined structure that improve cellular uptake and facilitate covalent attachment to target molecules [21]	Anti-inflammatory activity, enables controlled and continuous drug delivery [21]	Polyamidoamine dendrimers (PAMAM) modified with chondroitin sulfate and anti-TNF α antibodies for targeted delivery to cartilage [21]
Nanogels	Responsive to environmental stimuli, high stability, good biocompatibility, high loading capacity, controllable release [22]	Penetrating the skin and migrating to the epidermis, offers anti-inflammatory benefits without inducing immunogenic or toxic effects [22]	Agarose-curdlan based nanogel for etanercept, enhancing permeability and retention at inflammatory sites, improved biological half-life [22]

4. Conclusion

The integration of nanotechnology with mAbs drugs represents a pivotal advancement in the field of cancer therapy, aiming to surmount the limitations of traditional mAbs treatments by enhancing their delivery, efficacy, and safety. Nanocarriers, such as gold nanoparticles and albumin nanoparticles, have emerged as promising tools, offering targeted delivery to tumors, reduced systemic toxicity, and the potential for personalized treatment approaches. Optimizing these nanocarrier systems requires further research to address challenges like variability in synthesis, potential aggregation, and ensuring precise targeting and stimuli-responsive release mechanisms. As such, the future of mAbs therapy lies in the continuous development of nanotechnology applications, tailored to overcome the complex barriers presented by solid tumors and individual patient variability, ultimately leading to more effective and safer cancer treatments.

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