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Nano Technology In Cancer Treatment

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ABSTRACT

Cancer is one of the primarily reasons of death worldwide and advanced techniques for therapy are urgently needed. The major aim of most nanocarrier applications has been to protect the drug from rapid degradation after device delivery and permitting it to reach tumour site at therapeutic concentrations, meanwhile averting drug delivery to normal sites as much as possible to reduce destructive effects. Cancer is a leading cause of death and negative quality of life globally. Even though numerous techniques are devised to reduce deaths, reduce chronic pain and improve the quality of life, there stays shortfall in the adequacies of these cancer therapies. Among the cardinal steps towards ensuring optimal cancer treatment are early detection of cancer cells and drug application with high unique it to reduce toxicities. Due to increased device toxicities and refractoriness with traditional cancer diagnostic and therapeutic tools, other strategies which include nanotechnology are being employed to improve diagnosis and mitigate disease severity. Over the years, immunotherapeutic agents based on nanotechnology have been used for several cancer types to reduce the invasiveness of cancerous cells while sparing healthy cells at the target site. Nanomaterials which includecarbon nanotubes, polymeric micelles and liposomes have been used in cancer drug design where they have shown considerable pharmacokinetic and pharmacodynamic benefits in cancer diagnosis and treatment. In this review, we outline the commonly used nanomaterials which are employed in cancer diagnosis and therapy. We have highlighted the suitability of these nanomaterials for cancer management based on their physicochemical and biological properties. We further reviewed the challenges that are related to with the various nanomaterials which limit their uses and abate their translatability into the scientific setting in certain cancer types.

INTRODUCTION

Cancer devastates tens of millions of lives each year despite great advances in medicine and technology [1, 2]. Decades of research continuously reveal the ever-dynamic nature of the disease, and although treatment options have improved, severe aspect consequences from harsh

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chemotherapies persist [3, 4]. Particularly, when aggressive cancers lie dormant then re-emerge, patients suffer when the need arises for more aggressive therapies [5–7]. One of the greatest challenges in finding a successful cancer treatment is the pervasive emergence of resistance mechanisms. Upon shutdown of initial oncogenic routes, resistance mechanisms are activated in parallel signaling pathmanners and re-route to allow for cancer to thrive [8, 9]. Heterogeneity can be found within different tumor cells, between patient tumors, amongst genetic mutations, and epigenetic patterns, all of which can limit responses to therapeutics, further permitting for drug resistance [10–13]. Clonal heterogeneity affects overall tumor biology and is known to force metastasis and cancer progression [14]. Although new targets and therapies can advance cancer treatments, the dynamic nature of cancer finds a manner to survive. The strategy against cancer needs to shift from finding new therapies to improving existing therapies and diagnostics in innovative, effective, and plausible manners. Pain is experienced by 55% of patients undergoing cancer treatment and 66% of patients with advanced stage cancer [15]. Chemotherapies without distinct targeting mechanisms kill cancerous and noncancerous cells alike, therefore the deviceic toxicity will continue to deteriorate patient quality of life. Furthermore, the benefts of early detection are clear. Cancer detected in early stages has a signifcantly higher 5-year survival rate, appreciably lower overall cost to the patient, and typically less aggressive treatment course. Te solution may be found in nanotechnology: equipping existing therapies with higher focused on capability, increasing localized drug efcacy, limiting deviceic toxicity, improving diagnostic sensitivity, improving imaging, and refining radiation therapy. scientific translation of cancer nanomedicine dates back several decades, and the number of nano-based therapies and components for imaging, diagnostics, and radiation therapy in scientific use has steadily increased. For example, the CellSearch® device is the frst FDA- approved diagnostic blood test which utilizes magnetic nanoparticles (NPs) targeting EpCAM and cell staining to identify circulating tumor cells. (Gd)-based contrast agents enhance detection of tumor and imaging in vivo when using traditional scanning devices, along withmagnetic resonance imaging (MRI), positron emission tomography (PET), and computed tomography (CT). Nanoformulations can counter resistance mechanisms by targeting multiple components with dual- drug loading, increasing specifcity with triggered release, and utilizing physical modalities to eradicate cancerous cells. Nanoscale carriers can cross a tumor endothelium and passively acquire in tumors owing to the leaky blood vessels and negative lymphatic drainage.

Nanoparticles in Cancer Therapy:

The NPs applied in medical treatment commonly have unique sizes, shapes, and surface characteristics as these three aspects have a major influence on the performance of the nano-drug delivery and hence control therapeutic efficacy.

NPs with a diameter range of 10 to 100 nm are commonly considered suitable for cancer therapy, as they can successfully deliver drugs and obtain more enhanced permeability Therefore, NPs are commonly modified to become hydrophilic, which increases the time period of drugs in circulation and increases their penetration and accumulation in tumours.

Types of Nanoparticles

Organic Nps	Inorganic Nps	Hybrid Nps
Liposome based Nanoparticles Liposomes	Gold Nanoparticles	Lipid Polymer hybrid Nanoparticles

Polymer Based Nanoparticles Polymeric Nanoparticle Polymeric Micelles	Carbon Nanoparticles	Organic Inorganic hybrid Nanoparticles Liposome Silica Hybrid
Dendrimers	Quantum Dots	Cell membrane covered Nanoparticles Cancer cell membrane covered
	Silica Nanoparticles	
	Magnetic Nanoparticles	

Organic NPS:

Organic NPs were broadly explored for decades and contain many types of materials. Liposome, the first nano-scale drug approved for scientific application (16). consists of an outer lipid layer and a core entrapping either hydrophobic or hydrophilic drug. Liposomes can performmany functions by modifying the lipid layer structure, which includeimitating the biophysical characteristics (e.g., mobility and deformation) of living cells (17), which can assist obtain the purpose of more effective therapeutic drug delivery. With decades of research, the development of liposomes has gone through several generations. With regard to cancer therapy, liposomes provide a good platform for in vivo delivery of many anti-tumor drugs, along withdoxorubicin and paclitaxel, among other chemotherapeutic agents, as well as nucleic acids (18). In the field of breast and prostate cancer the application of liposomes has been increasingly common. Multiple paclitaxel liposomes have been demonstrated to have higher anti-tumor efficiency and improved bioavailability compared to free paclitaxel. Liposomal doxorubicin has been established to reduce cardiotoxicity and has comparable efficacy in breast cancer. Furthermore, liposome-based nano devices have also offered an option for drug combination, which can enhance the therapeutic effect and even reverse the drug resistance Nowadays, more varieties of liposome-based drugs have entered into scientific use for cancer treatment. Polymer-based NPs are another type of NP with unique structural arrangements for drug delivery formed by different monomers. Polylactic-co-glycolic acid (PLGA), a common polymeric NP, encompasses copolymerization of glycolic acid and lactic acid. Given its higher biocompatibility and biodegradation, as well as the EPR effect, PLGA is widely used as a carrier for drug delivery Additionally, dendrimers are another class of polymers which havebeen applied to nanomedicine.

They are flexible and biocompatible macromolecules that are characterized by a three-dimensional branch structure. Their multiple functional groups on the surface enhance the capability of loading and delivering therapeutic agents. Furthermore, polymeric micelles, which are characterized by polymer self-assembly into nano-aggregates as they are composed of amphiphilic copolymers, constitute another kind of widely investigated polymer NPs. The hydrophobic core enables the insoluble anticancer drugs to be absorbed and delivered smoothly, while the hydrophilic segment increases stability, thus reducing the uptake of the drug by the reticuloendothelial device and prolonging their time period in circulation.

Inorganic NPs :

Inorganic NPs have the advantages of a higher surface area to volume ratio. They have a wide and easily modified surface conjugation chemistry and facile preparation, although this commonly occurs at the expense of negative er biocompatibility and biodegradability. The inorganic NPs which havebeen studied include gold NPs (AuNPs), carbon nanotubes (CNTs), quantum dots, magnetic NPs (MNPs), and silica NPs (SNPs). AuNPs are the most widely studied inorganic NPs, and mixed monolayer-protected clusters based on the gold core are considered to be a promising candidate in the drug delivery device. The gold core is inert and non-toxic, and surface-functionalized AuNPs have been establish to enhance drug accumulation in tumors as well as to overcome the drug resistance. Moreover, AuNPs are thought to be involved in multimodal cancer treatment which includegene therapy, photothermal therapy and immunotherapy. carbon nanotubes are a type of tubular material which havebeen shown to have broad potential in the drug delivery field due to their unique biological, physical, and chemical properties. As a result, they have been used to deliver anticancer agents which includedoxorubicin, paclitaxel, and methotrexate siRNA for a variety of cancers. Meanwhile, CNTs produce heat when they are exposed to near-infrared radiation, which could be applied to thermal ablation for cancer therapy. Mesoporous silica nanoparticle carriers are a type of SNPs which are suitable for drug delivery. The hugeinternal pore volume enables them to encapsulate the maximum number of anticancer drugs, and the supramolecular components act as a cap, permitting capture and release of drugs. Due to higher pharmacokinetics and treatment efficacy, as well as high stability, SNPs are considered one of the best vehicles for drug delivery. Moreover, porous silicon NPs have shown great potential in immunotherapy as its immunoadjuvant properties include promotion of antigen cross presentation, polarization of lymphocytes and secretion of interferon-γ (IFN-γ). Magnetic NPs (MNPs) used for drug delivery commonly contain metal or metal oxide NPs. In order to improve the stability and biocompatibility, MNPs are commonly covered with organic materials, which includepolymers and fatty acids. They have been shown to demonstrate high efficacy in chemotherapy and gene therapy for cancer treatment. Furthermore, magnetic hyperthermia using MNPs can obtain thermal ablation of tumors, which offers alternative cancer treatment.

Hybrid NPs:

As both organic and inorganic NPs have their own advantages and disadvantages, combining the two in a single hybrid drug delivery device endows the multifunctional carrier with higher biological properties that can enhance treatment efficacy as well as reduce drug resistance. Lipid-polymer hybrid NPs, which consist of an inner polymeric core and a lipid shell, have been demonstrated to be a promising drug delivery platform in the treatment of pancreatic cancer, and metastatic prostate cancer This type of hybrid NPs combines the high biocompatibility of lipids with the structural integrity provided by polymer NPs, and are therefore capable of encapsulating both hydrophilic and hydrophobic drugs in order to obtain a higher therapeutic effect. Meanwhile, this device can be effectively internalized by cancer cells and avoids fast clearance by the reticuloendothelial device. The combination of organic and inorganic hybrid nanomaterials is a common method of NP design. For example, a liposome-silica hybrid (LSH) nanoparticle consists of a silica core and a surrounding lipid bilayer and has been synthesized and shown to be valid in delivering drugs to kill prostate and breast cancer cells. The LSH nanoparticle has also been reported to offer a platform for the synergistic delivery of gemcitabine and paclitaxel to

pancreatic cancer in a mouse model of the disease. created an advanced nano-in-micro platform by assembling the porous silicon NPs and giant liposomes onto a microfluidic chip, and co-delivery of synthesized DNA nanostructures and drugs in this platform was establish to significantly enhance cell death of doxorubicin-resistant breast cancer cells. Furthermore, CNTs and the chitosan hybrid NP used in the vectorization of methotrexate to lung cancer cells tend to increase anticancer activity while reducing drug toxicity on normal cells. Moreover, half-shells of metal multilayers (along withmanganese and gold) and PLGA hybrid NPs have the potential of combining targeted drug delivery and hyperthermia, which can enhance the destruction of tumor cells. The hybridization of natural biomaterial with organic or inorganic NPs is another method for NP design. For example, cell membrane coating nanotechnology is emerging and has increasingly gained more attention. This technology tends to bestow the NPs with biological characteristics directly by coating NPs with naturally derived cell membranes, which enhances the potency and safety of traditional NPs.The coatings include cell membranes derived from leukocytes, red blood cells, platelets, cancer cells, and even bacteria. Parodi et al. (2013) have shown that coating nanoporous silicon particles Frontiers in Molecular Biosciences | www.frontiersin.org 4 August 2020 | Volume 7 | Article 193 Yao et al. Nanoparticles-Based Drug Delivery in Cancer with a cell membrane which is purified from leukocytes can prevent the nano-carrier from clearance by phagocytes, and the characteristics of this hybrid particle allow the drug to have extended time period in circulation, leading to increased accumulation in the tumor. Similarly, some studies have applied cancer cell membrane-cloaked mesoporous silica NPs for cancer treatment, which improves the stability and targeting ability of nano-carriers. Moreover, the development of dual-membrane covered NPs can further enhance the function of NPs. For instance, erythrocyte-platelet hybrid and erythrocytecancer hybrid membrane-covered NPs were establish to exhibit higher stability and longer circulation life. Furthermore, (Wong et al., 2011) proposed a multistage NP delivery device to obtain deep penetration into tumors by changing the size and characteristics of NPs at different stages. In their study, the size change of NPs was achieved by protease degradation of the cores of 100-nm gelatin NPs within the tumor microenvironment in order to release 10-nm quantum dot NPs.

Nanotechnology in Diagnosing Cancer:

Doctors frequently order imaging tests like X-rays, CT scans, and MRIs to assistdiagnose cancer. But these tests can find the disease only once it's big enough to see. By then, the cancer may have copied itself many times and spread to other parts of the body. These scans also can't show whether a tumor is cancer or not. You commonly need a biopsy to know for sure. Because of its small size, nanotechnology can discoverchanges in a very small number of cells. It can tell the difference between normal and cancer cells. And it can get to cancer at its earliest stages, when the cells have just started to divide and the cancer is simpler to cure. Nanotechnology can make tumours simpler to see on imaging tests. Coating nanoparticles with antibodies or other substances helps them find and stick to the cancer cells. Particles can also be covered with substances that send out a signal when they find cancer. For example, nanoparticles made from iron oxide bind to cancer cells and send off a strong signal that lights up the cancer on MRI scans.

Nanotechnology In Treating Cancer:

Nanotechnology can assistto make cancer treatments safer and more precise. Specially designed nanoparticles deliver medicines like chemotherapy straight to the tumour. They do not release the medicine until they reach it. This stops

the drugs from damaging healthy tissues around the tumour. That harmis what causes side effects.

The small size of nanoparticles permitsthem to deliver medicines into areas of the body that would normally be hard to reach. One example is the blood-brain barrier, which prevents toxic substances from getting into the brain. It also blocks some medicines. Nanoparticles are small enough to cross this barrier, which makes them a beneficial treatment for brain cancer.

Nanotechnology Uses in Cancer:

Doctors have used nanotechnology deal withcancer for more than a decade. Two approved treatments -- Ambraxane and Doxil -- assist chemotherapy drugs work better. Abraxane is a nanoparticle made from the protein albumin attached to the chemo drug docetaxel. It stops cancer cells from dividing. Abraxane treats breast and pancreatic cancers which havespread, and non- small-cell lung cancer. Doxil is the chemo drug doxorubicin wrapped innera liposome, a fatty sac. It disrupts cancer genes so the cancer cells can't divide. Doxil treats ovarian cancers, multiple myeloma, and Kaposi's sarcoma. Researchers are studying other nanotechnology treatments in scientific trials. Some of these treatments wrap toxic drugs in nanoparticles to make them safer, or to assistthe drug survive the trip through the bloodstream. One day, nanoparticles might also be able to deliver radiation to cancer.

Aspect consequences of Nanotechnology

Nanotechnology targets cancer cells more exactly to spare healthy tissues. In theory, it should cause fewer aspect consequences than current treatments like chemotherapy and radiation. Current nanotechnology-based treatments along withAbraxane and Doxil do cause aspect consequences like weight loss, nausea, and diarrhea. But these problems may be from the chemotherapy drugs they contain. Researchers should learn more about the aspect consequences of these treatments as they study them in scientific trials.

Characteristics of nanoparticles:

Physical and chemical characteristics of nanoparticles which includesize, charge, shape, and surface properties individually play major roles for in vivo biodistribution and cellular internalization of these drug carriers. In this section, we will focus on the major parameters that decidethe lifetime and delivery of the nanoparticles.

Size:

Particle size is one of the crucial primary factors in determining the circulation time of the nanoparticles. After device administration, nanoparticles aquire in spleen due to mechanical filtration and removed by reticulo-endothelial device (RES). For example, as the primarily constituent of RES, Kupffer cells play a major role for the removal of the particles aquire d in the liver. Currently, 100– 200 nm is accepted as optimal size for drug delivery devices since nanocarriers take the advantage of EPR effect in tumors and avoid filtration in the spleen whereas they are hugeenough to avoid the uptake in the liver (Petros and DeSimone, 2010). Particles with a smaller diameter than 5nm are rapidly cleared from blood circulation through renal clearance or extravasation. However, particles with a size up to 15 μm; aquire in liver, spleen and bone marrow. In addition, particle size has a significant impact on cellular internalization through phagocytosis, macropinocytosis, caveolar- mediated endocytosis, clathrin-mediated endocytosis. As mentioned above, size range has high influence on biodistribution and cellular internalization. In addition, recent studies show that the geometry of the particles is as important as size range in terms of cellular internalization and distribution. In addition, Gratton and coworkers studied the correlation between shape and size on the internalization frequency in HeLa cells and

interestingly. Author Manuscript particles with different shapes but similar volumes were internalized at extremely assorted rates. In a distinct study, Godin and coworkers demonstrated that the accumulation of discoidal particles in breast tumors were five times higher than spherical particles despite their similar diameters. As a result, accumulating evidence shows that although size is a major parameter in the design of nanocarriers for decades, the shape as well, has a high impact along with the size.

Shape:

Degradation properties of nanoparticles and subsequent payload release have been shown to be depending on particle shape. The importance of surface area and diameter were also demonstrated to be critical for cellular uptake of the nanoparticles. Hemi-spherical particles were generated as sustained release devices in order to obtain zero-order. Spherical particles, however, can provide different degradation profiles as their shapes are susceptible upon degradation. Additionally, deformability of spherical nanoparticles is also playing a key role to avoid spleen filtration since spleen exhibit asymmetric filtering units. Therefore, nanoparticles which are especially larger than 200 nm should be either deformable enough to bypass the filtration in spleen or flexible as erythrocytes which could keep away fromfiltration even with 10 μm diameter. In an elegant study, Decuzzi and co-workers studied the effect of size and shape of nanoparticles on biodistribution and tumor accumulation after intravenous injection. Spherical silica particles were generated in different sizes ranging from 700 nm to 3μm also in different shapes along withquasi-hemispherical, discoidal, and cylindrical silicon-based particles. After a single, intravenous particle injection to tumor bearing mice, tumors and the major organs which includeliver, spleen, heart, lungs, kidneys, and brain were analyzed for silicon content and histological evaluation. This study elucidated the importance of shape properties of nanoparticles in addition to size distribution, indicating that geometry of the nanoparticles contributes to opsonization, in vivo biodistribution, the strength of adhesion and internalization rate in the cells.

Surface characteristics

Surface properties play a key role on the period of nanoparticles in blood circulation subsequent deviceic administration. After administration, nanoparticles may be related to with proteins which are known as ‘opsonins’, along withimmunoglobulins and complement proteins that contribute to recognition of nanoparticles by macrophages. Therefore, opsonization is the key factor that determines the fate of nanoparticles to an extent in blood circulation. Modifying the surface of nanoparticles can be used as a strategy to enhance or reduce their circulation time in blood and tissues. For instance, negatively charged nanoparticles result in rapid RES clearance from circulation. Cationic surfaces may induce cell membrane permeability and enhance cellular uptake however, cationic nanoparticles prepared from polycationic polymers along withpolyethyleneimine and diethylaminomethyl-dextran can induce disruption in the cell, through formation of holes, membrane thinning and membrane erosion in lipid bilayers. On the other hand, the use of neutrally charged particles as well as particles Aslan et al. Page 7 J Drug Target. Author manuscript; available in PMC 2014 June 13. NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript covered with polyethylene glycol (PEG) lead to a major reduction of particle uptake by the RES. The surface modification of PEGylated liposomes with rat serum albumin (RAS), compared with non-modified PEGylated liposomes, showed prolonged blood circulation in rats. To further analyze, total serum protein amounts were determined quantitatively in the absence and

presence of RAS coating. As a result, RAS-modified liposomes significantly reduced the total amount of serum proteins that can induce opsonization in serum. In addition, doxorubicin-loaded and albumin-modified liposomes demonstrated enhanced pharmacokinetics and tissue distribution of doxorubicin. Tumor accumulation and therapeutic index of albumin-modified PEGylated liposomal doxorubicin was significantly higher than non-modified PEGylated liposomal doxorubicin indicating that surface modification of nanoparticles with albumin, enhances their safety and effectiveness. In addition, nanoparticle surface can be modified with ligands that recognize and bind to unique receptors. Also, monoclonal antibodies can be conjugated onto nanoparticle surface to provide unique ity. For instance, nanoparticles modified with HER2 unique antibody, delivers the drug, particularly HER2 expressing cells. Torchilin's group has also designed different approaches for active targeted delivery to the tumor with liposomes and micellar delivery devices. They have developed monoclonal antibody 2C5-modified doxorubicin loaded liposomes to enhance the therapeutic activity of the payload in brain tumor xenografts. These studies demonstrate that surface characteristics are fundamentally important for nanoparticles to avoid their rapid clearance from the blood circulation before reaching the tumor site, and to provide active targeting through surface modifications with antibodies or ligands.

MECHANISMS OF TARGETING

Targeting of cancer cells unique ally is a vital characteristic of nano-carriers for drug delivery, as it enhances the therapeutic efficacy while protecting normal cells from cytotoxicity. Numerous studies have been carried out to explore the targeting design of NP-based drugs. In order to higher address the challenges of tumor targeting and the nano-carrier device design, it is crucial to first understand tumor biology and the interaction between nano-carriers and tumor cells. The targeting mechanisms can be broadly divided into two categories, passive targeting and active targeting.

PASSIVE TARGETING :

Passive targeting is designed to utilize the different characteristics of tumor and normal tissue. In passive targeting, the drugs are successfully delivered to the target site in order to play a therapeutic role. High proliferation of cancer cells induces neovascularization, and hugepores in the vascular wall lead to a worsening permselectivity of tumor vessels compared to normal vessels. The rapid and defective angiogenesis enables macromolecules, which includeNPs, to leak from blood vessels that supply the tumor and aquire within tumor tissue. Meanwhile, the negative lymphatic drainage related to with cancer increases the retention of NPs, permitting the nanocarriers to release their contents to tumor cells. These processes cause the EPR effect, one of the driving forces of passive targeting (Maeda, 2001). The EPR effect is influenced by the size of NPs, as many studies have demonstrated that smaller NPs have higher penetrability but do not leak into normal vessels). On the other hand, larger particles are more likely to be cleared by the immune device. In addition to the EPR effect, the tumor microenvironment is also an important factor in the passive delivery of nanomedicines. Glycolysis is one of the metabolic characteristics of cancer cells and is the primarily source of energy for cancer cell proliferation. Glycolysis yields an acidic environment and reduces the pH of the tumor microenvironment. Subsequently, some pH-sensitive NPs are triggered by the low pH level and are able to release drugs within the vicinity of cancer cells. However, there are some limitations with regards to passive targeting, which include on-unique drug distribution, nonuniversal existence of the EPR effect and

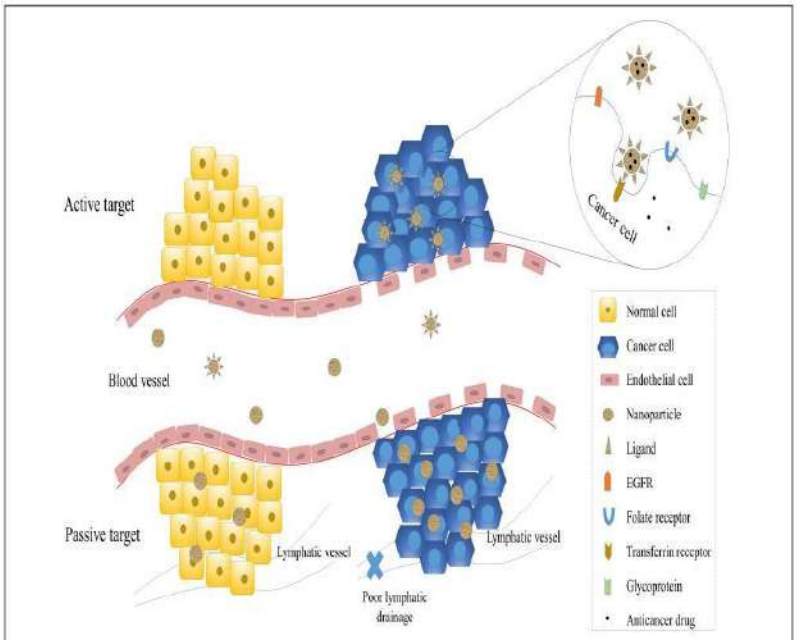
different permeability of blood vessels across various tumors (Jain, 1994).

ACTIVE TARGETING:

Active targeting unique ally targets cancer cells through direct interactions between ligands and receptors. The ligands on the surface of NPs are selected to target the molecules that are overexpressed on the surface of cancer cells, which permitsthem to distinguish targeted cells from healthy cells. The interaction between ligands on NPs and the receptors on the surface of cancer cells induces receptor-mediated endocytosis, which permitsinternalized NPs to successfully release therapeutic drugs (Farokhzad and Langer, 2009). Therefore, active targeting is particularly suitable for macromolecular drug delivery, along withproteins and siRNAs. The types of targeting moieties include monoclonal antibodies, peptides, amino acids, vitamins, and carbohydrates (Danhier et al., 2010). These ligands unique ally bind to receptors on targeted cells, and the widely investigated receptors include transferrin receptor, folate receptor, glycoproteins, and the epidermal growth factor receptor (EGFR).

Targeting to Cancer Cells:

Transferrin, a type of serum glycoprotein, functions to transport iron into cells. Transferrin receptors are overexpressed in most solid tumor cells and are expressed at low levels in normal cells. Thus, transferrin-conjugated NPs are used as an active targeting method to deliver drugs for cancer treatment. Compared to unmodified NPs, transferrin-modified NPs have been shown to exhibit higher cellular uptake efficiency and enhanced intracellular delivery of drugs (Cui et al., 2017). Moreover, evidence indicates that transferrin-conjugated polymeric NPs play a significant role in overcoming drug-resistant chemotherapy. Folic acid, a type of vitamin, is essential in nucleotide synthesis. It is internalized by a folate receptor that is expressed on few normal cell types. However, the alpha isoform of folate receptor (FR-α) is overexpressed in approximately 40% of human cancers, while FR-β is expressed on the surface of hematopoietic cancers. Thus, the folate receptortargeting strategy by folate-conjugated nanomaterials has been widely used for cancer. In addition, cancer cells commonly express various types of glycoproteins, which includelectins, which are non-immunological proteins that recognize and unique ally bind to certain carbohydrates. Targeting cancer cell-surface carbohydrates by lectins conjugated to NPs constitutes the direct lectin targeting pathmanner, while inversely targeting lectins on cancer cells using carbohydrates moieties that are incorporated into NPs is referred to as the reverse lectin targeting pathmanner. Epidermal growth factor receptor is a member of the ErbB family of tyrosine kinase receptors. EGFR, which is overexpressed in varieties of cancers, is involved in several processes of tumor growth and progression and has already been applied as a target for cancer treatment (Nicholson et al., 2001; Sigismund et al., 2018). For example, targeting human epidermal receptor2 (HER-2) is a common therapy for HER-2 positive breast and gastric cancer. Hence, NPs which havebeen designed to incorporate modified ligands that bind to EGFR in order to target EGFR-overexpressed cancer cells is a promising method of drug delivery (Alexis et al., 2008). Furthermore, conjugating two cancer- unique ligands into a single NP is another manner of active targeting, as it can assistimprove target unique ity



ADVANCES IN NANOTECHNOLOGY FOR TARGETED DELIVERY:

Cancer treatment based on nanomaterials shows advantages over using free drugs, particularly for targeted delivery. Compared to free drugs, targeted delivery exhibits reduced toxicity, decreased degradation, increased half-life, and enhanced capacity (20, 21). Recent advances have been made in nanomaterial-based targeted drug delivery devices, which includein active or passive targeting. Active targeting is achieved using antibodies or small moleculeconjugated nanoparticles, whereas passive targeting occurs through enhanced permeability and retention effects. Active targeting displays great potential and acted as an alternative strategy to passive targeting and the ability of tumor localization in active targeting was improved by increased efficiency and retention (22). Compared with traditional chemical therapies, nanomaterial-based drugs display increased unique ity, improved bioavailability, lower cytotoxicity, higher loading capacity, and a longer half-life. To date, many nanomaterials for cancer treatment have been developed based on remarkable advances in nanoscience, technology, and cancer pathology. However, few nanomaterial-based drugs have been intensively studied and applied in scientific practice. Nanomaterials can be broadly classified into several categories.

MONOCLONAL ANTIBODY NANOPARTICLES:

Because of their anticancer effect and unique targeting ability, monoclonal antibodies (mAbs) are widely used in targeted treatment. More recently, mAbs have been applied in anticancer nanoplatforms and as frontlines in the fight against cancer. Cytotoxic drugs are conjugated with mAbs to strengthen the therapeutic efficacy of anticancer drugs, known as antibodydrug conjugates. According to the unique antigens expressed in cancer cells, less toxicity and higher unique ity can be achieved (19). Different antibody-drug conjugate devices display enhanced therapeutic efficacy in breast cancer (26, 20). Based on these effects of antibody-drug conjugates, trastuzumab nanoparticles are promising and widely studied nanoplatforms for cancer treatment (21-22)

LIPID-BASED NANOMATERIALS:

Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers are three main categories of lipid-based nanomaterials. Liposomes (20 nm to >1 mm) were the first microcosmic phospholipid bilayer nanodevice

(24) . Both hydrophilic and hydrophobic drugs can be delivered depending on the liposome structure. Drugs are shielded from degradation by the central cavity of liposomes (25). Liposomes may be phagocytized by the mononuclear phagocyte device, known as human guards; therefore, liposome membranes should be modified to prolong their half-life (26). This can be achieved through polyethylene glycol conjugation. For example, PEG-liposomes carrying doxorubicin (DOX) were developed and applied deal with Kaposi sarcoma (27) . Liposomes are widely applied in codelivery and controlled release and have been combined with chemical drugs. How to load drugs and control release must be considered when designing liposome nanocarriers. Drug efficacy is affected by bioavailability in cancer chemotherapy, and DOX liposomes have a lower bioavailability than free DOX, suggesting that bioavailability should be improved during liposome design (28) . A new PEGylated liposome carrying cobimetinib and ncl240 displayed an enhanced cytotoxic effect through synergistic effects, leading to higher efficacy (29) . Moreover, liposomes loaded with floxuridine and irinotecan exhibited higher effects on advanced solid tumors, whereas a new liposome containing multilayer siRNA molecules and that co-delivered DOX displayed higher DOX efficacy (30), decreasing the tumor mass in breast cancer (31-32) . Notably, unique liposomes can release drugs depending on the pH value, as cancerous regions are more acidic compared to healthy tissues (33). pH-sensitive cationic liposomes were prepared using a pH-sensitive material. The release of sorafenib was increased at pH 6.5 (34). In summary, liposomes exhibit low immunogenicity, low cytotoxicity, and high biodegradability (35). However, the disadvantages of liposomes include their rapid removal by the mononuclear phagocyte device, low stability, and obstacles in membrane transfer. Therefore, the application of liposomes stayslimited. SLNs have been acted as alternative carriers to liposomes. Because of the rigid confinement of the scale, SLNs (1–100 nm) are known as “zero-dimensional” nanomaterials compared with other larger nanomaterials. SLNs contain solid materials, in contrast to liposomes. Examples of these materials include solid lipids, emulsifiers, and water. PEGylated lipids, triglycerides, and fatty acids are applied in SLNs (20). The outer layer and delivery function of SLNs are similar but show some differences from traditional liposomes. Some SLNs have a micelle-like structure rather than a contiguous bilayer, with drugs packaged in the core (35). Compared with liposomes, SLNs show higher stability and longer release. However, because of their crystalline structure, SLNs exhibit some limitations, along withinherently low incorporation rates and an unpredictable gelation tendency (37). Nanostructured lipid carriers (NLCs) have been fabricated to overcome the drawbacks of SLNs and termed as the second lifetime of lipid nanoparticles. Compared with SLNs, NLCs exhibit a higher loading capacity and show a less inclination of gelation (38). NLCs have received considerable attention in recent years because many drugs used in cancer therapy are lipophilic and can be administered through various routes (oral, parenteral, inhalational, and ocular) (39). NLCs are manufactured as devices that carry both liquid and solid lipids. Over the past two decades, the stability and loading capacity of NLCs have evolved.

CONCLUSION AND FUTURE PROSPECTIVE:

Nanotechnology applied to cancer therapy has led to a new era of cancer treatment. Various types of NPs, which includeorganic and inorganic NPs, have already been widely used in the scientific treatment of several cancer types. Compared to traditional drugs, NP-based drug delivery devices are related to with improved pharmacokinetics,

biocompatibility, tumor targeting, and stability, while simultaneously playing a significant role in reducing deviceic toxicity and overcoming drug resistance. These advantages enable NP-based drugs to be widely applied to chemotherapy, targeted therapy, radiotherapy, hyperthermia, and gene therapy. Moreover, nanocarrier delivery devices provide improved platforms for combination therapy, which helps overcome mechanisms of drug resistance, which includeefflux transporter overexpression, defective apoptotic pathmanner, and hypoxia tumor microenvironment. According to different mechanisms of MDR, NPs that are loaded with varieties of targeting agents combined with cytotoxic agents can obtain the reversal of drug resistance. With increasing research, various types of hybrid NPs have shown improved properties for delivery and aroused more attention. Further studies on the biological characteristics of individual cancers will lead to more precise research directions for these drugs. Furthermore, designing hybrid NPs that are more suitable for cancer therapy and engineering NPs that target cancer cells more unique ally using targeting moieties merits further exploration. Notably, the interactions between NPs and the immune device are complex (Najafi-Hajivar et al., 2016). The NP size, shape, composition, and surface are all the factors that affect the interactions of NPs with the immune device. Although nanovaccines and artificial APCs have demonstrated increased efficacy compared to traditional immunotherapy, the scientific efficacy of this treatment staysunsatisfactory, and the safety and tolerance of these new approaches need to be further investigated. Moreover, developing immunomodulatory factor-loaded NPs may improve the effectiveness of vaccines for immunotherapy. Accordingly, a higher understanding of the TME and a further investigation of the crosstalk between NP-based drug delivery devices and tumor immunity are warranted for drug design and exploitation. Advances in nanomedicine offer new opportunities to improve the anticancer armamentarium. Targeted and nontargeted nanoparticles are currently in prescientific and scientific phases indicating the impact of delivery devices on the field. Further studies in nanomedicine will improve therapeutic window of drugs with immensely reduced aspect consequences leading to improved patient outcomes.

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