Multifunctional Antibody-drug-nanoparticle Conjugates for precision Cancer Therapy

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Abstract

Cancer medicine has stepped into the era of multidisciplinary treatments, calling for synergistic therapeutic regimens. Single therapeutic strategies, including chemotherapy, radiotherapy, surgical treatment, targeted therapy, and immunotherapy, are no longer sufficient to support cancer treatment. Various therapeutic systems based on Antibody-drug-nanoparticle conjugates (ADNCs) have been developed as promising strategies for more effective cancer therapy. The rapid advances in nanotechnology, molecular biology, pharmacy and immunology have driven the innovative development of actively targeted nanoparticles for safer and more effective precision cancer therapy. With excellent targeting capability, ADNCs can act as efficient drug carriers and tumor microenvironment (TME) regulators. In this review, we focus on the classification, structure, and applications of monoclonal antibodies (mAbs), as well as the conjugation between antibodies and nanocarriers. Meanwhile, we systematically summarize the latest progress in nanoparticles (NPs) as mainstream drug delivery systems, such as liposomes, nanoemulsions, dendrimers, carbon-based NPs, polymeric NPs, and metallic NPs. Furthermore, we discuss the design and optimization of ADNCs. Despite the tremendous potential of ADNCs, we also admit their shortcomings and challenges associated with their implementation and the clinical applications. This review aims to propose a novel and synergistic perspective of ADNCs in precision and personalized cancer treatment, offering patient-specific therapeutic alternatives for clinical practice.

Keywords

Cancer, Nanoparticle, Antibody, Targeted therapy, Drug delivery

Introduction

Cancer-related deaths currently dominate global disease-related deaths, including lung cancer (18.7%), colorectal cancer (9.3%), liver cancer (7.8%), female breast cancer (6.9%), and stomach cancer (6.8%) [1]. Faced with such a significant challenge, monotherapies including surgery, radiotherapy, and chemotherapy are often insufficient for effective tumor control. This is primarily attributed to tumor heterogeneity, an immunosuppressive tumor microenvironment (TME), inherent or acquired drug resistance, distant micrometastases, and dose-limiting toxicities. Cancer medicine has now entered a paradigm shift toward multidisciplinary and personalized comprehensive treatment, which underscores the urgent requirement for innovative and synergistic therapeutic strategies.

Nanomedicine, the application of nanotechnology in healthcare, originated in the 1960s and has been greatly expanded with the practical development of nanotechnology during the past few decades [2]. Nanomedicine integrates a wide array of disciplines, including medicinal chemistry, pharmacology, pharmacokinetics, pharmacodynamics, immunology, biomaterials science and nanotechnology, offering a revolutionary perspective for advancing traditional medicine. Nanocarriers have unique physical, chemical and biological properties, such as high surface area, adjustable optical and magnetic properties, and biocompatibility, which make them show great potential in drug delivery, imaging, and treatment. A significant advance with the synthesis of novel nanomaterials,

including liposomes, nanoemulsions, dendrimers, carbon-based NPs, polymeric NPs, and metallic NPs, make it possible to manipulate materials at the nanoscale, laying the groundwork for nanomedicine [3]. By regulating the size, morphology and surface functionalization of bionanomaterials, it is promising to meet specific application requirements.

Generally, following the rapid and uncontrolled growth of solid tumors, the deficient tumor lymphatic system and the permeable tumor vasculature, which is characterized by discontinuous epithelium as well as defective basement membrane, allow nanoparticles (NPs) to flow through the cell-connecting pores and accumulate in tumor tissue. This phenomenon is called the enhanced permeability and retention (EPR) effect, facilitating nanocarrier penetration and aggregation to achieve passive targeting [4,5]. However, EPR effect is highly heterogeneous. One of the most obvious major challenges in solid tumors is attributed to the poor vascularization, interstitial fibrosis, dense ECM and high interstitial fluid pressure, which make EPR effect-based passive targeting not efficient enough to meet the demands of treatments. Therefore, active targeting strategies have been proposed to achieve highly efficient and precise targeted therapy.

Antibodies and their derivatives are the most well-known and effective ligands for receptor-mediated targeted drug delivery systems in the past few decades. Over more than a century of exploration, the development of monoclonal antibodies (mAbs) has brought significant breakthroughs for precise cancer therapy, distinguished by exceptional specificity, prolonged serum half-life, strong affinity, and immune effector capabilities [6]. Since the approval of muromonab as the first monoclonal antibody (mAb) in 1986, more than 200 mAbs have been approved by 2024 [7]. This advancement laid the foundation for systemic therapies based on mAbs. Antibody-drug conjugates (ADCs), composed of mAbs conjugated with cytotoxic drugs, represent a promising therapeutic strategy in the field of oncology and biopharmaceuticals. However, the development and clinical application of ADCs still face numerous challenges, including the instability of antibody-drug linkages, the uncontrollable release of cytotoxic drugs, and the gradual emergence of adverse effects and drug resistance. Antibody-drug-nanoparticle conjugates (ADNCs) refers to emerging conjugates ushered by synthetic biochemistry, merging the precise targeting capability of mAbs, the multifunctionality of NPs, and cytotoxicity of payloads. By virtue of the diversity of functionalized NPs, targeted drug delivery can be integrated with stimuli-responsive drug release, chemotherapy, immunotherapy, photothermal therapy (PTT), chemodynamic therapy (CDT), photodynamic therapy (PDT), sonodynamic therapy (SDT) and some other treatment strategies, remarkably enhancing antitumor efficacy and overcome drug resistance.

In this review, we elaborate on the classification, structure, and applications of monoclonal antibodies, as well as the conjugation between antibodies and nanocarriers. Meanwhile, we highlight the recent advances and applications in mainstream nanocarriers, including liposomes, nanoemulsions, carbon-based NPs, polymeric NPs, and metallic NPs. Furthermore, we discuss the design and optimization of ADNCs. Nevertheless, we also acknowledge the limitations and challenges related to their clinical application and translational prospects. This review provides novel insights into personalized cancer therapy from the perspectives of precision medicine and synergistic therapeutic strategies. These insights will strongly facilitate the development of global oncology and substantially contribute to human health science.

Antibody-mediated active targeting

ADNCs not only can passively extravasate into tumor tissues by virtue of the EPR effect, but also exhibit efficient internalization by targeted cancer cells through active targeting recognition. Active targeting ADNCs can be prepared by surface modification of mAbs to recognize specific to tumor-related receptors, which further promotes exclusive endocytosis and uptake. In 1907, the biologist Paul Ehrlich proposed the concept of the “magic bullet”, envisioning an ideal therapy capable of precisely targeting diseased cells without affecting healthy ones [8]. In 1975, Kohler and Milstein discovered hybridoma technology, which enabled the production of mAbs with superior homogeneity and target specificity [9]. Encouragingly, phase I clinical trials of ADCs in oncology were firstly initiated in the 1990s [10]. It was not until 2000 that Gemtuzumab ozogamicin (Mylotarg®), a CD33-targeted ADC, became the first ADC approved by the United States

Food and Drug Administration (U.S. FDA) for the treatment of relapsed and refractory acute myeloid leukemia [11]. Nevertheless, it was withdrawn from the market in 2010 due to adverse events that outweighed its therapeutic benefits. Since then, the unremitting efforts of scientists and rapid advances in antibody engineering have led to the successful development of therapeutic ADCs. Nine ADCs have been approved by the U.S. FDA, seven of which are indicated for the treatment of solid tumors, including lung cancer, breast cancer, gastric cancer, esophageal cancer and ovarian cancer [12]. These ADCs are characterized by long serum half-life, exquisite specificity, excellent tumor affinity and immune effector functions. All these properties further cement the critical role of ADNCs based on mAbs as the cornerstone of targeted cancer therapy.

Structure of antibody

Antibody-relevant targeting agents can be devided into three groups, including monoclonal antibodies (mAbs), antibody fragments, and bispecific antibodies [13]. MAbs are glycoproteins produced by plasma cells that can specifically bind to corresponding antigens. Among the five distinct immunoglobulin isotypes in humans, Immunoglobulin G (IgG) accounting for 80% of them and constitutes the predominant type exploited in the development of therapeutic antibodies [14]. Structurally, the human IgG molecule is a glycoprotein with an approximate molecular weight of 150 kDa, adopting a characteristic "Y"-shaped configuration and being composed of two identical heavy (H) chains and two identical light (L) chains (Figure 1). Each H-chain is composed of four immunoglobulin domains, including one variable domain (VH) as well as three constant domains (CH1, CH2 and CH3).

Conversely, each L-chain consists of two immunoglobulin domains, including one variable domain (VL) and one constant domain (CL), and associates with the corresponding H-chain through disulfide bonding between the CL and CH1 domains [15]. Functionally, the immunoglobulin domain can be broken down into discrete functional antibody fragments, including two F(ab) arms that can achieve specific antigen binding, and an Fc fragment, which can promote immune effector functions and facilitate subcellular transport and affecting the half-life in blood circulation. Notably, these regions are critical for maintaining structural integrity, modulating receptor interactions, and optimizing a wide variety of effector functions and the overall therapeutic performance of antibody molecules.

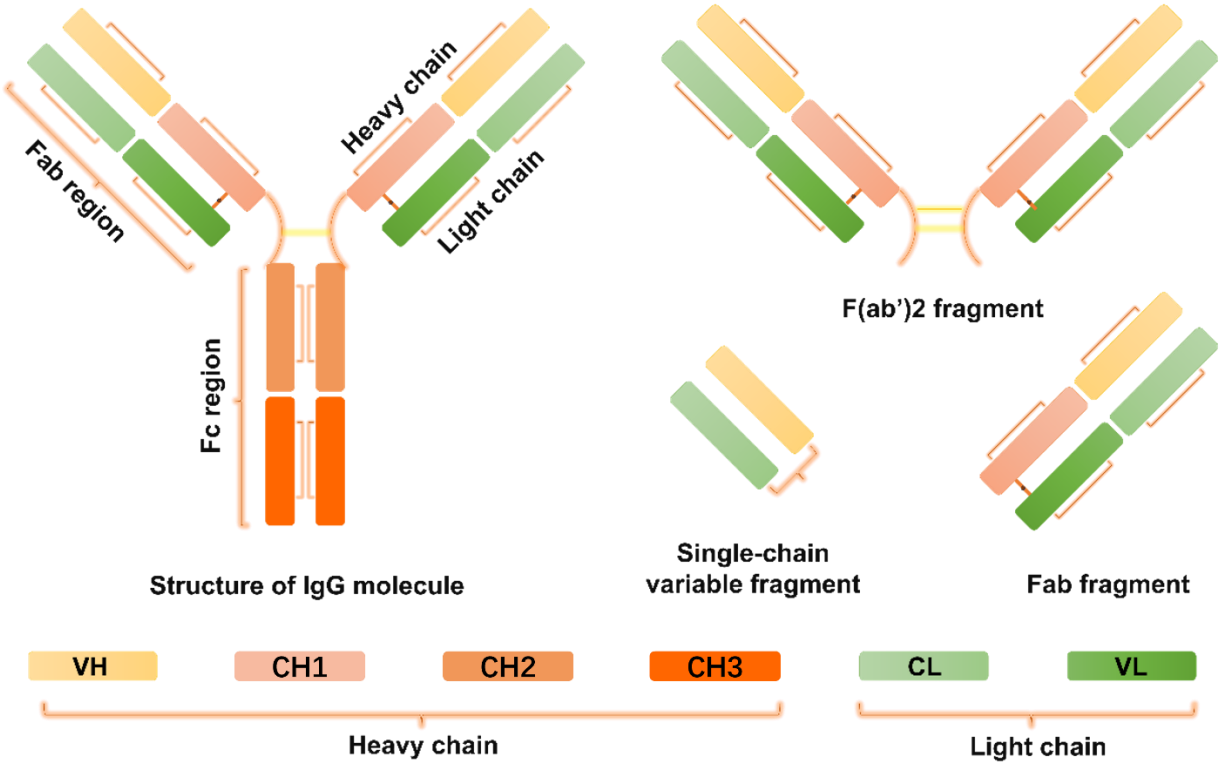

Figure 1. Structure of IgG molecule and its fragments. The IgG structure consists of two heavy chains (VH, CH1, CH2 and CH3) and two light chains (CL and VL). The Fab region includes VL, CL, VH and CH1. The Fc region

includes CH2 and CH3.

Antibody-based targeting

The targeting capacity of antibodies enables ADNCs to achieve precise drug delivery, induce target cell apoptosis, enhance antitumor efficacy, and reduce systemic toxicity. Tumor cell-targeting is the primary application of antibodies-mediated targeted therapy. In recent years, strategies aimed at modulating the TME have attracted considerable attention in the field of cancer immunotherapy, as the TME is closely associated with tumor growth, invasion, metastasis, and therapeutic resistance [16]. Rationally designed ADNCs can efficiently penetrate the TME and enable targeted delivery to its major components. These include dendritic cells, tumor-associated macrophages, cancer-associated fibroblasts, tumor-draining lymph nodes, structurally abnormal tumor vasculature, and hypoxic regions arising from the high metabolic activity of cancer cells [17]. In addition to direct antigen blockade, mAbs leverage the crystallizable fragment (Fc) domains to include antibody-dependent cellular cytotoxicity that driven by natural killer (NK) cell, antibody-dependent cellular phagocytosis mediated by macrophages, and complement-dependent cytotoxicity motivated by membrane attack complex formation [18-20].

Furthermore, antibodies specifically targeting epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) can induce receptor conformational changes, facilitate receptor internalization and downregulation, and disrupt key downstream signaling pathways, thereby effectively suppressing tumor growth [21]. Some ADNCs exhibit a significant bystander effect, which is likely attributed to the passive diffusion of cytotoxic payloads into surrounding neighboring cells [22]. This bystander activity is particularly critical for overcoming the limitations of conventional antibody-based therapies that act only on antigen-positive cells. When the target antigen is heterogeneously expressed within tumor tissues or when a subset of tumor cells develops drug resistance, ADNCs possessing a bystander effect exhibit unique therapeutic advantages. They can not only directly act on target cells but also indirectly eradicate adjacent cells that are not bound by the antibody, including tumor cells lacking target antigen expression, as well as surrounding stromal cells and certain resistant cell populations.

Conjugation of mAb to nanocarriers

Active targeting ADNCs can be prepared by surface-modification with specific ligands to the receptors over-expressed on tumor cells. The conjugation of antibodies to nanoplatform primarily involves two strategies, including noncovalent binding and covalent cross-linking [23].

Noncovalent binding of antibodies onto the NPs is the simplest approaches to prepare ADNCs, including electrostatic interactions, hydrophobic associations, and specialized interactions. Through non-covalent interactions, monoclonal antibodies can be immobilized on the NPs surface such as thermal-induced unfolding, modulation of pH, application of reducing agents and chemical denaturation [24]. However, this strategy often suffers from low efficiency and poor physical stability. In contrast the covalent bonds are more resistant to degradation, provide stronger binding forces, and enable more controlled antibody orientation on the nanoparticle surface [25]. Covalent conjugation can be achieved via biotin-neutravidin coupling strategy, thiol chemistry, carbon diimide method and bio-click chemistry [26-29].

ADNCs-based therapeutic systems and applications

In cancer nanomedicine, NPs can be used for molecular imaging, drug delivery, and TME regulation. Biological nanomaterials are significantly different from traditional chemotherapeutic drugs for various characteristics, including the size, shape, mechanical properties, surface crosslinking, hydrophilicity, and degradation rate in physiological environments. Typical bionanomaterials have advantages that warrant thorough investigation, such as high surface-to-volume ratio, enhanced conductivity, excellent drug encapsulation capability, outstanding EPR effects at the tumor sites, and unique stimulus responsiveness [30].

Generally, a desirable nanocarrier maintains the stability of ADNCs during systemic circulation, enables efficient intracellular release of cytotoxic drugs in target cells, minimizes systemic toxicity, and reduces both administration frequency and dosage. Several nanomaterials have been well developed as nanocarriers and involved in clinical use for cancer research (Figure 2). NPs-based therapeutic systems, such as liposomes, nanoemulsions, dendrimers, graphene, and metallic NPs,

have attracted substantial attentions in cancer nanomedicine due to the enhanced drug delivery capability, controlled release profiles, excellent biocompatibility.

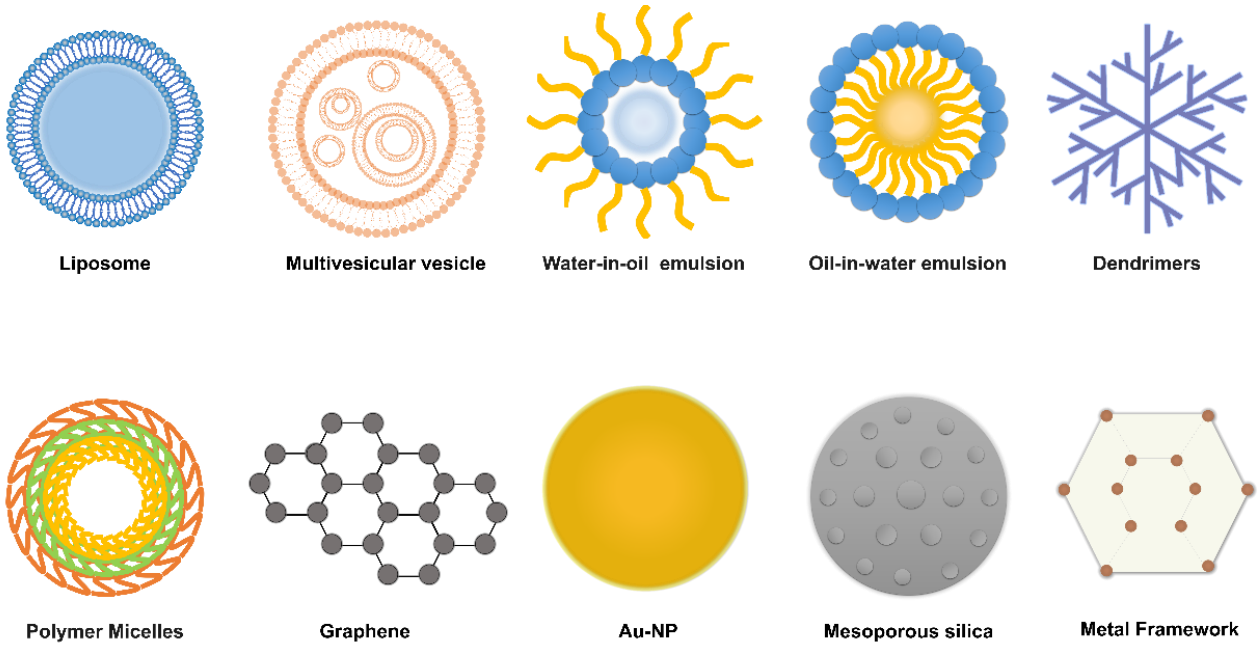

Figure 2. Nanocarriers include liposome, multivesicular vesicle, water-in oil emulsion, oil-in -water emulsion, dendrimers, polymer micelles, graphene, Au nanoparticle, mesoporous silica, and other metal framework.

Lipid NPs

Lipid-based nanomaterials are the most widely utilized class of nanomedicines approved by FDA, owing to the remarkable effectiveness and safety as drug delivery systems [31]. Liposome is a spherical spatial structure composed of aqueous phase area in the middle as the core and a phospholipid bilayer structure similar to biological membrane, which makes them have good biocompatibility in the body and can effectively reduce immune rejection and toxicity [32]. Each phospholipid molecule that makes up the vesicle membrane have hydrophobic tail and hydrophilic heads. Therefore, liposomes can be utilized to load hydrophobic and hydrophilic drugs, and are widely used in drug delivery, gene delivery, vaccine development and other fields [33]. Due to the good biocompatibility, biodegradability, drug encapsulation ability, targeted drug delivery, sustained release function, and enhanced drug bioavailability, liposomes have been successfully applied as nanocarriers [34,35]. Dae-Hyuk Kweon and colleagues developed antibody-functionalized ADNCs for targeted cancer therapy by fusing HER2-targeting antibody trastuzumab with apolipoprotein A1 to create “Grab Antibody (GrAb)”, and subsequently anchoring the fusion construct onto liposomal nanoparticles [36]. Benefiting from the targeting capability of GrAb, GrAb-lipid NPs achieved a 5.9-fold higher accumulation in tumors than the non-targeted group, accompanied by improved mRNA delivery efficiency and potent antitumor activity. In addition, the phospholipid material of liposomes can be naturally degraded in the body and eventually decomposed into small molecules such as single molecules or diacylglycerols, which can be further metabolized and utilized by the body or excreted from the body, reducing the long-term retention problem of drug carriers and not easily causing inflammation or adverse reactions [37].

Nanoemulsions

Nanoemulsions are usually made of aqueous phase, emulsifying agents as well as oil Nanoemulsions, and generally divided into three types, including water in oil emulsions, oil in water emulsions and bi-continuous emulsions [38]. Nanoemulsions are characterized by large surface area, ideal superficial charge, excellent drug loading capacity, and elevated half-life during circulation [39]. For example, a novel system based on nanoemulsions was successfully fabricated by co-encapsulating both baicalein and paclitaxel, thereby providing an effective strategy for overcoming MDR in breast cancer [40]. In this study, the synergistic baicalein-paclitaxel nanoemulsions exhibited higher sensitivity and superior antitumor efficacy than monochemotherapy

of paclitaxel. Andrey S. Klymchenko and colleagues successfully synthesized biotinylated nanoemulsions carrying biotinylated trastuzumab using biotin-neutravidin coupling systems. Compared with trastuzumab alone, this nanoplatform exhibited enhanced and selective targeting toward HER2-amplified breast cancer cell models, indicating that conjugation of trastuzumab with the nanoemulsion significantly improved both targeting capability and cytotoxic efficacy. In another study, multifunctional nanoemulsion (NSNEDOX-αHER2 IgG) co-loaded with αHER2LPETG IgG and the chemotherapeutic drug doxorubicin (DOX) was developed. Compared with free DOX, NSNEDOX-αHER2 IgG demonstrated outstanding targeting ability and significantly reduced cancer cell viability.

Dendrimers

Dendrimers are nanomaterials with highly branched structures and easily modifiable surfaces. Structurally, dendrimers comprise three key components: a central core, repetitive branching units (dendrons) and an external surface equipped with functional groups [41]. Dendrimers exhibit unique advantages due to their specialized structure, including well-defined molecular weights, tunable branching, a narrow polydispersity index, high solubility and bioavailability for hydrophobic drugs, and potential imaging capacity [42]. Several types of dendrimers have been developed for cancer therapy, such as poly (amidoamine) dendrimers (PAMAM), tacto-dendrimers, hybrid dendrimers, peptide dendrimers, and glico-dendrimers. Dendrimers possess ample steric space both at the core and between the branches, demonstrating excellent drug encapsulation capacity and controlled drug release.

To overcome clinical trastuzumab resistance in breast cancer, the group of Fadilah Sfouq Aleanizy developed PAMAM dendrimers co-loaded with trastuzumab and neratinib [43]. Compared with unmodified neratinib dendrimers, trastuzumab-functionalized neratinib dendrimers demonstrated significantly higher cellular uptake, achieving synergistic antitumor effects and mitigating therapeutic resistance. In addition to drug delivery, dendrimers can also be used for tumor bioimaging. Jessica Hersh and coworkers successfully engineered a nanosystem composed of a G5-polyamidoamine dendrimer as the nanocarrier, an EGFR-binding affibody for tumor targeting, and Gaussia luciferase serving as a bioluminescent reporter to enable bioluminescence imaging of pancreatic ductal adenocarcinoma (PDAC) [44]. This nanosystem enabled visualization of tumor morphology and metastatic dissemination, thereby facilitating the monitoring of tumor progression and the evaluation of therapeutic responses.

Carbon-based NPs

Carbon-based NPs represent a class of nanomaterials in which carbon serves as the primary structural framework. Based on their structural characteristics and physicochemical properties, they can be broadly categorized into several types, including fullerenes, graphene, graphene quantum dots, graphene oxide (GO), and reduced graphene oxide (rGO) [45]. Due to the remarkable electrochemical and mechanical properties, carbon-based nanocomposites have emerged as multifunctional nanoplatforms [46]. For example, Liang Luo and colleagues integrated sorafenib-loaded GO with a hydrogel encapsulating anti-CD47 antibodies (aCD47) [47]. This system effectively activated tumor-associated macrophages, locally reprogrammed the immune-suppressive TME, and successfully blocked the CD47-mediated immune escape, ultimately inhibiting tumor recurrence and metastasis. Fullerenes are a class of molecules composed of carbon allotropes in the forms of hollow spheres, ellipsoids, and nanotubes. Compared with other nanomaterials, the photothermal responsiveness of fullerenes enables them to exhibit excellent reactive oxygen species (ROS) generation efficiency and heat production capability in PTT and PDT [48,49]. Carbon nanotubes (CNTs) are generally regarded as the member of fullerene family, which are classified into single-walled carbon nanotubes and multi-walled carbon nanotubes [50]. For instance, Yu Sun and colleagues developed anti-CD44 antibody-functionalized magnetic CNTs for the treatment of chemoresistant glioblastoma [51]. The magnetic CNTs demonstrated efficient tumor-targeting capability and triggered significant mechanical damage to tumor cells under a rotating magnetic field, ultimately leading to cell death.

Metallic NPs

In cancer therapy, metal materials, such as gold (Au), copper (Cu), and iron (Fe), are widely applied in cancer

therapy. Metal materials can be combined with liposomes, polymeric nanoparticles, dendrimers, or other nanocarriers in various forms. Lance T. Dockery and Marie-Christine Daniel developed a stimulus-responsive AuNP-Fab bioconjugate system in which dendrimer-coated AuNPs were functionalized with EphA2-targeting antibody fragments and loaded with DOX for prostate cancer therapy [52]. As a drug-delivery platform, this system exhibited significant targeting capability and outstanding anti-prostate cancer activity, reducing the viability of prostate cancer cells to 38.0% after 48 h even at low concentrations.

In another study, AuNPs were coated on the surface of poly (lactic-co-glycolic acid) (PLGA) NPs loaded with superparamagnetic iron oxide NPs encapsulated inside to reverse the immunosuppression in TME. With antiPD-L1 antibody on the surface to block the PD-L1/PD-1 checkpoint pathway, this nanosystem enhanced radiosensitivity of melanoma and achieved significant antitumor effect in conjunction with radiotherapy. Aiguo Wu and co-workers developed a core-shell structured Fe_3O_4@TiO_2@VISTAmAb (FTV) as a multifunctional nanoplatform for the treatment of pancreatic cancer [53]. FTV utilized Fe_3O_4 core as the magnetic resonance imaging contrast agent to enable visualized tracking, VISTA mAbs loaded onto the surface as location navigation to achieve specific recognition and phagocytosis, and TiO_2 shell as a sonosensitizer for SDT, inducing tumor cell apoptosis and immunogenic cell death.

Design of ADNCs and considerations

ADNCs apply synergistic strategies and multifunctional nanoplatforms to enhance the therapeutic efficacy. However, at different pharmacokinetic stages within systemic circulation, the optimal properties of NPs vary according to specific requirements. The physiological characteristics of nanocarriers (such as size, shape, surface charge, stability, degradability, safety, etc.) always play critical roles in determining the efficiency of drug penetration and aggregation [54]. These bio-interface interactions further govern cellular uptake, intracellular trafficking, and ultimate therapeutic outcomes in a context-dependent manner. On the other hand, the interaction of NPs with DNA, organelles, proteins, membranes, and cells establishes a series of nanoparticle-bio-interfaces that depend on the properties of the nanomaterials and dynamic biological and physicochemical interactions. Therefore, at the beginning of ADNCs design, various factors should be fully considered, including morphological features, components and coatings, binding affinity, systemic administration as well as the complex TME (Figure 3).

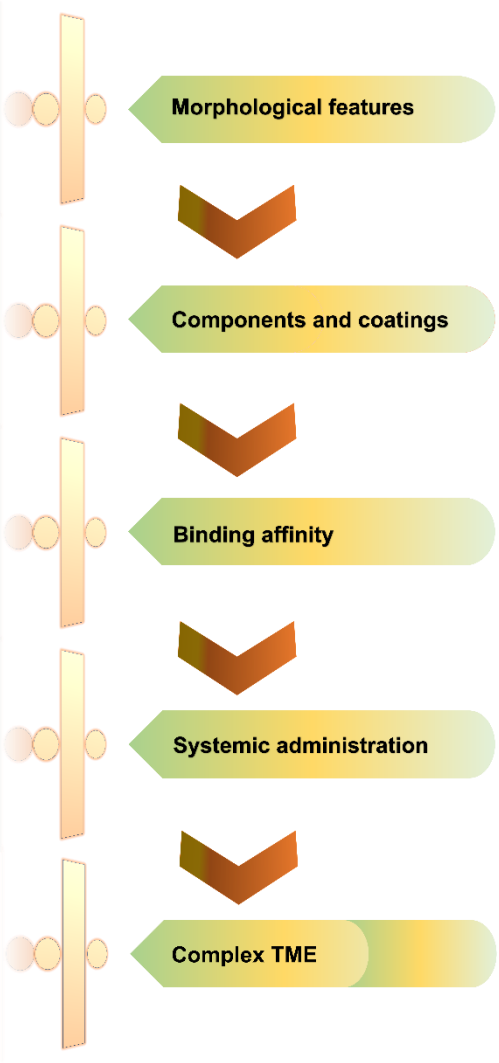

Figure 3. Factors for design and optimization of ADNCs, including morphological features, components and coatings, binding affinity, systemic administration as well as the complex TME.

Morphological features

The morphological features of ADNCs, including particle size, shape, and surface topography, play a critical role in pharmacokinetics, biodistribution, and cellular uptake. Particle size is a key determinant of the ability of NPs to extravasate through the endothelial barrier and accumulate within tumor tissues. Smaller NPs generally exhibit enhanced tissue penetration and wider distribution. NPs size within the range of 100-200

nm can generally evade hepatic and splenic filtration, thereby exhibiting prolonged circulation times and serving as optimal candidates for exploiting the enhanced EPR effect in tumors [55]. Modulating particle dimension can reduce clearance by the MPS. Spherical, ellipsoidal, cylindrical and discoidal NPs had been proved to display more uniform biodistribution and enhanced interactions with cell membranes, thereby promoting more efficient cellular internalization [56]. However, when multiple components are incorporated into nanocarriers to achieve synergistic effects, the particle size and morphology of the nanoparticles are prone to alteration. Consequently, determining and standardizing the optimal ratio of these components should be carefully considered.

Components and coatings

The stability of ADNCs is largely influenced by the interactions between their constituent materials and the surrounding environment. During systemic circulation, the formation of the protein corona on NPs surfaces is influenced not only by parameters such as particle size, shape, and surface topography, but also by components and coatings [57]. Surface modification or stealth technology can prolong the circulation time and reduce immune clearance to a certain extent [58]. It has been realized that liquid ordered phases can be affected and switched phases (liquid disordered phase, liquid ordered phase, and the solid gel phase) by thermodynamics and complex biological environments, the stability and function become a great challenge [59].

Fortunately, some previous experimental studies have confirmed that it can be optimized through chemical modification, such as the preparation of PEGylated liposomes, or via the addition of components like cholesterol. For instance, multifunctional ADNCs loaded with glypican-1 mAb, termed GCP@NBs, were developed to combine paclitaxel-mediated chemotherapy and chlorin e6-assisted SDT for PDAC, showing remarkable targeting capacity and excellent antitumor efficacy [60]. In this study, the DC-cholesterol was added in PEGylated liposomes to establish the shell of GCP@NBs, showing outstanding stability. Tin monosulfide (SnS), which has a two-layer orthorhombic crystal structure with low symmetry and high stability, can be activated by external stimuli and exhibits potential for photo-mediated and sono-mediated biomedical applications. By coating tin SnS-NPs with DSPE-PEG, SnSNPs@PEG showed improved stability in structure and enhanced advantages for desirable ROS generation under the US irradiation, achieving remarkable anti-tumor efficacy [61]. It has been proved that cross-linking technology can increase stability of ADNCs and prolonged circulation time [62]. For example, the hydrophobic PLGA, which has the capability to load a wide-range of hydrophobic drugs, can be wrapped with a hydrophilic shell composed of BSA for long circulation half-life [63].

Binding affinity

The balance between binding affinity of ADNCs and specificity of antigen was considered as the most crucial factors for remarkable targeting process and localization of ADNCs in targeted issues. An ideal target antigen should be highly expressed in tumor-specific tissues while exhibiting minimal or negligible expression in normal tissues, thereby ensuring the selective delivery of therapeutic payloads to target cells without inducing toxicity in healthy cells. Meanwhile, the target receptor should exhibit minimal or negligible secretion into the bloodstream; otherwise, antigen-antibody interactions in the circulation may deplete the systemic pool of ADNCs. This phenomenon reduces the availability of ADNCs for uptake by tumor cells and consequently leads to insufficient tumor targeting and potential off-target effects. Researchers had attempted to improve potent neutralization of antibodies through increasing binding affinity. However, there is still no substantial evidence to standardize the optimal affinity for the greatest *in vivo* efficacy. Additionally, the binding-site barrier effect, where high-affinity ADNCs preferentially saturate cells near the vasculature, deplete the pool of ADNCs available for deeper tumor penetration, leading to poor therapeutic efficacy [64]. Therefore, optimizing the binding ratio of ADNCs and antibodies deserve further exploration.

Systemic administration

Although topical administration can bypass some of the challenges confronted by systemic drug delivery, it is limited due to the demand of high-standard and complex techniques. Therefore, systemic administration is still the more common method in cancer medicine. During the pharmacokinetic procedure, which involves circulation, accumulation, penetration, cellular internalization, and

subsequent drug release, the physical and biological barriers encountered by ADNCs are influenced by multiple factors. Mononuclear phagocyte system (MPS), previously known as the reticuloendothelial system, represents the primary biological barrier faced by intravenously administered nanoparticles. MPS comprises tissue-resident macrophages in various organs (such as liver and spleen) in parallel with circulating monocytes and dendritic cells originating from the bone marrow [65]. MPS, primarily dendritic cells and macrophages, primarily participate in receptor-mediated phagocytosis and receptor-independent pinocytosis to internalize NPs [66].

Besides, the formation of a protein corona on the surfaces of NPs during the circulation process is one of the crucial obstacles for ADNCs delivery. Plasma proteins are usually negatively charged, making positively charged ADNCs easily covered by blood proteins, which are composed of apolipoproteins, complement components, serum albumin and immunoglobulins [67]. The formation of a protein corona accelerates the attachment of nanoparticles to phagocytes and promotes the sequestration of nanoparticles within phagosome vesicles as well as the subsequent formation of phagolysosomes. This process ultimately facilitates the enzymatic and biochemical degradation that leads to nanoparticle clearance, thereby significantly shortening the systemic circulation time [68].

At the same time, opsonization of the plasma proteins on the surface of ADNCs can impact on overall hydrodynamic size and surface charge. Additionally, the presence of this protein corona temporarily hides the specific targeting ability of nanoparticles, which is probably part of the reason why the active targeting strategy fails. Therefore, these circulatory barriers should be considered during the initial design of ADNCs, and corresponding solutions should be proposed - for instance, employing ultrasound-targeted microbubble destruction technology to modulate the surface plasma protein corona.

Complex TME

The complexity of the tumor microenvironment can be divided into two aspects: “physical” and “chemical”. Even with the EPR effect and active targeting, the complex TME poses physical challenges to effective nanoparticle accumulation and penetration. The limited perfusion in the central regions of solid tumors results in a reduced local NPs reservoir, while elevated interstitial fluid pressure (IFP) and a dense extracellular matrix (ECM) further impede the efficient delivery and deep penetration of nanomedicines [69]. The structure of most tumor blood vessels is generally characterized by discontinuous epithelium and defective basement membrane, which cannot ensure adequate vascular perfusion [70]. These defective blood vessels promote the extravasation of plasma and proteins through the discontinuous basement membrane, aggravating the deposition of ECM. The accumulation of EMC increases the IFP in the tumor tissues, causing structural collapse of immature neovascularization and the dysfunctional lymphatic drainage. These processes create a vicious cycle that promotes tumor development and metastasis. Additionally, the immune microenvironment of most solid tumors is driven by cancerous inflammation and characterized by immunosuppression, ultimately mediating tumor immune escape, leading to the chemical challenges for tumor treatment [71]. Leveraging the versatility of nanocarriers to combine targeted recognition, drug delivery, and TME remodeling allows for the partial resolution of these challenges.

Conclusion

ADNCs strategy represents a highly promising synergistic strategy with the potential to enable safer and more effective precision cancer therapy. By integrating the high specificity of antibodies with the versatile physicochemical properties of nanomaterials, ADNCs can function as efficient multifunctional platforms for tumor-targeted recognition, controlled drug delivery, stimulus-responsive drug release, and modulation of the TME.

In this review, we comprehensively summarize the recent advances in antibody engineering and nanoparticle design, highlighting their integration within ADNC platforms for cancer therapy. Particular emphasis is placed on the emerging applications of ADNCs as a synergistic therapeutic modality capable of enhancing therapeutic efficacy while minimizing off-target toxicity. Furthermore, we discuss the key design considerations and remaining challenges associated with ADNC development, including antigen selection, nanoparticle biocompatibility, payload loading efficiency, and in vivo pharmacokinetics. Collectively, these insights

underscore the significant potential of ADNC-based systems as next-generation therapeutic platforms, which may ultimately pave the way for more precise, personalized, and clinically translatable cancer treatments.

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Authors' contributions

Bo Ren and You Yang contribute equally to this article.

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Conflict of Interest

The authors declare no conflict of interest.

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