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Application of Carbon Nanomaterials to Enhancing Tumor Immunotherapy: Current Advances and Prospects

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Abstract: Recent advances in tumor immunotherapy have highlighted the pivotal role of carbon nanomaterials, such as carbon dots, graphene quantum dots, and carbon nanotubes. This review examines the unique benefits of these materials in cancer treatment, focusing on their mechanisms of action within immunotherapy. These include applications in immunoregulation, recognition, and enhancement. We explore how these nanomaterials when combined with specific biomolecules, can form immunosensors. These sensors are engineered for highly sensitive and specific detection of tumor markers, offering crucial support for early diagnosis and timely therapeutic interventions. This review also addresses significant challenges facing carbon nanomaterials in clinical settings, such as issues related to long-term biocompatibility and the hurdles of clinical translation. These challenges require extensive ongoing research and discussion. This review is of both theoretical and practical importance, aiming to promote using carbon nanomaterials in tumor immunotherapy, potentially transforming clinical outcomes and enhancing patient care.

Keywords: carbon nanoparticles, immune cell, tumor immunotherapy, drug delivery, immunosensors

Introduction

Cancer is a genetically autonomous disease characterized by malignant cells that bypass normal cellular control mechanisms.[1] According to the latest cancer statistics published by "A Cancer Journal for Clinicians", in 2022, nearly 20 million new cancer cases were reported globally, with approximately 9.7 million cancer deaths.[2] Tumors can be classified as cancerous, characterized by their invasive growth and spread to surrounding tissues, or non-cancerous, which remain localized, do not recur, and maintain a consistent size and smooth morphology.[3] Cancer treatment primarily involves surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy. However, due to late-stage diagnosis, residual cancer cells may persist, leading to recurrence or metastasis post-treatment.[4–7]

The human immune system, comprising immune organs, cells, and active substances, is crucial for defending against diseases, malignant tumors, and xenobiotic exposures, and interacts with nearly all organ systems.[8] The advent of cancer immunotherapy marks a significant milestone in precision medicine. Common strategies include immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 or CTLA-4 pathways, which reinvigorate the immune system by enhancing anti-tumor T-cell responses. ICIs have demonstrated substantial survival benefits in numerous clinical trials and are now primary treatments for advanced solid tumors.[9,10] Although conventional immunotherapy has demonstrated significant potential in recognizing and eliminating cancer cells, many patients with advanced cancer have not achieved durable

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clinical remission due to primary or secondary resistance mechanisms.[11–13] Additionally, these therapies can lead to unpredictable or even very severe toxic reactions, such as immune-related adverse events.[14,15] Furthermore, the cost of these treatments is quite high; for example, the annual expense of checkpoint inhibitors is approximately $150,000, while CAR-T cell therapy can cost up to $450,000 per year, which severely limits the patient's autonomy in treatment.[16,17] To address these challenges, combination immunotherapy strategies and nanoparticle therapy are gaining attention. By integrating various treatment methods, especially the precise delivery offered by nanoparticles, these approaches aim to enhance treatment efficacy, reduce side effects, and improve the overall effectiveness and accessibility of cancer immunotherapy.[18,19]

Nanoparticles (NPs), first identified by German scientists in the 1980s, are defined by having at least one dimension on the nanometer scale.[20] Their unique characteristics, such as a high surface-to-volume ratio, tunable size, distinctive optical properties, and multifunctionality, make NPs highly suitable for cancer immunotherapy.[21] NP-mediated drug delivery involves several stages: circulation through the bloodstream,[22] tumor accumulation and retention,[23] tumor penetration,[24] cellular internalization,[25] and potential nuclear localization.[26] Delivery methods include passive targeting, relying on enhanced permeability and retention, and active targeting via surface-bound ligands.[27] NPs can improve the pharmacokinetics and toxicity profiles of both chemotherapeutic and immunotherapeutic agents,[28] with capabilities such as specific immune cell binding, controlled drug release, and precise drug delivery (Figure 1).[29,30] Despite the potential, many nanomedicines have underperformed in clinical trials due to the tumor microenvironment's complexity, leading to inadequate drug penetration and accumulation.[31,32] Larger NPs accumulate at the tumor site but penetrate poorly, while smaller NPs penetrate better but accumulate less.[33] Surface charge, shape, materials, and surface groups also affect permeability.[34] Thus, careful selection of nanomaterials is crucial for enhancing immunotherapy efficacy.

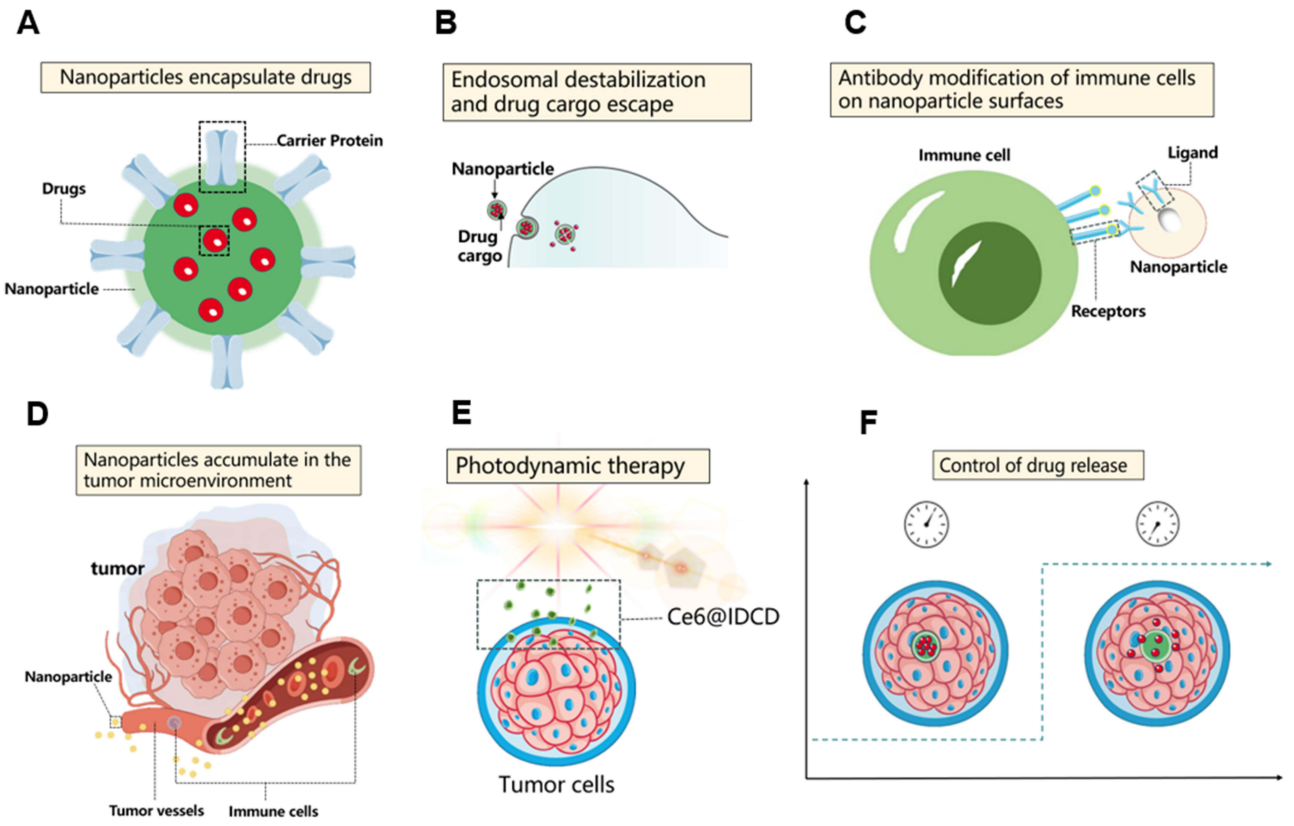

Figure 1 Schematic of recent application strategies and characteristics of carbon nanomaterials in tumor immunotherapy. (**A-F**) This figure highlights key strategies for leveraging carbon nanomaterials in tumor immunotherapy. These strategies include encapsulating drugs to improve their stability and bioavailability, facilitating cytoplasmic drug release for enhanced therapeutic efficacy, and modifying nanoparticle surfaces with antibodies to specifically target and activate immune cells. Additionally, the figure emphasizes how the high permeability and strong retention effects of nanomaterials can localize drugs at tumor sites. It also showcases the use of external energy sources to boost the immunological properties of nanoparticles, as well as the regulation of drug release dynamics through pre-programmed compositions or external stimuli.

Carbon nanomaterials (CNMs) are of particular interest due to their exceptional properties and versatile structures. Carbon's stability and capacity for functional group attachment make CNMs valuable in various applications, including biomedical devices and bone implants.[35–38] Known for their superior electrical, thermal, and optical properties, CNMs are applied in drug delivery,[39] bioimaging,[40–42] biosensing,[43] and tumor diagnostics and therapy (Figure 2). Functionalization of CNMs with biomolecules enhances drug carriage, site-specific targeting, and biological adaptability.[44] Consequently, CNMs are increasingly utilized for developing new diagnostic and therapeutic mechanisms, drug delivery systems, and medical imaging tools, including photothermal therapy and photoacoustic imaging.[45] They are also used in photothermal therapy and photoacoustic imaging for cancer treatment, demonstrating remarkable efficacy in thermal ablation techniques.[46,47] This review highlights the biological properties of CNMs and their promising applications in augmenting anti-cancer immunity (Table 1).

How Carbon Dots Work in Immunotherapy

Carbon dots (CDs) are fluorescent carbon nanomaterials with diameters ranging from 1 to 10 nm. Their appeal in scientific research stems from their ultra-small size, water solubility, photostability, cell membrane permeability, and biocompatibility.[59] CDs are readily synthesized from graphite and organic molecules such as citric acid or glucose and can emit blue, green, and red fluorescence. CDs have been successfully implemented in various applications. Liu et al from South China Normal University demonstrated that embedding CDs into silica nanoparticles to form CDs@SiO2 particles can produce delayed fluorescence (TADF) or phosphorescence (Phos). These particles can generate reactive oxygen species (ROS) through intersystem crossing (ISC), efficiently prolonging the half-life of ROS generation. This method produces ROS without damaging tooth enamel or surrounding soft tissues.[60]

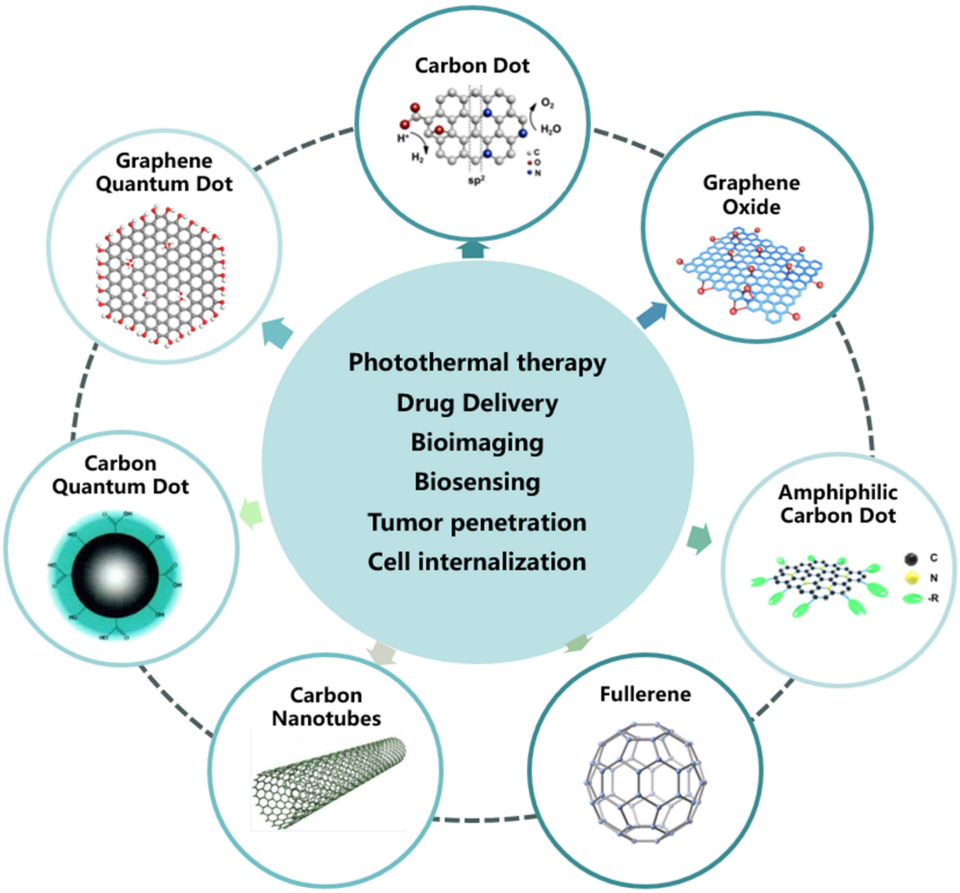

Figure 2 Categories of carbon nanomaterials and their function in immunotherapy. This figure categorizes the latest carbon nanomaterials utilized in immunotherapeutic applications, and decides their details their specific functional properties.

Table 1 Application of Carbon Nanomaterials in Anti-Cancer Immune Response and Immunotherapy

Nanomaterials	Bonding Pattern	Dimensions	Target Cells	Cancers	Biological Functions	Refs
CD-MSN	Hydrogen bond/ electrostatic-assisted co-assembly	50.0–60.0 nm	Macrophages	Breast cancer	Stimulating the proliferation and activation of NK cells and macrophages, regulating the increase of IFN-γ and Granzyme B.	[48]
CD-OVA	Covalent bonding and electrostatic interactions	50.0–100.0nm	DC cells	B16 Melanoma	Increasing the expression of CD80 and CD86, along with TNF-α production, strongly stimulating splenocyte proliferation and IFN-γ production.	[49]
CD-Man	Electrostatic force, Van der Waals force	241.3nm	DC cells	Hepatocellular carcinoma	Promoting DC maturation, enhancing antigen processing and delivery of DCs.	[50]
CDTAC	Chemical conjugation	2.5–3.5nm	DC cells	Colorectal cancer	Decreasing PD-L1 expression, activating STING pathway, and promoting DC maturation.	[51]
Ce6@IDCD	Hydrophobic interactions;	131.1±7.8 nm	$CD8^+$T cells	Colorectal cancer	Inducing the recruitment of CD8+ T cells, NK cells and mature DCs into tumor tissue	[52]
GQD-PEG	Chemical conjugation	2.0–9.0 nm	CD8+T cells	Oral squamous cell carcinoma	Promoting tumor infiltration by CD8+ T cells, increasing TNF-α and IFN-γ expression	[53]
ChA-CQD	Chemical conjugation	5.0–10.0 nm	T cells, NK cells, and macrophage	Hepatocellular carcinoma	Decreasing GPX4 and SLC7A11, promoting the infiltration of T cells, NK cells, and macrophages, and inducing iron metamorphosis in HepG2 cells.	[54]
MWCNT-MHR	Carboxylic interactions	10.0 −100.0 nm	$CD4^+$ and $CD8^+$ T-Cells	Prostate cancer	Increasing CD4+ and CD8+ T cells, upregulating TNF and IL-6	[55]
Au-NCNCs	Chemical vapor deposition	50.0 −100.0 nm	Myeloid -Derived Suppressor cells	Melanoma	Stimulating myeloid-derived suppressor cells differentiation into DCs	[56]
O12-Tta-CD @OVA-mRNA	Michael addition reaction	80.0 −500.0 nm	DC cells	T-cell lymphoma	Stimulating the maturation of BMDCs and prolonging tumor survival	[57]
C70-FTCD-SRGD	Chemical conjugation	150.0 −400.0 nm	Effector T cells	Breast cancer	In combination with anti-PD-L1 antibody, PDT activates immune responses to fully inhibit deep hypoxic tumors.	[58]

Wang's group from Southeast University has utilized quantum-sized CDs with zincophilic groups and bright fluorescence as additives. This approach enables dual functions: zinc anodic protection and fluorescence, offering a novel strategy for lightweight prevention and safety in electronic products.[61] When combined with metal-organic complexes, CDs target immune cells and are widely used in biosensing, bioimaging, drug delivery, and cancer therapy.[62,63] Subsequent sections detail the applications of carbon dots in targeted immunotherapy, The immunomodulatory mechanism of carbon dots in this article is illustrated in Figure 3.

Macrophages

Macrophages are essential elements of the innate immune response and exhibit significant plasticity, capable of polarization under various physiological and pathological conditions into two phenotypes with distinctly opposing functions: classically activated M1-type macrophages and alternatively activated M2-type macrophages.[64,65] M1-type macrophages can directly kill tumor cells and are involved in upregulating genes and co-stimulatory molecules that facilitate antigen processing and presentation, enhancing T-cell-mediated immune responses. In contrast, M2-type macrophages, also called alternatively activated macrophages, contribute to immune protection against tumors and promote tumor growth, invasion, and metastasis.[66–68] As carrier systems, nanomaterials offer innovative approaches to drug delivery, with distinct advantages in targeted delivery, controlled release, and safety. Targeting macrophages using nanomaterials also presents new opportunities for tumor diagnosis and treatment. On the one hand, macrophage imaging can provide direct evidence of tumorigenesis and progression and the efficacy of treatments. On the other hand, targeting macrophages for selective destruction or promoting macrophage phenotypic transformation can modulate the immunosuppressive tumor microenvironment and improve treatment outcomes.[69,70]

The Ricin toxin B (RTB) subunit is a heterodimeric toxin protein derived from the seeds of the castor bean plant, known for its ability to bind to cell surface galactose or glycolipids. This binding stimulates macrophage activation and mediates cell immunity. However, the clinical application of RTB has been restricted because of its poor stability,

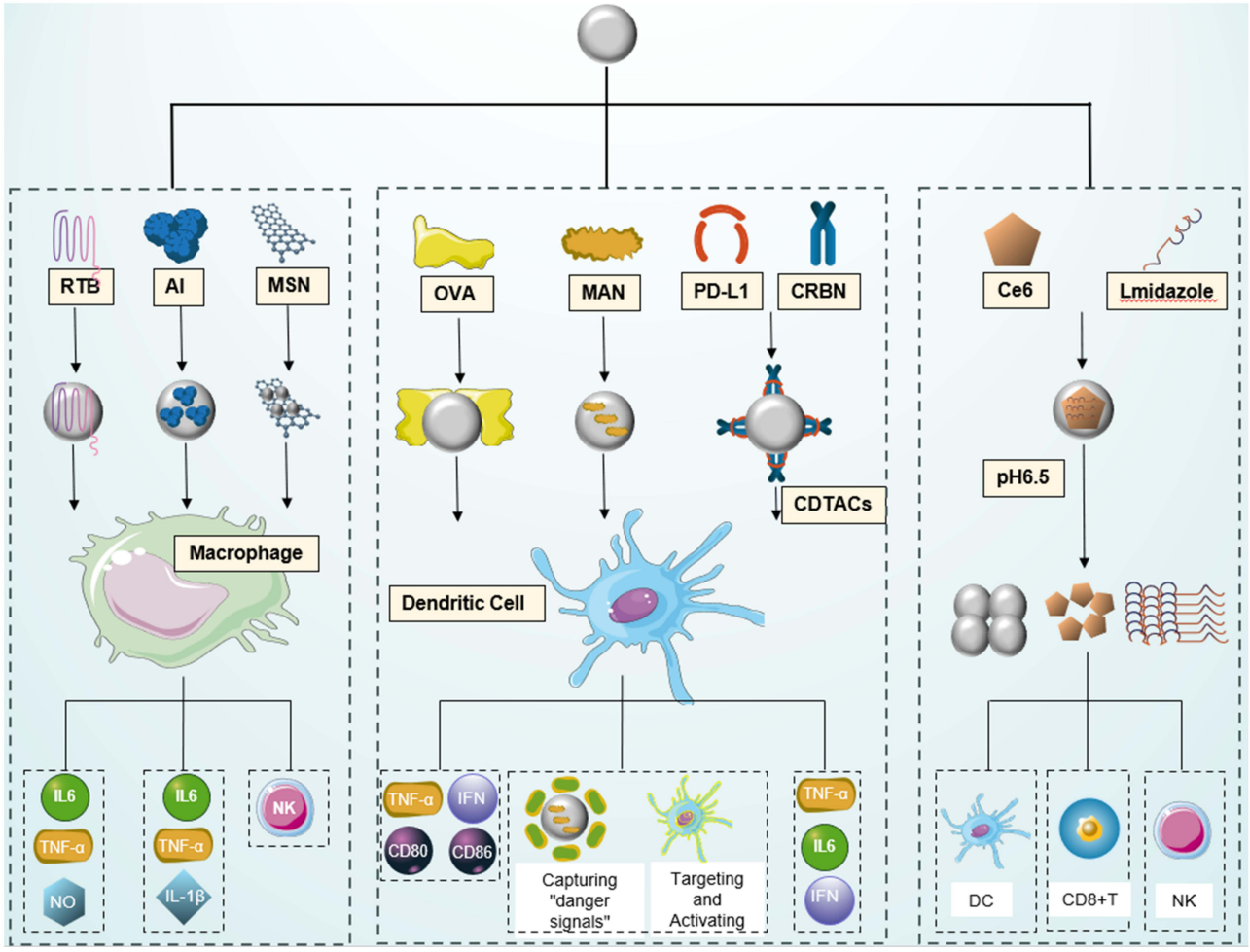

Figure 3 Schematic of carbon dots in anticancer immunotherapy. This figure illustrates the diverse effects of carbon dots (CDs) in anticancer immunotherapy: CD-RTB promotes macrophage proliferation and enhances the release of nitric oxide (NO), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α); CD-AI acts as an immunostimulant, activating macrophages to produce TNF-α and interleukin-1 beta (IL-1β); CD-MSN enhances the activation of natural killer (NK) cells and macrophages, adding value to their immune functions; CD-OVA boosts the expression of co-stimulatory molecules CD80 and CD86 on dendritic cells (DCs), increases TNF-α production, and significantly stimulates splenocyte proliferation and interferon gamma (IFN-γ) production; CD-MAN efficiently captures danger signals and transmits them to DC cells, thereby enhancing the immune response of antigen-presenting cells (APCs); CDTAC promotes DC maturation by inducing PD-L1 downregulation or activating the STING signaling pathway, resulting in increased secretion of TNF-α, IFN-γ, and IL-6; Ce6-IDCD maintains stable morphology and size at physiological pH and releases Ce6 at tumor pH, facilitating reactive oxygen species (ROS)-induced photodynamic therapy (PDT) mediated apoptosis, necrotic signaling, and an increase in CD8+ T cells, NK cells, and DC cells.

characterized by low bioavailability, a short half-life, and susceptibility to enzymatic hydrolysis. Li's group engineered nanoparticles to overcome these limitations by assembling RTB with carbon dots through supramolecular interactions, creating CD-RTB. This new formulation exhibited a smaller size and increased stability, effectively activating macrophages and increasing immune regulatory activity.[71] Comparative studies have shown that CD-RTB activates macrophages more effectively than RTB alone, increasing nitric oxide (NO) secretion and significantly increasing interleukin (IL)-6 and tumor necrosis factor-α (TNF-α) proteins in a concentration-dependent manner. It increases the mRNA expression of these inflammatory mediators.[72–74]

In another approach, Ayaz et al employed an in situ thermal synthesis technique to bind metallic aluminum (Al) with CDs through electrostatic interactions, resulting in CD-Al particles. Upon exposure to hazardous stimuli, these particles accelerate the secretion of the pro-inflammatory cytokines IL-1β and TNF-α from macrophages.[75] Furthermore, modifying the surface passivators on carbon dots can enhance their anti-inflammatory properties. Among the three passivators tested, polyethylene glycol (PEG), polyvinyl alcohol (PVA), and sodium alginate (ALG), CD-PVA exhibited the most potent anti-inflammatory activity, demonstrating the potential of CDs as drug release carriers.[76]

Qian et al discovered that using hydrogen bonding/electrostatic forces, CDs can be uniformly coated with mesoporous silica (mesoporous silica nanoparticles, MSN), resulting in the biodegradable CD-MSN complex. This complex specifically accumulates in vitro and in vivo, allowing its biodegradable fragments to collect antigens from photothermally ablated tumor cells. These antigen-laden fragments escape from necrotic tissues, activating natural killer cells and macrophages and selectively targeting immune organs for an enhanced therapeutic effect.[48]

Dendritic Cells

Dendritic cells (DCs) are a crucial link between innate and adaptive immunity. They are the most potent specialized APCs in the body, playing a central role in anti-infection and anti-tumor responses. However, tumor cells can suppress both the immune system and the functionality of DCs, limiting the effectiveness of dendritic cell-based antitumor immunotherapy. Therefore, enhancing the antitumor immune response by modulating DC function and overcoming immune tolerance is vital.

One promising strategy involves targeting DCs by loading antigens and adjuvants into nanomaterial-based carriers, which deliver high doses of immunogens and significantly improve immune efficacy.[77] Luo et al employed luminescent carbon dots as vaccine adjuvants, covalently bonded with the tumor protein antigen model ovalbumin (OVA), exhibiting various luminescence at different wavelengths. Their carbon dot-OVA nano complexes (CDs-OVA) effectively upregulated the co-stimulatory molecules CD80 and CD86 in DCs, increased the production of TNF-α, and stimulated splenocyte proliferation and interferon-gamma (IFN-γ) production. In vivo, CDs-OVA was efficiently processed by immune cells, inducing a robust antigen-specific cellular immune response, and inhibiting the growth of B16-OVA melanoma in C57BL/6 mice.[49]

Microwave ablation (MWA) is a common treatment for hepatocellular carcinoma that releases tumor-associated antigens by lysing tumor cells.[78,79] Zhou et al demonstrated that mannose carbon dots can enhance the immune response of APCs post-MWA, effectively capturing danger signals and activating DCs, inducing a strong tumor-specific immune response and inhibiting tumor growth and metastasis.[80] Further enhancements using mannose-modified carbon dots doped with metallic aluminum (M/A-CD) improved DC maturation and antigen presentation through a synergistic effect.[50]

Combining carbon dots with proteolysis targeting chimeras (PROTACs) to form carbon-dot-based PROTACs (CDTACs) offers a novel approach to target and degrade PD-L1 proteins within tumor cells. Su et al reported that CDTAC binds to PD-L1, facilitating its entry into lysosomes where it is degraded and subsequently engaging the newly synthesized PD-L1 in the cytoplasm for ubiquitination and degradation. This continuous process reshapes the immunosuppressive tumor microenvironment by activating the Stimulator of Interferon Genes (STING) pathway and promoting dendritic cell maturation.[51]

As our understanding of immune regulation and the interactions between DCs and biomaterials deepens, engineered biomaterials have been shown to significantly enhance DC-based immunotherapy. Optimizing these biomaterials involves adjusting parameters such as size and shape to improve DC activation and address various in vivo delivery challenges. Innovative forms of biomaterials, such as microneedles, 3D scaffolds, and nanogels, demonstrate substantial potential in enhancing antigen delivery efficiency and DC activation.[81]

CD8+ T Cells

Cytotoxic T lymphocytes (CTLs), also known as $CD8^+$ T cells, are essential components of the adaptive immune system, playing a critical role in defending against pathogens such as viruses, bacteria, and tumors.[82] In the immunosuppressive tumor microenvironment, insufficient infiltration of $CD8^+$ T cells often results in a decreased antitumor response. If CD^+ T cells are absent, the body will lack antitumor immune function and will no longer be susceptible to tumor growth. Dysfunction in $CD8^+$ T cells can trigger excessive immune responses, leading to immune-mediated tissue damage or pathological reactions.[83] Thus, enhancing $CD8^+$ T cell infiltration and promoting their functional activity are vital strategies in tumor treatment.

Advances in nanomedicine have used carbon dot materials to modulate T-cell function and influence tumor progression. Researchers synthesized Ce6-loaded pH-sensitive carbon dots doped with imidazole (Ce6@IDCD) through microwave pyrolysis using citric acid (CA) and 1-(3-aminopropyl) imidazole (API) as carriers. Ce6@IDCD maintains stable

morphology and size under physiological pH conditions, but at tumor pH, the protonation of the imidazole moiety triggers the release of Ce6. This release initiates ROS-induced PDT-mediated apoptosis and necrosis signaling pathways, systematically activating various antitumor immune cells such as $CD8^+$ T cells, NK cells, mature dendritic cells, and increased levels of pro-inflammatory cytokines. This mechanism directly contributes to therapeutic outcomes and potently enhances antitumor immunity, using endogenous adjuvants in colorectal cancer treatment through photosensitizers.[52]

As an emerging carbon-based nanomaterial, CDs have promising potential in immunotherapy. The high biocompatibility of CDs is particularly advantageous for human tissues, making them suitable for cell labeling and imaging techniques. These properties enable detailed monitoring of the distribution and function of immune cells. CDs can serve as efficient drug carriers, enhancing both the bioavailability and efficacy of therapeutic agents. They also improve immune recognition of tumor cells and activate immune cell functions. Despite these benefits, several factors limit the development of CDs in clinical applications. Their use in immunotherapy remains primarily experimental, with critical aspects such as optimal dosage, toxicity, and long-term effects still under investigation. High concentrations of CDs may induce inflammation and allergic reactions,[84] and technical challenges are associated with delivering immune drugs to target cells through CDs.

The prospects for CDs in immunotherapy are highly promising. Ongoing research is likely to expand their applications in several key areas: (a) enhancing the delivery and stability of immunotherapy drugs to improve therapeutic outcomes; (b) facilitating real-time monitoring and evaluation of immunotherapy effects, assisting clinicians in optimizing treatment protocols; (c) increasing immune recognition of tumor cells and bolstering the immune system's response; and (d) minimizing undesirable reactions and reducing the toxicity associated with immunotherapy.

Other Carbon Nanomaterials in Tumor Immunotherapy

Influence of Graphene Quantum Dots on Tumor Cells

Graphene quantum dots (GQDs) represent a burgeoning field in biomedical applications, with significant contributions to bioimaging,[85] drug delivery,[86] and biosensing.[87] GQDs, small graphene fragments typically within the nanometer size range, are characterized by sp^2 hybridization.[88] This structural feature imparts unique electronic and optical properties, making GQDs highly promising for various applications in nanoscience and technology. Research has shown that at low concentrations, GQDs can enhance the expression of inflammatory cytokines such as IL-8, IL-1, and TNF-α.[89] They also activate the p38MAPK pathway, leading to inflammatory responses, apoptosis, and autophagy through p38MAPK and NF-κB signaling pathways, influencing various immune responses, including cell proliferation, apoptosis, and autophagy.[8]

In terms of normal cellular signaling, ROS produced by mature myeloid cells helps maintain the stability of the organism. However, excessive ROS in malignant tumors impedes immune cells' anti-tumor activities and triggers apoptosis in cytotoxic lymphocytes.[90] High expression of the transmembrane glycoprotein CD44, which predominantly adheres to the extracellular matrix and serves as a receptor for hyaluronic acid, has been identified in various cancers, including pancreatic, colon, and bladder cancers.[91,92] Cherukula et al demonstrated that a GQD-HDC complex, formed by loading histamine dihydrochloride (HDC) onto GQDs, can target CD44 on leukemia cells (K-562), effectively scavenging free radicals produced by these cells in a concentration-dependent manner. GQDs exhibit non-cytotoxic behavior at higher concentrations, enhancing their suitability for treating leukemia-induced immunosuppression.[93] Exploiting their unique quantum confinement and edge effects, GQDs also exhibit tunable luminescent properties. Researchers have developed a nanomaterial with low cytotoxicity and excellent endocytotic capabilities by combining GQDs with PEG to form a GQD-PEG complex. Under specific light irradiation, GQD-PEG activates potent anti-tumor activities and significantly increases the production of pro-inflammatory factors such as $CD8^+$ T cells, IFN-γ, and TNF-α. This pivotal role of GQD-PEG in photodynamic therapy further underscores the potential of nanomaterials to trigger anti-tumor immune responses and as part of combined therapeutic strategies.[53]

Impact of Carbon Quantum Dots on Tumor Cells

Carbon quantum dots (CQDs) are carbon-based nanoparticles characterized by their photoluminescence and typically spherical shape, with sizes less than 10 nm.[94] These nanoparticles exhibit unique physicochemical properties, exceptional biocompatibility,

eco-friendliness, and ease of surface functionalization. The diminutive size of CQDs allows them to approximate the glomerular filtration barrier, making them suitable as carriers for drug or gene delivery and mediators of ROS generation.[95]

Yao's group reported on a biocompatible nano-enzyme based on CQDs synthesized from chlorogenic acid (ChA), a significant biologically active compound extracted from coffee. These ChA-CQDs demonstrated significant glutathione (GSH) oxidase-like activity and promoted ferroptosis in cancer cells by disrupting the GPX4-catalyzed lipid repair system. In vivo studies showed that ChA-CQDs inhibited tumor growth in HepG2 tumor-bearing mice with minimal paratoxicity. In hepatocellular carcinoma H22 mice, ChA-CQDs recruited many tumor-infiltrating immune cells, such as T cells, NK cells, and macrophages. This recruitment transformed "cold" tumors into "hot" ones, activating systemic anti-tumor immune responses.[54] He et al developed an adhesive hydrogel based on a polyphenol carbon quantum dot-supported single-atom palladium nanozyme (DA-CQD@Pd SAN). This nanozyme catalyzed the decomposition of H_2O_2 into hydroxyl radicals (OH), enhancing local immune modulation and immunotherapy. It effectively catalyzed the formation of a hydrogel around tumors and induced immunogenic cell death, triggering an anti-tumor immune response.[96]

The Chatterjee research group has advanced the use of CQDs in immune regulation. They have developed a CQD formulation bound with S-nitro-N-acetyl penicillamine (SNAP) to create an aerosol spray. This spray slows cell entry and provides thermodynamic stabilization for the sustained NO release, which protects the vasculature and pulmonary branches from adverse effects, inhibits the viral replication cycle, reduces the synthesis of early viral progeny, and enhances intervention against human coronaviruses (HCoVs).[97]

Carbon Nanotubes Against Tumor Cells

Carbon nanotubes (CNTs) are cylindrical molecules composed of graphitic carbon with distinct mechanical properties, categorized into single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). MWCNTs exhibit superior structural stability compared to SWCNTs.[98] Due to their unique physicochemical properties in mechanics, thermal, and electrical conductance, CNTs have been utilized effectively in tumor imaging and diagnostics.[99] CNTs can bind microtubule proteins in tumor cells, effectively blocking cell proliferation. Research indicates that polymer modified CNTs can treat tumors not only through photothermal effects but also by acting as immune adjuvants to promote the maturation of DCs and release anti-tumor factors.[100]

Xia et al carboxylated MWCNTs with the peptide H3R6 to create the carrier MHR. When electrostatically interacted with the immune activator CpG, the MHR/CpG nanocomposite promotes the secretion of IL-6 and TNF-α, accumulates effectively at tumor sites and tumor-draining lymph nodes, and exhibits strong inhibitory effects on prostate cancer proliferation while stimulating the differentiation and proliferation of CD4 and CD8 T cells in vivo.[55] Ji et al reported on chitosan-modified SWCNTs, which specifically target SMMC-7721 hepatocellular carcinoma cells to deliver the anticancer drug doxorubicin when conjugated with folic acid. This modification allows nanotubes to kill hepatocellular carcinoma cell lines, inhibit tumor growth in nude mice, and demonstrate high potency with low in vivo toxicity compared to controls.[101]

Ren's group developed PEG-loaded doxorubicin-oxidized MWCNTs, using vasopressin-2 as a target ligand for glioma treatment. This complex showed enhanced anti-glioma effects, demonstrating cytotoxicity against C6 glioma cells in vitro and prolonging the median survival time in glioma-bearing mice in vivo.[102] Burkert et al have advanced the technology by introducing sp^3 nitrogen atoms into the conjugated sp^2 graphite structure of CNTs and synthesizing gold nanoparticles at the open edges to form Au nitrogen-doped nitrogen nanotube cups (Au-NCNCs). These Au-NCNCs, carrying the chemotherapeutic drug paclitaxel, target the tumor site, modify the tumor microenvironment, and reduce tumor growth rate, suggesting a novel approach to developing targeted treatments against immunosuppressive macrophages.[56]

Roles of Amphiphilic Carbon Dots Against Tumor Cells

Amphiphilic carbon dots (ACDs) are a novel category within the broader family of carbon dots. Characterized by their dual affinity, hydrophobic and hydrophilic, ACDs can stably disperse in aqueous and non-aqueous media.[103] This amphiphilicity makes them exceptionally useful in biomedical applications, including aqueous solutions for cell imaging and drug delivery.[104] Due to their inherent fluorescence properties, ACDs can efficiently bind to mRNA to form bio-imageable ACD-mRNA nano complexes. By screening ACDs, scientists identified O12-Tta CD as having high transfection efficiency and potent delivery capabilities, particularly to the spleen. Using this discovery, the researchers

developed O12-Tta CD@OVA-mRNA complexes capable of effectively transfecting immune cells. These complexes promote bone marrow-derived dendritic cells' maturation and antigen presentation (BMDCs), activating cytotoxic T lymphocytes (CTLs). The interaction triggers CTL cytotoxicity and significantly inhibits tumor growth by initiating CTL-mediated immune responses in both the spleen and tumors. The O12-Tta CD@OVA-mRNA complex can potentially prevent tumor recurrence and act as tumor prevention, offering promising new directions for designing mRNA vectors in tumor immunotherapy.[57]

In the preceding discussion, we have comprehensively Elucidated the pivotal roles of carbon nanomaterials in immunotherapy, particularly focusing on their mechanisms for activating the immune system to enhance tumor cell recognition and eradication. In this context, fullerene (C70) has emerged as a promising carbon-based nanomaterial with significant potential in immunotherapy. Recently, Li et al developed an innovative hypoxia-sensitive nanotherapeutic system (FTCD-SRGD), which combines C70 with the hypoxia-activated prodrug tirapazamine (TPZ). This system leverages C70's ability to deplete oxygen and generate reactive oxygen species (ROS), thereby intensifying the hypoxic tumor microenvironment and activating TPZ to release toxic free radicals. This dual approach enhances the effectiveness of both PDT and chemotherapy under hypoxic conditions. Moreover, it significantly improves therapeutic outcomes for deep-seated tumors and promotes immunogenic cell death (ICD), thereby increasing tumor responsiveness to immunotherapy.[58] Nevertheless, due to the relatively limited research on the roles of fullerene in immunotherapy, its precise mechanisms and clinical efficacy remain inadequately explored, indicating that the application of fullerene-related materials in immunotherapy is still in the exploratory phase.

Application of Carbon Nanomaterials in Immune Sensors

The analysis and detection of tumor markers have become increasingly crucial in medical diagnostics; however, traditional methods such as chromatography and mass spectrometry often fall short of clinical needs. In contrast, electrochemical detection has garnered significant attention due to its simplicity and rapid analytical capabilities. This section explores the role of carbon nanomaterials in the detection of tumor markers (Table 2), and discusses the future prospects in detecting tumor markers.

Single-walled carbon nanohorns (SWCNHs) are a novel class of carbon nanomaterials, similar to SWCNTs but distinct in their closed conical structure at one end. Exhibiting properties such as excellent electrical conductivity, high porosity, purity, biocompatibility, and low toxicity, SWCNHs are promising in various applications, including drug delivery, gas storage, fuel cells, and biosensors.[109,110] Previous research has shown that SWCNHs can act as safe anticancer agents by inducing mitochondrial dysfunction and apoptosis in HepG2 cells by up-regulation of SIRT3.[111] SWCNHs are being developed into nanosensors to promote innovations in immune governance. For example, Zhang et al constructed a biosensor using GNPs-SWCNH nano complexes for the sensitive detection of hypoxanthine and xanthine.[105] Gao's group synthesized a new carbon nanocomposite, PtNPs-SWCNHs, functionalizing SWCNHs to solidly load antibodies on the surfaces of modified electrodes for the detection of the atherosclerosis marker protein MCP-1 through antigen-antibody reactions.[106]

MWCNTs, known for their excellent biocompatibility, electrical conductivity, and specific surface area, utilize their outermost tubes to protect the inner tubes while maintaining unique electrochemical properties. Niu used nanocomplexes

Table 2 Carbon Nanomaterials for Immune Sensor Application

Electrode	Nanomaterials	Target	LOD	Linear Range	Electrolyte	pH	%Recovery	Ref
Platinum	GNPs-SWCNH	Hypoxanthine, xanthine	0.6μM, 0.7μM	1.5μM −35.4μM; 2.0μM-37.3μM	PBS	7.4	96.4±0.4 98.3±0.6	[105]
Platinum	PtNPs-SWCNHs	MCP-1	2.0×10^{-2}pg/mL	6.0×10^{-2}pg mL^{-1}–450pg mL^{-1}	PBS	7.4	95.3–102.3	[106]
Glassy carbon	C-MWCNT-PAMAM	α2,3-sial-Gs	3.0 fg/mL	10.0fg mL^{-1}–50.0ng mL^{-1}	Ultrapure water	7.0	96.0–103.9	[107]
Nanocomposites-modified electrode	CS-MWCNTs-GO-PB-PTA	ST6Gal-I	3.0 pg/mL	1.0×10^{-2} $ngmL^{-1}$ −250.0$ngmL^{-1}$	PBS	7.0	94.8–110.4	[108]

of carboxylated MWCNTs (p-MWCNTs) and polyamidoamine dendrimers (PAMAM) to modify glassy carbon electrodes. This setup achieved highly sensitive detection of the tumor marker α2,3-sialylated glycans (α2,3-sial-Gs) using differential pulse voltammetry (DPV).[107]

Graphene oxide (GO) is distinguished by its abundance of oxygen-containing functional groups and modifiable active sites, making it ideal for creating high-quality nano complexes. Zhang et al demonstrated a new immunosensor, CS-MWCNT, based on a hybrid nanocomposite that includes GO, MWCNT, a derivative of 3,4,9,10-perylenetetracarboxylic acid hydride (PTC-NH2), and chitosan (CS). This composite forms the foundation of a novel immunosensor, CS-MWCNTs-GO-PB-PTA, which features good electrical conductivity, high catalytic activity, and plentiful active sites. This sensor uses gold nanoparticles (AuNPs) loaded onto a Prussian blue (PB) nanocomposite film, capable of sensitively and quantitatively detecting the potential tumor marker β-galactoside α-2,6-sialyltransferase (ST6Gal-I) on thin films.[108]

Modern carbon nanomaterials boast tunable physical, chemical, electronic, and mechanical properties alongside advantages such as high specific surface area, good biocompatibility, and excellent electron transport capability. These attributes expand the range of electrochemical activity and enhance the efficiency of electron transfer. Such improvements contribute to the high sensitivity and specificity of detecting target molecules and improve the stability of the detection system. As a result, new carbon nanomaterials are continually being developed and implemented in various electrochemical biosensors.

Using the unique properties of carbon nanomaterials to construct electrochemical sensors with high specificity and sensitivity or suitable for other applications holds significant potential in tumor immunology. These advances provide a solid foundation for future clinical detection applications, underscoring their importance in advancing medical diagnostics.

Clinical Perspectives and Biocompatibility in Tumor Immunotherapy

In clinical research, various nanoparticles have been employed as carriers for the targeted delivery of specific immunotherapeutic drugs, showing high efficacy and low toxicity in cancer treatment. For example, Xia et al developed pH-/enzyme-responsive TLR7/8 agonist-conjugated nanovaccines (TNVs) that, once taken up by antigen-presenting cells (APCs), are directed to lymph nodes, promoting APC maturation and inducing specific T cell immunity. These nanovaccines have demonstrated significant prophylactic and therapeutic effects in B16-OVA melanoma and MC38 colon cancer models.[112] Moreover, magnetic nanoparticles (MNPs), particularly iron oxide nanoparticles, are increasingly replacing traditional MRI contrast agents. They play a pivotal role in tracking and staging lymph nodes (LN) pre- and post-surgery in cancer bioimaging, offering improved accuracy and biocompatibility for LN staging in cancer patients.[113]

Given the promising potential of nanoparticles in the clinical treatment of solid tumors, carbon nanoparticles stand out as an ideal platform for tumor detection and immunotherapy due to their remarkable chemical and physical properties. However, the small size of carbon nanomaterials, which allows them to penetrate cellular membranes, can also trigger inflammatory responses that may lead to harm in both animals and humans. For instance, the toxicity study about multi-walled carbon nanotubes (MWCNTs) revealed high phagocytic activity towards undifferentiated HL60 cells and cytotoxic effects on differentiated HL60 cells. Additionally, the strong mechanical properties of graphene oxide have been shown to cause substantial damage to cells.[114]

Currently, the precise mechanisms by which carbon nanomaterials harm animals remain unclear, largely due to a lack of critical clinical evidence. Nonetheless, many studies suggest that with effective modification, carbon nanomaterials can play a significant role in the biomedical field. To address concerns surrounding their safety and enhance credibility, it is crucial for scientists to conduct thorough research in toxicology and pathology. Looking ahead, researchers are expected to develop innovative synthetic methods or create novel composite materials to improve cancer treatment outcomes and enhance human health.

Discussion and Future Remarks

Limitations of Traditional Treatments

Cancer remains a major global health challenge with 14 million people are diagnosed with cancer, and approximately 8 million succumb to tumor-related complications.[115,116] Traditional cancer treatments include surgery, chemotherapy,

radiotherapy, and phototherapy (including photodynamic and photothermal therapy).[117–121] However, these treatments still have several limitations. Surgery often fails to eliminate all tumor cells, while chemotherapy and radiation therapy, although targeting rapidly dividing cancer cells, can also cause adverse effects on various organs.[122] For example, 5-fluorouracil (5-FU), the third most commonly used chemotherapeutic agent worldwide for treating malignant solid tumors, has been shown by Sara et al to cause significant cardiotoxicity, with reported incidence rates ranging from 0 to 19.9% in clinical trials.[123] Oxaliplatin, widely used as a first-line treatment for gastrointestinal malignancies, particularly colorectal cancer, can cause moderate to severe neuropathy when administered at high doses (>85 mg/m² IV). As a result, the chemotoxicity and radiotoxicity associated with cancer treatment significantly affect both treatment efficacy and patient quality of life.[124] Moreover, challenges such as immune tolerance,[125] high metastatic rates,[126,127] and recurrence[128] still led to the persistently high cancer mortality rates.

Integration of Carbon Nanomaterials with Immunotherapy

With the continuous advancement of science and technology, immunotherapy has increasingly integrated with nanotechnology, offering new hope for cancer treatment.[129–137] Due to their enhanced stability, flexible surface binding, controllable physicochemical properties, and efficient drug delivery capabilities,[138] nanomaterials can effectively serve as carriers for targeted drug delivery.[139–141] Among various exceptional nanomaterials, carbon-based nanomaterials have garnered significant attention in tumor immunotherapy due to their superior electrical conductivity,[142] chemical stability,[143] biocompatibility,[144] and versatility.[145] Notably, carbon dots, as zero-dimensional carbon-based nanomaterials, stand out for their excellent optical properties, biocompatibility, and low toxicity, making them highly promising for applications in biosensing,[146] bioimaging,[147] drug delivery,[148] and photothermal/photodynamic therapy[149,150].

In the previous discussion, we observed that carbon dots can form recombinant carriers by binding with materials such as RTB, mannose, and OVA. This interaction stimulates immune cells, including macrophages, dendritic cells, and NK cells, to release inflammatory cytokines such as IL-6, IL-1β, and TNFα, strongly inducing the expression of immune responses and thereby remodeling the suppressive tumor microenvironment. Additionally, other carbon nanomaterials have demonstrated positive outcomes in immunotherapy. For instance, graphene quantum dots (GQDs) form complexes through π-π interactions, effectively treating leukemia-induced immunosuppression. Carbon quantum dots (CQDs) combined with chlorogenic acid to form ChA-CQDs composites recruit a substantial number of tumor-infiltrating immune cells, activating anti-tumor immune responses. Furthermore, multi-walled carbon nanotubes (MWCNTs) conjugated with peptides can enhance cytokine secretion, stimulating T cell differentiation and proliferation.

Carbon Nanocomposites in Tumor Biomarker Detection

Carbon nanomaterials exhibit a range of "anomalous" physical and chemical properties due to quantum size effects, macroscopic quantum tunneling effects, surface effects, and their small size. These distinctive features make them promising candidates for use in immunosensors.[151,152] Their high specific surface area enhances the loading capacity of biomolecules and facilitates faster electron transfer rates, thus addressing some of the inherent limitations of biomolecular sensors. Additionally, carbon nanoparticles can act as carriers for signal molecules, improving the stability, selectivity, and sensitivity of electrochemical immunosensors used for tumor marker detection[153,154].

Recent studies have increasingly explored materials such as SWCNH, MWCNTs, and GO in the context of biomedical immunosensors. For example, functionalized SWCNH composites have shown the capability to detect the atherosclerosis biomarker protein MCP-1. Carboxylated MWCNTs, when combined with polyamidoamine (PAMAM) dendrimers, have been utilized in pulse voltammetry for detecting the tumor marker α2,3-sial- gs. Furthermore, the CS-MWCNTs-GO-PBPTA electrochemical immunosensor, which integrates MWCNTs and graphene oxide, enables quantitative detection of the tumor marker ST6Gal-I. These findings highlight that carbon nanomaterials offer significant potential not only in tumor immunotherapy but also in the detection of tumor biomarkers.

Conclusion

This review provides an overview of the recent advancements in carbon nanomaterials, for cancer immunotherapy, emphasizing their potentials as drug carriers and their capabilities in tumor biomarker detection. Specifically, it covers carbon dots, graphene quantum dots, carbon quantum dots, carbon nanotubes, and amphiphilic carbon dots. The review also examines the potential opportunities, future prospects, and challenges associated with their clinical translation. Despite the promising applications, the use of carbon nanomaterials in clinical oncology presents several significant challenges. Conventional preclinical models, which typically involve the implantation of cancer cell lines, often fail to accurately mimic the human immune system's authentic response to tumors. Additionally, because cancer evolves over an extended period within the human body, the immune system undergoes continuous reprogramming, a dynamic that preclinical models struggle to replicate, particularly in terms of the ongoing accumulation of mutations associated with cancer progression.[155] Furthermore, the distribution, metabolism, and organ accumulation of carbon nanomaterials within the human body remain poorly understood.[156] Even if nanocarriers can penetrate tumor blood vessels, they still face significant challenges in overcoming tissue barriers to effectively deliver drugs into cancer cells, limiting their therapeutic efficiency.[157] Another major hurdle is the identification of novel receptors or targeting molecules to precisely direct nanocarriers to specific organs or tumors, enhancing the accuracy of drug delivery.[158,159] Future research should focus on developing stimulus-responsive nanocarriers capable of controlling the release of anticancer drugs, thereby increasing the local concentration at the target site while minimizing side effects on healthy tissues, ultimately aiming for more effective and durable cancer treatment[160].

Data Sharing Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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