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REVIEW

How Advanced are Cancer Immuno-Nanotherapeutics? A Comprehensive Review of the Literature

Dhananjay Yadav[1,*], Nidhi Puranik[2,*], Anju Meshram[3,*], Vishal Chavda[4], Peter Chang-Whan Lee[5], Jun-O Jin[6]

[1]Department of Life Science, Yeungnam University, Gyeongsan, 38541, South Korea; [2]Biological Sciences Department, Bharathiar University, Coimbatore, Tamil Nadu, 641046, India; [3]Department of Biotechnology, Kalinga University, Naya Raipur, Chhattisgarh, India; [4]Department of Pathology, Stanford School of Medicine, Stanford University Medical Center, Stanford, CA, 94305, USA; [5]Department of Biomedical Sciences, University of Ulsan College of Medicine, Asan Medical Center, Seoul, 05505, South Korea; [6]Department of Microbiology, University of Ulsan College of Medicine, Seoul, 05505, South Korea

*These authors contributed equally to this work

Correspondence: Peter Chang-Whan Lee, Department of Biomedical Sciences, University of Ulsan College of Medicine, Asan Medical Center, Seoul, 05505, South Korea, Email pclee@amc.seoul.kr; Jun-O Jin, Department of Microbiology, University of Ulsan College of Medicine, Seoul, 05505, South Korea, Email junojin@amc.seoul.kr

Abstract: Cancer is a broad term for a group of diseases involving uncontrolled cell growth and proliferation. There is no cure for cancer despite recent significant improvements in screening, treatment, and prevention approaches. Among the available treatments, immunotherapy has been successful in targeting and killing cancer cells by stimulating or enhancing the body's immune system. Antibody-based immunotherapeutic agents that block immune checkpoint proteins expressed by cancer cells have shown promising results. The rapid development of nanotechnology has contributed to improving the effectiveness and reducing the adverse effects of these anti-cancer immunotherapeutic agents. Recently, engineered nanomaterials have been the focus of many state-of-The-art approaches toward effective cancer treatment. In this review, the contribution of various nanomaterials such as polymeric nanoparticles, dendrimers, microspheres, and carbon nanomaterials in improving the efficiency of anti-cancer immunotherapy is discussed as well as nanostructures applied to combination cancer immunotherapy.

Keywords: nanotechnology, combination therapy, cancer therapy, engineered nanomaterials, nanotoxicity, synergistic therapy

Introduction

Cancer is a major cause of morbidity and mortality around the world in recent years.[1,2] The 5-year relative survival rate for all cancer-related malignancies diagnosed between 2009 and 2015 was 67% based on data reported in Cancer Statistics, 2020.[2] Lack of early tumor diagnosis and effective therapies remain major problems to be addressed. The conventional cancer treatment approach involves surgical intrusion, phototherapy, and chemotherapy to diminish tumors and prevent cancer metastasis. Chemotherapy is frequently associated with side effects induced by off-target toxicity as a result of drug non-specificity.[3] Rapid advancements in nanomedicine have led to the implementation of novel therapeutic nanotechnology-based applications and improved patient care.[4] Cancer immunotherapy in combination with functionalized nanoparticles has emerged as an alternative treatment option that is highly effective.[5,6] The relevance of stimuli-responsive nanosystems and nanomaterial-based cancer immunotherapy should not be underestimated.

Cancer immunotherapy is a new type of treatment that stimulates the immune system to attack cancer cells.[7,8] Despite the existence of various immunotherapeutic drugs to treat cancer, low patient response rates and the possibility of immune-related side effects are two important obstacles to successful treatment. The development of activatable cancer immunotherapies can help to address both of these challenges. Due to the fast evolution and integration of

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nanotechnology, material science, and biomedical engineering, different nanomaterials have been developed and utilized in the field of cancer immunotherapy.[9–11] Activatable immunotherapeutic nanoagents are the result of the convergence of stimuli-responsive nanomedicine and immunotherapy.[12,13] Immunotherapeutic nanoagents require activation via internal or external stimuli to function,[14,15] rewire the tumor microenvironment, and activate anticancer immunity, while lowering the risk of immune-related side effects. Immunotherapeutic nanoagents exhibit advantages such as optimal biodistribution, selective cell targeting, and regulated immune activation.

Nanomedicines contribute to the safe and effective use of immunotherapies in clinical trials due to their controlled delivery and modular flexibility. The convergence of nanomedicine and immunotherapy, with an emphasis on molecular and nanoengineering approaches to cancer immunotherapy, is the subject of this review. Specifically, this article discusses different strategies of cancer immunotherapy and the role of nanoparticles in enhancing the immunotherapeutic effect of different immunomodulatory drugs with a focus on activatable immunotherapeutic nanoagents, as well as the advantages and obstacles of clinical translation.

Where Do We Stand in Cancer Immunotherapeutics?

In cancer immunotherapy, tumor cells are eliminated by manipulating the immune system to produce long-lasting anticancer immune responses. Adoptive T cell therapy and chimeric antigen receptor (CAR)-T cell therapy are two of the most popular immunotherapy modalities today. Adoptive cell therapy (ACT) is another common immunotherapy in which effector immune cells, primarily autologous T cells with CAR and T cell receptors (TCR), are sampled from patients, activated, and expanded ex vivo before being returned to the patients in expectation of a therapeutic outcome. Clinical trials using CAR-T cells have yielded impressive and encouraging results, particularly in patients with B-cell acute lymphoblastic leukemia, although their impact on solid tumors has been muted. Adoptive T cell therapy, however, has been associated with problems such as cytotoxicity, poor in vivo persistence, and cytokine release syndrome (CRS).[16] Therefore, achieving high selectivity against cancer cells is crucial in immunotherapy. Various cancer treatment and management strategies, such as CAR-T cell therapy, cell-assisted delivery, checkpoint blockade, and cancer vaccines are illustrated in Figure 1.

How Advanced are Cancer Therapeutic Vaccines?

Vaccines are used to deter future infections by inducing the production and activation of memory cells. To create memory responses, the overall immune response mechanism must be activated starting with the antigen-presenting cells (APCs).

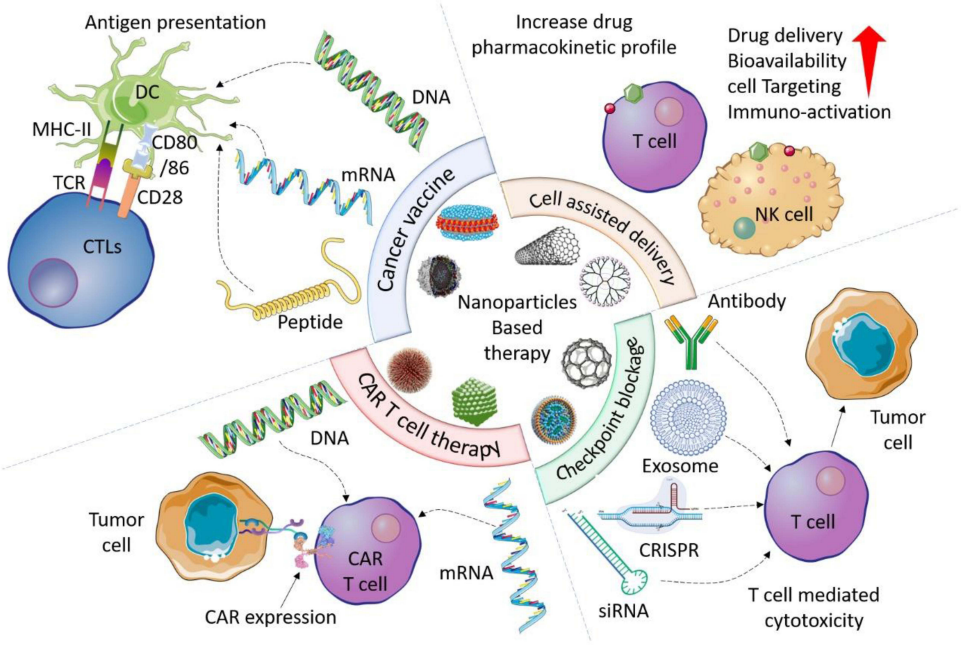

Figure 1 Strategies for cancer management and treatment, currently in use. Data from these studies.[16–18]

Among APCs, dendritic cells (DCs) are well-known direct inducers of T cell activity. DCs present phagocytic antigens on their surface by utilizing either an MHC class II extracellular antigen or an MHC class I intracellular antigen. Antigens bound to MHC class II are recognized by CD4 T cells, and antigens bound to MHC class I are delivered to CD8 T cells to activate respective cells, which are subsequently differentiated into helper T (Th) cells and cytotoxic T lymphocytes (CTLs), respectively. Therefore, the vaccines utilizing cancer antigens induce antigen-specific T cell immunity which can be exploited for cancer treatment.

The immune system's ability to distinguish between self-antigens that are normally expressed on the surface of healthy cells and those that are abnormally expressed on cancer cells is key for cancer vaccine development. The key benefits of cancer vaccines are their moderate toxicity, rapid response to tumor-associated antigen (TAA) exposure, induction of extremely precise adaptive immune responses, and establishment of immunologic memory while controlling or removing residual disease.[17] However, for a therapeutic vaccine to be effective in cancer treatment, DC-mediated immune activity is required. Cancer antigens are derived from normal cells and do not produce an immune response in our body. Thus, immune stimulatory molecules in the form of appropriate adjuvants must be combined with cancer antigens to induce DC-mediated antigen-specific T cell immunity.

What is the Potential of Immune Checkpoint Inhibitors?

A novel class of cancer medicines known as immune checkpoint inhibitors has demonstrated remarkable success over a relatively short period of clinical testing. These medications have shown a sharp rise in clinical use since their first approval in 2011 for metastatic melanoma.[18] Immune checkpoints are receptors expressed on cells of the immune system; they allow for the dynamic regulation of immune homeostasis and play an important role in T cell activity. Programmed cell death protein 1 (PD-1) and PD-1 ligand (PD-L1) are immune checkpoint proteins expressed on T lymphocytes, tumor cells, and myeloid cells that have invaded tumors.[19]

Many aspects of cancer therapy have been revolutionized by the recent introduction of immune checkpoint inhibitor (CPI) antibodies, although their efficacy remains restricted since several patients fail to respond for unspecified reasons. Local signaling has been shown to establish immunosuppressive microenvironments within tumors in several human and animal studies. Emerging evidence suggests that introducing immunostimulatory molecules into tumors can have therapeutic effects. Such molecules in the form of carrier nanoparticles provide a realistic technique for increasing CPI distribution and efficacy.[20]

What is the Potential of Natural Killer (NK) Cell-Mediated Immunotherapy?

NK cells are part of the innate immune system's lymphoid cells and play a crucial role in immunological surveillance. NK cells act as a link between innate and adaptive immunity, while their infiltration into tumor areas is positively correlated with increased patient survival. Target cells are exposed to the cytolytic effect of NK cells, which induce apoptosis.[21] NK cells are toxic to cancer cells without causing any sensitization to cancer antigens. Similar to CTLs, NK cells also secrete granules such as perforin and granzymes to lyse cancer cells. In addition, NK cells secrete interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) to trigger adaptive immune responses. Due to the immunostimulatory function and anti-cancer effect of NK cells, their immunotherapeutic potential is being actively investigated. Current challenges for using NK cells in cellular immunotherapy include loss of NK cell cytotoxic ability and a decline in the number of activating receptors, which lead to a reduction in long-term effectiveness.

What Do We Know About the Tumor Microenvironment (TME)?

The tumor microenvironment (TME), a heterogeneous, complex organization consisting of tumor, stroma, and endothelial cells, is characterized by the crosstalk between the tumor and innate and adaptive immune cells. Over the past decade, immune cells in the TME have been demonstrated to be essential for both hindering and driving tumor growth. The role of T cells in this process has been extensively studied. Numerous studies have suggested that B cells play a crucial part in anticancer immunity. However, the TME contains a wide variety of B cell types, including memory and terminally differentiated plasma cells as well as naive B cells.[22]

TME induces the growth of cancer cells while preventing the attack from immune cells by tricking them to recognize cancerous tissue as peripheral tissue. Regulatory immune cells that are directly involved in this action include regulatory T cells, Type 2 macrophages, and myeloid-derived suppressor cells.

What is the Potential of Regulatory T Cells (Tregs) in Cancer Immunotherapy?

All organs, including the ones in the circulatory system, contain specialized immune cells called Tregs. Tregs maintain immunological homeostasis and regulate countermeasures to inhibit excessive immune activation to avoid autoimmune responses.[23] Activated immune cells not only remove invading pathogens but can also damage normal cells. Tregs help to regulate the immune system after it is activated. Since Tregs contribute to immune suppression, they play crucial roles in hindering antitumor immunity. The majority of solid tumors contain Tregs that inhibit the antitumor immune response, which can cause immunosuppression and result in a poor prognosis. By suppressing self-reacting T cells, avoiding autoimmunity, and regulating chronic inflammatory conditions, Tregs actively contribute to the preservation of immunological self-tolerance.[24] Inside the TME, naive T cells can differentiate into Tregs. As a result of their strong immunosuppressive ability, Tregs inhibit anti-cancer immunity, favoring the growth of cancer cells. Therefore, removing or inhibiting the activity of Tregs in the TME is a potential strategy for cancer immunotherapy.

What is the Role of Macrophage Polarization in Cancer Immunotherapy?

Due to their great phenotypic variability and functional diversity, macrophages are key players in both innate and adaptive immunity. Furthermore, they are important for immunology, tissue and systemic inflammation, and tissue regeneration.[25] Macrophages constitute more than 50% of the tumor mass in solid tumors, while tumor-associated macrophages (TAMs) can originate from both local and circulating progenitor monocytes.[26] TAMs participate in the formation of the tumor microenvironment and play a major role in the TME functions.[27] Inside the TME, cancer cells use various substances such as IL-10, CCL2/3/4/5/7/8, VEGF, CXCL12, and the platelet-derived growth factor (PDGF), to transform type 1 macrophages (M1) into type 2 macrophages (M2). TME M2 macrophages express various cytokines, chemokines, and growth factors that contribute to cancer potential, growth, and metastasis and lead to cancer exacerbation. Therefore, converting M2 macrophages into M1 macrophages is being investigated as a strategy to prevent cancer growth and improve immunotherapy efficiency.

What is the Role of Myeloid-Derived Suppressor Cells (MDSCs) in Cancer Immunotherapy?

MDSCs include a diverse population of immature myeloid cells that have immunosuppressive roles in tumor-bearing mice or humans with malignancies; they suppress T cell activity and encourage tumor immune evasion in the TME.[28,29] MDSCs can be divided into two main subsets, polymorphonuclear MDSCs and monocytic MDSCs. Both types of MDSCs are observed inside a tumor. Activated MDSCs promote cancer growth via several mechanisms, including immune evasion, angiogenesis, and the formation of a metastatic environment. Among these, immune evasion is the most common function of MDSCs.

MDSCs express high levels of inducible nitric oxide synthase (iNOS), leading to the production of nitric oxide (NO). The function of NO on T cells has been well studied and includes inhibition of activation, proliferation, and differentiation of T cells. Moreover, the MDSC-produced NO induces apoptosis in T cells, and MDSCs also produce reactive oxygen species (ROS) that inhibit T cell function (Figure 2). As T cells are the main cells that exhibit cytotoxicity against cancer cells in immunotherapy, eliminating MDSCs can be a strategy for enhancing cancer immunotherapy.

What are the Potential Carriers for Drug Delivery in Cancer Therapy?

Nanoparticles

Drugs with low solubility are difficult to formulate using traditional methods due to issues such as the slow onset of action, low oral bioavailability, dose proportionality, inability to maintain steady-state plasma levels, and undesirable side effects. Therefore, traditional formulations may lead to over- or under-medication, as well as poor patient compliance.[30,31] To overcome this problem, nanotechnology is being widely utilized as a promising technique for developing drug delivery systems, particularly for medications with poor solubility, limited permeability, insufficient bioavailability, and other biological shortcomings (Figure 3). Various theragnostic biodegradable carriers, liposomes, carbon nanoparticles, quantum

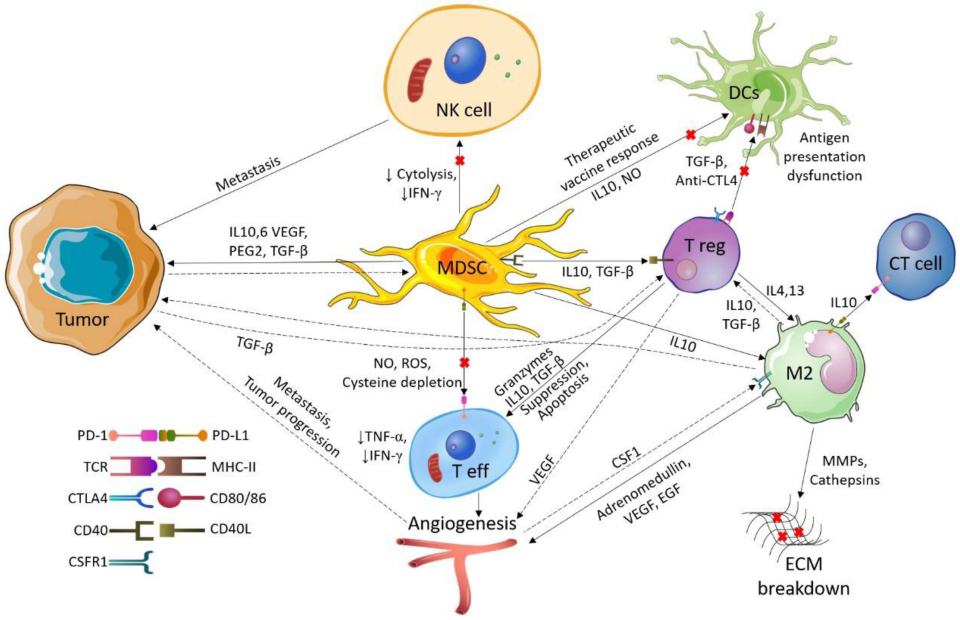

Figure 2 Role of MDSCs in tumor growth by targeting different immunological cells. Data from these studies.[24,29]

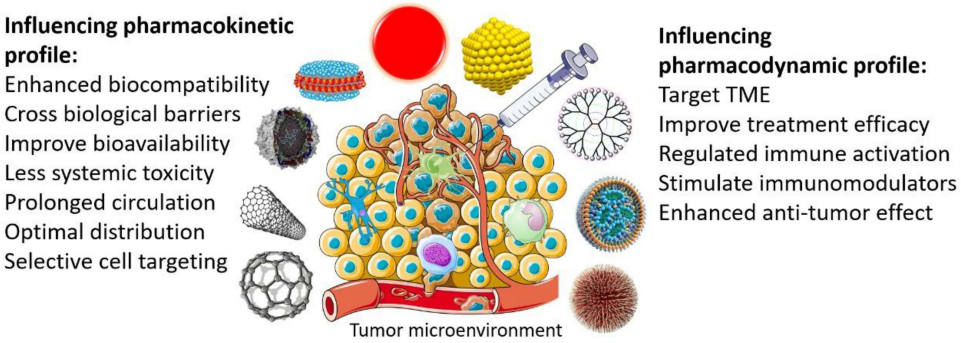

Figure 3 Role of different kinds of nanoparticles to increase the pharmacokinetic properties of drugs in cancer treatment. Data from these studies.[30,31,36]

dots, polymeric micelles, dendrimers, and metallic nanoparticles are examples of nanosystems used for drug delivery in cancer treatment.[32–36] Table 1 provides a quick overview of the various nanomaterials employed in cancer therapy.

Liposomes

Liposomes are colloidal or nano-particulate carriers with a size range of 80–300 nm. Among the various types of nanoparticles, liposomes are the first and most well-established drug-delivery vehicles, with a plethora of clinical products in the market today. Liposomes are bilayer spherical vesicles composed of amphiphilic lipid molecules widely used in cancer therapy.[56–58] Their advantages include effectiveness, biocompatibility, non-immunogenicity, increased solubility of therapeutic agents, and capacity to encapsulate a wide range of medications.[59] Furthermore, liposomes have demonstrated remarkable therapeutic potential as payload carriers for delivery to specific sites.[60] Overall, liposome-mediated drug delivery systems (DDS) improve the therapeutic payload's pharmacokinetic and pharmacodynamic profiles, stimulate controlled and sustained drug release, and have negligible systemic toxicity compared to free DDS.[61]

Polymeric Nanoparticles (PNPs)

PNPs have sparked a lot of interest in various fields because of their ability to modify drug activity, exhibit controlled drug release, and improve drug adhesivity or penetration time in the skin, which are all properties that render them ideal

Table 1 Characteristics of Various Nanomaterials Used in Cancer Therapy

Nanomaterial Category	Characteristic Structure	Advantages	Limitation	References
Liposomes	Lipid bilayer	Biocompatibility, non-immunogenicity, increase solubility of associated molecule	Less stable, hydrophilic drug	[37–39]
Polymeric nanoparticles (Nanospheres/ Nanocapsules)	Polymer-based NPs having lipophilic core	High stability, low outflow of drugs	Toxic when administered intravenously	[40,41]
Dendrimers	Three-dimensional branched polymers	Presence of functional group, enhances the solubility and availability of hydrophobic drugs	Quick elimination from the precorneal region	[42,43]
Microspheres	Polymeric	Large surface area, high absorption rate on surface and long-term bio-availability of drugs	Difficult to design	[44,45]
Gold nanoparticles	Surface of gold atom has negatively charged group	High surface-to-volume ratio, hydrophilic in nature, surface modification is easy	Toxicity, quick elimination	[46,47]
Carbon nanoparticles (Carbon nanotubes)	Fullerenes or one or more graphene sheets	High cell penetration abilities, high stability, flexible to modify the surface and function	Non-biodegradable, cytotoxic, less solubility in water	[48,49]
Metallic nanoparticles (MNPs)	Metallic property containing nanoparticles, wire, rods, and capsules	Antibacterial properties, magneto-optical response	Related toxicity	[50,51]
Polymeric micelles (PMs)	Core/shell lipid based self-assembled structure	Easy synthesis, delay and control drug release, variability, give stability to hydrophobic drug	Depolymerization at dilution	[52–54]
Inorganic Non-metallic Nanomaterials	Unique size with adjustable Pore size	More drug loading capacity because of the large surface area, suitable pore volume	Very slow biodegradation, high degree of toxicity of NPs	[55]

Abbreviation: NPs, nanoparticles.

for cancer drug applications.[62,63] PNPs are nanocapsules or nanospheres with an average diameter of fewer than 1 μm, depending on their composition. PNPs are manufactured by two methods: dispersion of prepared polymers and monomer polymerization. PNPs are primarily used in targeted delivery systems as drug carriers for cancer therapy because of their favorable properties including being decomposable, biocompatible, non-toxic, extended circulation, and having an extensive payload capacity for encompassing therapeutic molecules.[64]

Polymeric Micelles (PMs)

PMs have been widely used in pre-clinical trials to treat cancer patients by delivering poorly soluble chemotherapeutic drugs.[65] PMs are spherical nanoscopic core/shell structures generated by the self-assembly of amphiphilic polymers with a mean diameter of 10–100 nm. They have grown in popularity as a result of numerous advantageous properties, including their ability to solubilize a variety of low-solubility pharmaceutical agents, biocompatibility, vitality, and propensity to accumulate in pathological areas.[66,67] Various polymeric combinations are used for optimum loading, stability, and systemic circulation, and thereby contribute to the recognition of target cancer tissue by the wide range of polymeric blocks utilizing both hydrophobic and hydrophilic nanomaterials.[54] Furthermore, PMs are easily customized by altering the number of monomers in each polymeric chain.

Dendrimers

Dendrimers are a new type of polymer with easily modifiable structures and nanometric dimensions. Dendrimers are globular macromolecules that range in size from 1 to 100 nm and include domains such as a central core, a hyperbranched mantle, and a corona with reactive functional groups on the periphery.[68] Dendrimers are virtually perfect spherical nanocarriers with predictable features due to the high level of control over the synthesis of their dendritic architecture. Many different types of dendrimers have been effectively developed for drug delivery, including polyamidoamine (PAMAM), poly(propylene imine) (PPI), poly(glycerol-co-succinic acid), poly–l–lysine (PLL), melamine, triazine, poly(glycerol), poly[2,2–bis(hydroxymethyl)propionic acid], poly(ethylene glycol) (PEG), carbohydrate-based, and citric dendrimers. PAMAM and PPI are the most studied vectors for medical applications.[69]

Microspheres

Microspheres can be delivered using a syringe needle and are used to encapsulate a wide range of medications including tiny molecules, proteins, and nucleic acids. Polymeric microspheres are attractive carriers for numerous controlled delivery applications because of their ability to encapsulate a range of medications, their biocompatibility, high bioavailability, and prolonged drug release characteristics.[70]

Carbon Nanoparticles and Carbon-Based Nanosystems (CBNs)

Carbon-based nanoparticles (NPs) have attracted interest because of their unique structural dimensions and physico-chemical features.[71] Carbon nanotubes (CNTs) and carbon nanohorns (CNH) are two types of carbon nanocarriers utilized in DDS. CNTs have a unique design generated by rolling single or multiple layers of graphite with large surface areas and good electrical and thermal conductivity. CBNs such as graphite (GT), fullerenes, CNTs, graphene oxide (GO), reduced GO (rGO), and GO–Ag NP nanocomposites have been extensively used as drug delivery carriers.[72,73] These materials have great drug-loading capacity, post-chemical modification, increased biocompatibility, and decreased immunogenicity because of their high optical activity and large multifunctional surface area.[74]

Metallic Nanoparticles (MNPs)

Metallic nanoparticles have a wide range of properties that make them excellent drug-delivery vehicles. Easy handling with the aid of an external magnetic field, the ability to apply passive and active drug administration techniques, visibility (MNPs are used in MRI), and improved absorption by the target tissue resulting in efficient therapy at therapeutically relevant concentrations are a few manifestations of MNP effectiveness.[75] MNPs have been extensively used both in biological and engineering studies. MNPs can be manufactured and modified with different chemical functional groups, resulting in a variety of biomedical applications.[76] MNPs range in size from 1 to 100 nm and exhibit optical properties dependent on their form and size. MNPs employed in biological applications include Ag, Au, palladium, platinum, zinc oxide, iron oxide, and in various forms such as nanoshells and nanocages, to name a few.[62]

Cancer Immunotherapy Using Nanoparticles

Current trends in cancer treatment involve the enhancement of immunotherapy effectiveness by combining two or more treatment methods. One example of combination therapy is based on immunotherapy and nanomaterials. Nanomaterials have the advantage of enhancing the action of various drugs via their interaction mediated by a variety of functional groups. This was demonstrated in a study where bromelain encapsulated gold nanoparticles (B-AuNPs) formed a conjugate with cisplatin (CIS) and doxorubicin (DOX), resulting in a considerable increase in the efficiency of both chemotherapy drugs. The enhanced inhibitory effect of the combinations compared to single drug-based chemotherapy show that the use of combination medicines (B-AuNPs conjugated with CIS and DOX) can be extremely helpful in osteosarcoma treatment.[77] Shiva Prasad Kollur et al studied luteolin-fabricated ZnO nanostructures exhibiting PLK-1 mediated anti-breast cancer activity, which was superior to the activity exerted by each of the two components when tested individually.[78]

Curcumin is an active ingredient of dietary spice that has various pharmacological properties including anticancer activity and has been used recently in breast cancer treatment. Curcumin conjugated with poly-glycerol-malic acid-dodecanedioic acid (PGMD) NPs resulted in a formulation with increased anticancer activity compared to that of curcumin alone.[79] Similar results were reported in a drug delivery study with Diosgenin-loaded PGMD NPs, which displayed a significantly higher anticancer potential compared to the free drug.[80] Another study conducted by the same group showed that PLGA nanoparticles conjugated with PEI-EPI-PTX represent a feasible anti-cancer strategy with clinical advantages and may one day provide lung cancer patients with an effective treatment.[81]

Next, we will discuss nanomaterials used alone in therapeutic trials or combination with immunotherapy methods.

Induction of Antigen-Specific Immunity by Nanomaterials

Nanoparticles have the potential to initiate and influence immune responses by targeting APCs and delivering coordinated signals that can prompt an antigen-specific immune activation.[82] New formulations of NPs that can specifically calibrate the immune response have been made possible by innovative methods in NP design that enable them to interact with particular cellular and molecular targets.[83] Yang et al coated R837-loaded PLGA nanoparticles (NP-R) with cancer cell membranes and then modified them in the mannose moiety (NP-R@M-M) to increase their therapeutic effect.[84]

Immune Checkpoint Blockade Contained Nanoparticles

Immune checkpoint blockade (ICB) therapy has shown remarkable success in treating various human cancers, including melanoma and lung cancer by targeting PD-1 and its ligand.[85] However, the response rate of this treatment remains relatively low in most cases.[86] To enhance the success rate of ICB therapy, CPIs were combined with NPs shown to play a critical role in target-specific drug delivery. The encapsulation of immune CPI into NPs not only elevated the immunotherapeutic responses but also decreased off-target effects.[87,88] A recent study demonstrated high efficacy and immunotoxicity of small-sized silver NPs combined with an anti-PD-1 monoclonal antibody (mAb) for the treatment of melanoma in both immunodeficient and immunocompetent mouse models.[89] Based on several studies, the creation of peptide-based nanocomplexes containing immunostimulatory oligonucleotides greatly improved the effectiveness of selected drugs to trigger toll-like receptor activation.[90–93] In mouse cancer models, the administration of immunostimulatory nanocomplexes containing CpG oligonucleotides produced antitumor effects and improved the efficacy of CPI antibody therapy, allowing for a significant reduction in the dose needed to achieve therapeutic effects.[20,94]

Chemoimmunotherapy

Chemotherapy and immunotherapy are the third and seventh anticancer therapeutic cornerstones, respectively. Surgery and therapies including radiation, hormone, and cell therapy are the most common post-cancer treatments.[95] Combinations of basic chemotherapy and immunotherapy may achieve additive or even synergistic antitumor therapeutic effects by attacking different parts of tumor biology and overcoming their own limits.[96,97] Wang et al used an engineered therapeutic agent to develop a chemoimmunotherapy-based combinatorial method. In tumor-bearing mice, a hydrogel scaffold containing an ROS-sensitive moiety could locally distribute gemcitabine (GEM) and an anti-programmed death ligand antibody (αPDL1) with different kinetics promote the formation of an immunogenic tumor phenotype and result in immune-mediated tumor rejection.[98]

Min et al created eco-friendly and biocompatible antigen-capturing nanoparticles (AC-NPs) that ameliorated cancer immunotherapy outcomes. Delivering tumor-specific proteins to APCs via AC-NPs has been reported to dramatically boost the efficacy of PD-1 administration in the B16F10 melanoma model, resulting in a 20% increase in cure rate when compared to that of the control.[99] AC-NPs aided the proliferation of $CD8^+$ cytotoxic T cells and enhanced the ratios of $CD4^+$/Treg and $CD8^+$/Treg.[99] This could be considered a unique nanotechnology-based technique for improving cancer immunotherapy.[99]

Photoimmunotherapy

Photoimmunotherapy (PIT) is a well-known cancer treatment therapy that combines phototherapy with immunotherapy by injecting a conjugate photosensitizer (IR700) and a mAb to target an expressed antigen on the surface of cancer cells.

PIT improves the immune response in the treatment of residual tumors and metastatic cancer.[100] However, complete eradication of the tumor is hindered by the non-specific delivery of immunotherapeutic molecules. NPs play a crucial role in overcoming this problem by acting synergistically with PIT and acting as carriers for immunotherapeutic drugs.[101] Photothermal therapy (PTT) has the potential to directly trigger tumor cell apoptosis, and it can be paired with immune system adjustments to boost immune response levels. In previous studies, we have shown that PIT can treat 1st transplanted tumor and prevent 2nd challenged metastatic lung cancer growth in mice (Figure 4). The 1st tumor was treated by PTT, which induced the generation of tumor cell antigens. Furthermore, NPs containing immune stimulatory molecules promoted DC activation, which induced cancer antigen-specific immune responses and prevented 2nd tumor challenge in the mice.[102–106] Chen et al manufactured a PLGA nanoparticle to co-load indocyanine green (ICG) and imiquimod (R837, a Toll-like receptor 7 agonist) for PDT and immune response activation.[107]

Combination Nanoparticles with Checkpoint Small Interference RNAs (siRNA)

Small interference RNAs (siRNAs) are endogenous molecules that induce a variety of cellular responses. Although siRNA causes target mRNA to be degraded, it can also impede the translation of other slightly mismatched mRNAs when acting as miRNA.[108,109] The delivery of siRNA to the target cell population in vivo is a challenge for siRNA-based cancer and other disorder therapies. For siRNA-based therapies to be successful in combating cancer, tumor cells must undergo potent and effective gene silencing. An ideal systemic siRNA delivery system should be biocompatible, eco-friendly, and non-immunogenic, protect siRNA from serum nucleases during circulation and release into endosomes, and avoid rapid hepatic or renal clearance.[110] NPs have been proven to be effective carriers for the delivery of siRNA molecules. Due to the reduction of cytokine release, the interaction of PD-L1 on tumor cells with PD-1 on T cells may cause immune evasion, resulting in a weakened antitumor effect and metastasis.[111] As a result, specifically knocking down the expression of PD-L1 on tumor cells is a promising strategy. To load PD-L1 siRNA and the photosensitizer, Wang et al created 1,2-epoxytetradecane alkylated oligoethylenimine-containing (POP) hybrid micelles.[112]

Strategies Using Immune Checkpoint Inhibitors for Synergistic Cancer Therapy

Synergistic drugs based on ICB therapy have garnered interest in recent years and provided promising outcomes in tumor therapy, yet fundamental and clinical investigations of an immune checkpoint inhibitor (ICI)-based combination therapies are problematic. The selection of biocompatible and clinically appropriate DDSs is a main priority. The majority of magnetic nanostructure hydrogels, and particularly nanocarriers used in immune checkpoint blockade therapy-based synergistic therapy, contain a variety of organic and inorganic materials, including synthetic polymers and polymer-drug conjugates, altered natural polymers, and mesoporous silica, all of which have been proven to be "biocompatible" to some extent.[113]

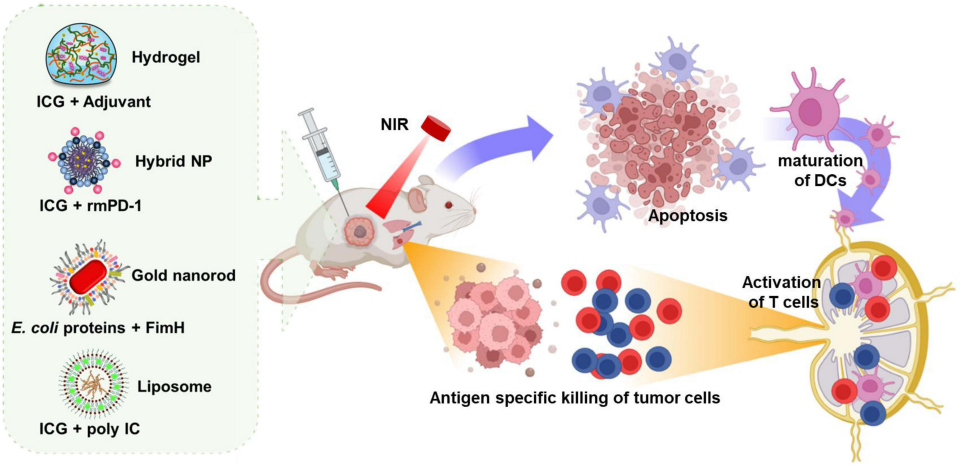

Figure 4 Photoimmunotherapy for treatment of tumor and its metastasis by nanomaterials. Data from these studies.[102–107]

Furthermore, the development of better DDSs intended to increase tumor targeting and lowering drug distribution in non-target organs should reduce immune-related adverse effects (irAEs) associated with ICIs (eg, integration of both chemotherapeutic drugs and ICIs in NPs). As a result, the clinical translation of synergistic therapies based on chemotherapy and radiation therapy in combination with ICB therapy is likely to be better and faster.[114] Overall, ICI-based synergistic medications have broadened the "arsenal" of cancer treatment choices. The current research progress has provided a breakthrough for the future widespread use of ICI-based synergistic medications. In the fight against cancer, synergistic therapy based on ICIs will give doctors more alternatives and patients greater hope.[113]

The term "viral oncolysis" refers to the viral infection that causes the death of tumor cells.[115] Oncolytic virus (OV) therapy has several benefits. Firstly, OVs can infect tumor cells and promote tumor lysis while avoiding the typical pathways of drug resistance.[116] Secondly, viruses constitute an efficient treatment because they can proliferate in tumor cells and disseminate to neighboring tumor cells. Thirdly, many OVs can cause immunogenic death in the cells they infect. This boosts the host's anti-cancer immunity by producing pathogen- and injury-related chemicals that encourage dendritic cells to present TAAs.[117] More crucially, OVs and ICIs work in tandem to cause non-overlapping tumor cell toxicity. Their combined applications have exerted a significant impact on cancer treatment.[118]

Immunological adjuvants are auxiliary compounds that can be injected into the body simultaneously or before other treatments to avoid the body's immune responses to those treatments.[119,120] Interleukins (IL), as well as their activators and antagonists, are extensively employed as immunological adjuvants nowadays. In pancreatic cancer, for example, IL-6 has been demonstrated to induce immune CPB resistance.[121] Liu et al revealed that IL-6 generated by cancer-associated fibroblasts promotes the advancement of hepatocellular carcinoma (HCC) by attracting immunosuppressive cells.[122,123] As a result, they used IL-6 inhibitors in combination with a PD-L1 to treat HCC and achieved a favorable therapeutic response. Furthermore, local IL-12 buildup in the TME triggered the host's adaptive immune activation. Fallon et al employed recombinant murine IL-12 in combination with a PD-L1, Avelumab, and found that the MC38 tumor was inhibited 70% of the time.[124]

Customized nanoparticles functionalized with specific ligands are capable of reliably delivering encapsulated payloads to cancer cells.[125] Taking advantage of their nanoscale size and exceptional physicochemical characteristics, various nanomaterials have been developed, including carbon-based materials, liposomes, metallic nanoparticles, and dendrimers as effective DDS for cancer treatment. Additionally, they exhibit better pharmacokinetic and pharmacodynamic profiles over traditional formulations. Anticancer medications containing nanomaterials play an important role in cancer treatment. Current drug targeting and release strategies for effective cancer administration have been integrated with recent breakthroughs in nanomaterial engineering for improving cancer therapy. Although nanotoxicity is a mostly ignored aspect of nanotechnology, the side effects of NPs should be seriously considered.[126]

Conclusion and Future Prospects

Combination therapy improves therapeutic results without increasing toxicity, improves efficacy, and overcomes medication resistance in cancer patients, assuring long-term treatment effectiveness. The advantages of employing nanoparticles with anticancer drugs in combination therapies include drug payloads, longer circulatory time in blood, lower dosage, and uniform, constant drug release. Nanoparticle-mediated combination therapy has numerous advantages, but also some drawbacks, including a lack of pertinent pre-clinical models for evaluating target efficacy and a gap in collaboration among different engineers, scientists, doctors, and pharmaceutical industries. Currently, CPIs are used in techniques for immune-mediated cancer cell clearance employing synergistic nanomedicines. Effective medical prospects for combination therapy with ICB inhibitors have been established due to the versatile and modular nature of NP synthesis.

Only a small number of medications based on nanomaterials are currently used in clinical settings despite the vast amount of research. In the future, more work needs to be done to reduce toxicity, illuminate the mechanism of protein corona, enhance permeability, and improve retention mechanisms in the human body. Nanoplatforms are being created to target not only cancer cells but also the tumor microenvironment. Additional research directions include improving nanomaterial targeting specificity, drug capacity, efficacy, and bioavailability, as well as lessening the toxicity of nanomaterials and loaded drugs toward normal cells. Practical approaches include using precise targeting methods, tumor microenvironment triggered release strategies, combined therapies, and self-assembly nanoplatforms. Another crucial area for research is testing nanomaterials in environments more similar to those seen in vivo.

Overall, we think that the growth of nanobiotechnology will help lead to more effective therapies and medications to effectively treat cancer.

Author Contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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