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Nanotechnology in Cancer Therapy and Diagnostics

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Abstract

Nanotechnology has emerged as a transformative tool in cancer treatment, enhancing targeted drug delivery and diagnostic therapy. Its application in targeted cancer therapy has been motivated by several benefits including reduced systemic toxicity and enhanced efficacy, which addresses some of the limitations posed by conventional cancer therapies such as site-specific targeted drug delivery and limited bioavailability. This review explores the evolution of nanotechnology in cancer therapy, detailing its applications in targeted drug delivery systems such as dendrimers, quantum dots, and nanoemulsions. These nano-carriers enable precise drug localization, minimizing damage to healthy tissues while improving therapeutic outcomes. Additionally, the role of nanoparticles in imaging and diagnostics such as magnetic resonance imaging and exosomes are examined, highlighting their potential to facilitate early cancer detection. The integration of nanotechnology in therapies, including radiotherapy and immunotherapy, showcases its ability to enhance treatment efficacy and reduce side effects. While the benefits of nanotechnology in cancer are significant, challenges still remain, including increased formulation costs and potential adverse effects, demonstrating the need for continued research in optimizing nanomedicine.

Keywords: nanotechnology; cancer; targeted delivery; diagnostics and imaging

Introduction

The World Health Organization (WHO) estimates that about 1 in 5 people develop cancer, with about 1 in 9 men and 1 in 12 women dying from the disease [1]. Despite the advancements in cancer treatments [2,3], it is projected that there will be over 35 million new cases of cancer globally by 2050 [1], highlighting the need for targeted and optimized cancer treatment. By providing more accurate and efficient methods to target and eliminate cancer cells while causing the least amount of harm to healthy tissues, nanotechnology has demonstrated great potential in transforming cancer treatment and diagnostics [4]. Compared to traditional therapeutic approaches including surgery, chemotherapy, and radiation, the use of nanotechnology in targeted medication delivery to cancer cells offers a number of potential advantages such as targeted drug delivery, enhanced imaging and cancer diagnostics [5]. Although these advancements still require further research and development, their potential to optimize cancer treatment outcomes and reducing side effects cannot be undermined.

The physicist Richard Feynman first introduced the concept of nanotechnology in 1959 [6], when he suggested that it would be possible to manipulate individual atoms to create objects at a small scale [7]. Nanotechnology was later defined by Japanese scientist Norio Taniguchi as the separation, merging, and distortion of materials by a single atom or molecule [8]. An emerging shift towards the use of nano-based technology in medicine advancements has been documented, with several studies [9, 10, 11] demonstrating the great potential of targeted drug delivery using nano-based medicines. Nanomedicine is the medical application of nanotechnology ranging from targeted drug delivery, diagnostics and imaging, as well as immunotherapy and gene therapy [12]. Submicron-sized nanoparticles are often used in nano-based medicine, with their small size making them useful in oncology, particularly in imaging. When used in conjunction with Magnetic Resonance Imaging (MRI), quantum dots (QD) can produce great images of tumour sites [13].

Nanotechnology has significantly impacted cancer research and treatment since its inception in the 1980s and significant progress has been made in the use of nano-based technology in drug delivery, therapy and diagnostics of cancer [14]. Its application in targeted cancer therapy has been motivated by several benefits including reduced systemic toxicity and enhanced efficacy (pharmacokinetic), which addresses some of the limitations posed by conventional cancer therapies such as site-specific targeted drug delivery and limited bioavailability [15,16]. The first

nanoparticle-based chemotherapeutic formulation, approved by the FDA in 1995 was Doxil, which is a nano-liposome containing doxorubicin, which demonstrates a high and selective tumour localization, developed with the aim of reducing side effects whilst increasing bio-distribution of the drug [17]. Since then, several other nano-based treatments have been approved including Abraxane, an albumin-bound nano-formulation of paclitaxel used in breast cancer treatment, which demonstrated significant reduction in systemic toxicity compared to conventional formulations of paclitaxel [18].

Nanotechnology Application in Cancer Therapy

Targeted Delivery

Nanoparticles can be engineered to deliver chemotherapeutic drugs directly to cancer cells, reducing systemic toxicity and enhancing the efficacy of chemotherapy [4]. Nanocarriers are systems of colloidal particles with sizes ranging from 1 to 100 nm [19] and include dendrimers, quantum dots and nanoemulsions [20], that are designed to encapsulate therapeutic agents and release them specifically at the tumour site [21]. They have been successfully implemented in the diagnosis, treatment and monitoring of various diseases and their ability to deliver drugs with precision, while minimizing adverse effects, shows significant promise in optimizing cancer therapy [22]. Compared to conventional therapy, nanocarriers offer several benefits such as increased drug penetration, reduced dosing frequency, site-specific targeting, improved bioavailability and stability, as well as constant maintenance of drug levels in the therapeutic range [23, 24]. Although several benefits accompany the use of nanocarriers, documented evidence of their limitations has been shown including increased formulation and production costs, a potential to generate free radicals and reactive oxygen species, possible trigger to allergic reactions and use of harsh toxic solvents in the preparation process [25].

Dendrimers

Dendrimers are a highly branched macromolecular nanocarrier with tree-like structures consisting of a central core covalently connected to branching tree-like units [20,26], designed to enhance the pharmacokinetics and biodistribution of drugs and ensure controlled drug-release to target site [27]. The concept of dendrimers was first introduced in 1978 by Buhleier and associates [28], with Tomalia [29] later synthesizing the first dendrimer in 1985 which they termed “starbust polymer”, owing to their topological structure. The controlled structure of dendrimer and their nano-scale nature allow large-scale synthesis of organic [30] and inorganic nano-structured polymers and can be combined with metallic and carbon nanostructures [31].

Their distinct physiochemical properties and several functional groups on their surface make them capable of binding to drugs and nucleic acids, and allow for site-specific targeted delivery while avoiding normal cells [32]. The central core functional moiety and peripheral groups form the basis of their classification into categories such as polyamidoamine dendrimers, polypropyleneimine peptide dendrimer, poly(L-lysine) dendrimers, citric acid dendrimers and carbohydrate-based dendrimers [33]. Dendrimers function by either non-covalently enclosing the drug inside the dendrimer or covalently bonding to the drug to generate macromolecular prodrugs [34]. Surface modification allows dendrimers to identify and bind to cancer cell markers enabling them to be specifically tailored to target cancer cells while minimising damage to healthy tissues [35]. The compatibility of dendrimers with organic structures such as DNA make them useful in gene therapy where genetic material can be delivered directly to the cancer cells for modification of defective genes [36]. Dendrimers can be used in cancer imaging to improve the detection and monitoring of tumours [37], and when used in combination therapy, such as photothermal and photodynamic therapy dendrimers may be used to enhance treatment efficacy [38]. Furthermore, dendrimers allow for controlled release of anticancer drugs optimizing drug efficacy while minimizing side effects, and have been used in the development of magnetic and pH-responsive controlled release doxorubicin which has the potential of improved targeted drug delivery in breast cancer treatment [39]. Dendrimer nano-technology has also been used in the development of Trastuzumab-dendrimer-fluorine drug delivery system, which demonstrated great potential of improving efficacy and optimizing the detection of Trastuzumab uptake in breast cancer treatment [40]. Although dendrimers offer several benefits, the use of dendrimer drug delivery technology is limited by lack of precise control of drug release at the site of action [41], as well as the incomplete reactions which can result in structural defects [42].

Quantum Dots

Quantum dots are semiconductor nanocrystals ranging between 2 to 10nm [43, 44], discovered around 1980 by Ekimov and associates [45]. They are made up of metals and materials that are semiconductors giving them their unique optical and electronic properties, which makes them useful in early cancer diagnosis, tumour imaging, targeted gene delivery, photodynamic and photothermal therapy [43]. Therapeutic medicines can be precisely delivered to cancer cells by conjugating quantum dots with medications and targeting molecules. This increases the treatment's effectiveness and reduces damage to healthy tissues [5, 46]. The diagnosis and early detection of cancer cells particularly for solid tumours is often difficult, occurring long after metastasis has already started. This makes the early detection and screening vital, particularly for aggressive or asymptomatic cancers difficult to detect in their early stages [47]. QD can be used in biosensors to visualize tumours with high precision and to detect cancer biomarkers, aiding in early detection and monitoring of cancer progression and treatment response [43].

The tunable and unique optical properties of QD makes them great candidates for tumour imaging due to their bright and stable fluorescence with higher resolution allowing for deeper imaging [44]. Tumour imaging can also be useful during surgery to allow complete removal of the tumour and prevent unnecessary healthy tissue removal [48]. While conventional methods such as radiolabelling and fluorescence imaging have been used in cancer imaging, the limited specificity and associated radiation of radiolabelling [47] as well as the suboptimal properties, photobleaching effect (loss in fluorescence capacity after illumination) and phototoxic effect (generation of reactive chemical species after illumination) of fluorescent molecules limits their use in cancer therapy [47, 49]. The crystal structure, size and composition of QD can be altered to optimize retention time and improve tumour targeting making QD useful in mapping sentinel lymph nodes and intraoperative surgery [47].

Photothermal therapy (PTT) and photodynamic therapy have sparked interest as non-invasive and targeted therapeutic approach for a variety of malignancies which work by converting light energy into heat. QD can generate reactive oxygen species when exposed to light, which can kill cancer cells [50]. The use of nano-based compounds for delivery of PTT agents reduces potential of side effects and increases PTT accumulation at target site [51]. The unique properties of graphene quantum dots such as photoluminescence, efficiency in converting light energy into heat, and surface functionalization capabilities makes them great candidates for targeted cancer treatment [52]. Selective death of cancer cells can be achieved by localized hyperthermia from the conversion of light into heat energy. Graphene QD systems can be designed to selectively target tumour cells while avoid healthy cells via targeted laser irradiation of tumour sites [53]. In photodynamic therapy death of cancer cells can also be induced by generating oxygen reactive species through light activation of photosensitizers. The ability of nano-based graphed QD to absorb light at varying wavelengths allow them to be good candidates as photosensitizers that can deeply penetrate tissues which increase therapeutic efficacy [54]. Although graphene QD offer several benefits their biodistribution and biodegradation present a challenge in effective target delivery and stability during cancer therapy [53]. Despite their limitations they still show great promise for use in cancer photodynamic and photothermal therapy.

Nanoemulsions

Nanoemulsions are a 2-phase colloidal system made up of liquid droplets dispersed in another liquid i.e., oil and water. They have an average size of about 50 to 200 nanometres [55]. Reference to an ultra-fine emulsion was first made by Nakajima et al. [56] and the term has since then been refined to nanoemulsion [57]. Their small size and hydrophobic core enable nanoemulsions to encapsulate poorly soluble drugs enhancing their bioavailability and stability [55]. Nanoemulsions can also be designed to selectively deliver drugs to the targeted tumour site through modification with various ligands that target specific components of tumour surfaces thereby reducing side effects to healthy cells and allowing use for different types of cancers [55, 58]. Due to their small size, nanoemulsions can penetrate deeper into tumour tissues and remain there longer, improving the efficacy of treatment [55]. Nanoemulsions have been used in the development of an optimized targeted drug delivery system for paclitaxel. Their study demonstrated the potential efficacy of paclitaxel-loaded lipid nanoemulsions in targeted cancer therapy due to its low toxicity and high tumour-accumulation [59].

Diagnostics and Imaging

Nanoparticles such as superparamagnetic iron oxide and gadolinium have been used as contrast agents in imaging techniques like magnetic resonance imaging (MRI), and computed tomography (CT) scans, allowing for earlier and more precise detection of tumours [4]. Nanotechnology enables the development of highly sensitive biosensors that can detect cancer biomarkers in blood, such as cancer-associated proteins and circulating tumour DNA, allowing for earlier and more accurate diagnosis [60]. Some of the nano systems that have been used in early detection and diagnosis of cancer include magnetic nanoparticles, and liposomes.

Magnetic Nanoparticles

Magnetic nanoparticles are highly functionalized nanostructured metal oxides with magnetic properties and include iron, nickel and cobalt amongst others. The low toxicity and biocompatibility of metals such as iron oxide and maghemite has enabled their use in cancer diagnostics [61]. Magnetic nanoparticles play a significant role in cancer therapy due to their unique magnetic properties and multifunctional design with magnetic nanoparticles commonly used as a contrast agent for MRI [62]. An alternative approach to focal treatment of tumours called magnetic hyperthermia has been introduced which utilizes the heat generated by the magnetic nanoparticles when exposed to an alternating magnetic field. Gilchrist et al. first introduced magnetic hyperthermia in 1957, when they exploited the magnetic properties in the presence of an alternating magnetic field to selectively heat tumours [63]. This exposure generates localized heat, which can kill cancer cells while minimizing damage to surrounding healthy tissue [61]. Magnetic nanoparticles allow for binding of antibodies and loading of chemotherapeutic drugs making them useful as drug carriers by binding to antibodies [64]. The colloidal instability of magnetic nanoparticles can be overcome by surface modification of nanoparticles thereby inducing the magnetic dipole interaction [65]. Magnetic iron oxide nanoparticles have been utilized in the detection and treatment of breast cancer with several formulations approved by FDA such as Feridex IV® (Ferumoxides) which is used in MRI imaging of liver tumours, as well as lymph nodes metastasis imaging agents such as Combidex® (Ferumoxtran-10) [66].

Liposomes

Liposomes are spherical-shaped vesicles composed of a phospholipid bilayer [67, 68], discovered in the 1960s by Alec Bangham [69], ranging in size from 50 to 100nm [70]. A variety of liposomes have been developed for therapy and imaging of different types of cancers and they function via passive or active targeting of cancer cells through enhanced permeability and retention effect or through ligand–receptor interactions imaging [71]. The enhanced permeability and retention mechanism of liposomes allows for passive targeting and disposal in tumours and inflammatory regions, as well as better pharmacokinetic features of the encapsulated medication and a prolonged circulation time [72]. Liposomes allow for loading of molecules with varying solubilities due to their hydrophobic hydrophilic nature such as imaging molecules e.g., radioisotopes and fluorophores, for enhancing contrast in cancer imaging [71]. Their unique properties have allowed liposomes to be useful as a diagnostic tool in cancer imaging such as positron emission tomography, magnetic resonance imaging, and ultrasound imaging improving the overall benefits and avoiding the limitations of certain imaging techniques [73]. Gold coated liposomes have been designed for efficient tumour targeting and photothermal therapy, which produces hyperthermia and kills cancer cells by combining photo absorbers and near-infrared light irradiation. According to the study, the biocompatibility and excretory properties of gold-containing liposomes made them an efficient PTT agent [74]. Liposomes have also been used in methylene blue based photodynamic therapy for active bioimaging against HER-2 positive breast cancer [75]. The study demonstrated the potential use of liposome-based nano systems in targeted bioimaging of breast cancer.

Exosomes

Exosomes are nano-scale extracellular vesicles ranging in size from 30-150nm [76], first described by Pan et al. [77] as vesicles released from the in-vitro culture of sheep reticulocytes [77]. They are formed via the inward budding of the cell membrane, encapsulating several macromolecules, which are then released into the extracellular space for uptake by target cells via endocytosis [78]. In cancer therapy exosomes regulate intercellular communication between tumour and immune cells, mediating tumour progression [79] and inhibiting tumour proliferation. They can be utilized in the delivery of proteins and RNAs which can be used as biomarkers for cancer diagnosis [80]. Exosomes can be found in various bodily fluids such as saliva, semen and urine [79], making them great

biomarkers for cancer diagnostics tools [81]. Studies have identified the relationship between the number of exosomes and tumour presence [82, 83], and exosomes such as CD63-positive exosomes [84], CD81-positive exosomes [85] and Hsp70-positive exosomes [86] have been studied for their potential use as biomarkers for diagnosis of breast cancer, lung cancer and colorectal cancer respectively, demonstrating their potential use in cancer diagnostics.

Therapeutic Applications

The advent of nanotechnology has offered several benefits which have allowed clinicians to safely and precisely administer chemotherapy, radiation, and the newest immuno- and gene treatments directly to the cancer. Furthermore, surgical excision of malignancies can be guided and enhanced using nano-technologies [24]. To date the FDA has approved several nano-based therapies since 1995 which include Doxil, Caelyx and Onivyde amongst others [87, 88]. The potential of several nanoparticle forms, including liposomes, dendrimers, and gold nanoparticles, to improve photothermal and radiation therapy is still being investigated [24].

Radiotherapy Enhancement

By increasing the quantity of radiation that cancer cells absorb, nanoparticles help to improve the effectiveness of radiotherapy and lessen damage to neighboring healthy cells. Radiation therapy has been widely used in clinical cancer treatment, including external beam radiation therapy and internal radioisotope therapy [89]. However, because of their limited absorption of radiation, tumours require frequent doses of ionising radiation, which significantly damages the surrounding normal tissues [90]. Through the generation of reactive oxygen species, which damage DNA, hinder the DNA-repair machinery, and regulate the tumour microenvironment, nanoparticle-based radiation treatment enables the killing of cancer cells [91]. Although their exact mechanism for radio sensitization is unknown, gold nanoparticles have been suggested in conjunction with radiation therapy for improved tumour control. The enhanced permeability and retention effect can be used to improve contrast image-guided radiotherapy and to improve the selective accumulation of nanoparticles within tumours [92].

Immunotherapy and Gene Therapy

Nano-based immunotherapies and gene therapies have been developed to overcome the immune escape ability of tumour cells [93]. Immunotherapy uses immunotherapeutic drugs, such as oncolytic viruses, chimeric antigen receptor T-cells, and immune checkpoint inhibitors, to use the immune system to identify and eliminate cancer cells. Talimogene laherparepvec (T-VEC) was the first gene therapy to be approved. It was an oncolytic herpes simplex virus that was altered to only multiply in tumour cells and carry the granulocyte-macrophage colony-stimulating factor gene, which was intended to create immunity specific to tumours [94]. Nanoparticles can deliver immune-stimulating molecules or genetic material directly to cancer cells, boosting the body's natural defences against cancer [95] and possess significant promise for safely delivering a variety of treatments to the appropriate cancer and/or immune cells [96]. Although cancer immunotherapy has been shown to produce long-lasting tumour reduction, the effectiveness of current immunotherapy techniques is constrained by the development of acquired resistance since various malignancies respond differently, with some tumours staying resistant [97].

Conclusion

Nanotechnology holds immense promise in revolutionizing cancer treatment through targeted drug delivery, early diagnosis, and effective therapy. The unique properties of nanoscale materials enable precise targeting of cancer cells while minimizing damage to healthy tissues, thus enhancing therapeutic efficacy and reducing side effects. The integration of multifunctional nanoparticles, nanoemulsions, and other nanotechnological advancements has opened new avenues for personalized medicine and improved patient outcomes. Despite the significant progress, challenges remain in translating these innovations from the laboratory to clinical practice. Issues such as biocompatibility and long-term safety need to be addressed to fully realize the potential of nanotechnology in oncology. Future research should focus on optimizing nanomaterial design, understanding their interactions within biological systems, and conducting comprehensive clinical trials.

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