Nanoparticles in Cancer Therapies and Clinical Diagnosis

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Contributor: Mariana Sell , Ana Rita Lopes , Maria Escudeiro , Bruno Esteves , Ana R. Monteiro , Tito Trindade , Luísa Cruz-Lopes

Timely diagnosis and appropriate antitumoral treatments remain of utmost importance, since cancer remains a leading cause of death worldwide. Within this context, nanotechnology offers specific benefits in terms of cancer therapy by reducing its adverse effects and guiding drugs to selectively target cancer cells.

cancer treatments nanotechnology nanoparticles drug delivery

1. Introduction

Recently, many accomplishments have been achieved in the field of nanomedicine regarding drug delivery systems. Among them, an abundant number of nanoparticle types have been developed to be used in cancer therapy due to their unique properties [1].

A nanovector is generally defined as a functionalized nanoparticle that can carry and deliver anticancer drugs or detection agents. Nanovectors have been classified into three different classes: first-, second-, and third-generation systems [2].

As an example of a first-generation nanovector, there is albumin-bound paclitaxel [3]. Paclitaxel can be used in breast cancer treatments and its solubility problem is solved by using Cremophor EL. However, first-generation nanovectors are not able to target any specific biomolecule in a tumor cell [2].

The second generation is an evolution of first-generation nanovectors and these are able to target a specific biomolecule in a tumor cell, which means they have active targeting capability. Examples of nanovectors from this generation are the antibody-targeted nanoparticles [3], such as mAb-conjugated liposomes [2]. The nanovectors of the second generation have an improved biodistribution and present a reduced toxicity level when compared to the first generation [2].

The third-generation nanovectors, such as the nanoshuttle, are multistage agents and can handle more complex functions [3]. According to Chatterjee and Kumar, this generation represents the next generation of the first-wave nanotherapeutics that are specially equipped to introduce biological barriers to improve the drug delivery to the tumor site [2].

2. Nanoliposomes and Nanoemulsions

Liposomes, which are made up of non-toxic and biocompatible lipid bilayers, can act as pharmaceutical carriers [4]. Their core is aqueous, their head is hydrophilic, and the tails are hydrophobic, which means they are oriented away from the intercellular fluid. The conventional nanoparticle size is up to 100 nm and liposomes fluctuate between 90 and 150 nm. Liposomes are used to deliver the drug to the outer membrane of targeted tumor cells and, meanwhile, the fatty layer protects the enclosed drug [5]. This mechanism can decrease the effect of drug toxicity on healthy cells and increase the efficacy [2].

Liposomes can be synthesized from cholesterol and phospholipids and they have one particular property, which is their amphipathic nature, that enables them to bind to both hydrophilic and hydrophobic compounds [6]. In other words, they can encapsulate water-soluble drugs in their core and non-polar compounds in their bilayer membrane simultaneously [6]. Liposomes have other advantageous properties, like biocompatibility and biodegradability, and they do not present toxicity or immunogenicity [7][8]. Moreover, the Food and Drug Administration (FDA) has already approved drug delivery systems based on liposomes like MyocetTM [9].

Zhang et al. developed a lyophilized system based on liposomes and paclitaxel applicable for cancer therapy [10]. It has an encapsulation efficiency of over 90% and physical and chemical stability for 12 months while the particles have an average size of about 150 nm. When the system was diluted, the size remained the same and the drug was encapsulated.

Zhao et al. focused on a pH-responsive liposome-containing system for glioma tumor cells [11]. As the system is made up of a tumor-specific pH-sensitive peptide and liposomes, it responds to the acidic pH of gliomas and releases the drug. The same occurs when doxorubicin is used.

Theranostic systems based on liposomes have been studied to be used in imaging and drug delivery [2]. Ren et al. designed a system in which a pharmaceutically active component was encapsulated and its biodistribution was imaged in real time by magnetic resonance imaging (MRI) [12]. The system was compared to a commercially available MRI contrast agent called Omniscan® and showed not only better results but also a longer circulation time in vivo. Furthermore, liposomes enable the entrapment of both polar and non-polar chemotherapeutic drugs providing synergetic therapy with sustained release and substantially lower toxicity.

In recent years, nanoemulsions have also been attracting the interest of researchers in cancer therapies [13][14][15], due to their advantageous characteristics when compared to nanoliposomes, such as larger surface area, elevated half-life circulation, specific targeting, superficial charge, and imaging capacity. Nanoemulsions are heterogeneous emulsions (droplet size of ~100 nm) that simultaneously contain oil, water, and an amphiphilic emulsifier. The dosage form can be tuned to optimize the stability and solubility of drugs in different environments: in this way, poorly water-soluble drugs can be encapsulated into nanoemulsions with a hydrophobic nature, protecting them from degradation and increasing their half-life in the plasma [16].

For example, Ragelle et al. [17] described that the incorporation of fisetin (a naturally occurring flavonoid) into nanoemulsions enhances its water solubility, bioavailability, and efficacy. The formulation was composed of Miglyol® 812N/Labrasol®/Tween® 80/Lipoid E80®/water (10%/10%/2.5%/1.2%/76.3%), with a droplet diameter of ~153 nm. When administered intraperitoneally, the nanoemulsion showed a 24-fold increase in fisetin relative bioavailability when compared to free fisetin. Therefore, the antitumoral activity in mice bearing Lewis lung carcinoma was improved in the nanoemulsion (36.6 mg/kg) when compared to free fisetin (223 mg/kg).

Hu et al. developed a nanoemulsion formulation containing an oil phase (oil with lycopene), water phase (aqueous gold nanoparticle solution), and an emulsifier (Tween 80®), which showed promising results in the regression of a human colon cancer cell line (HT-29) [18]. Briefly, the authors found out that this formulation decreased the expression of procaspases 3 and 8 and Bcl-2 (tumoral markers), while enhancing Bax and PARP-1 expression, accompanied by apoptotic cell death.

In another study, Kretzer et al. developed lipid nanoemulsions containing paclitaxel, which were able to bind to low-density lipoprotein receptors, thus decreasing the drug toxicity and antitumoral potential [19].

Nanoemulsions are currently being used for clinical trials, such as superficial basal cancer cell photodynamic therapy (ClinicalTrials.gov ID: NCT02367547) [20], treatment of lentigo maligna (ClinicalTrials.gov ID: NCT02685592), multiple actinic keratosis (ClinicalTrials.gov ID: NCT01893203), and actinic keratosis (ClinicalTrials.gov ID: NCT01966120 and NCT02799069). However, up to the present, no formulation of this type has been approved by the FDA, as the long-term stability and safety have yet to be further studied.

3. Polymeric Nanoparticles

Polymeric nanoparticles have been considered efficient carriers for prolonged drug delivery systems. In the 1990s, the synthesis of polymeric nanoparticles using polylactic acid (PLA) and poly lactic-co-glycolic acid (PLGA) was explored and reported as “long-circulating” [21]. Since then, the interest in polymeric nanoparticles and their use in cancer therapy has increased. These nanoparticles are considered very versatile because they can be manipulated to be either biodegradable or non-biodegradable, either synthetic or derived from natural sources [22] [23]. Biodegradable polymers have the advantage that they can break down into monomers that can be simply eliminated by the body’s natural metabolic pathways [6].

Natural polymers such as polyhydroxyalkanoates (PHAs), as well as synthetic polymers like PLGA, have been studied for targeted drug delivery applications paired with anticancer agents like paclitaxel [24][25], doxorubicin [26] [27], and cisplatin [28][29]. These studies were tested in vivo and there are some that have been used in preclinical trials on mice [30].

A conjugation between folic acid and PLGA nanoparticles with chitosan as the vehicle was tested for the treatment of prostate cancer [31]. The compound was loaded with bicalutamide and tested in vitro. In comparative studies, unfunctionalized PLGA nanoparticles were also synthetized and exposed to the same circumstances. It was

observed that the functionalized nanoparticles showed improved efficiency compared to the unfunctionalized nanoparticles, because of their altered surface and specific targeted delivery [31]. Folic acid coupled with poly(3-hydroxybutyrate-co-3-hydroxyoctanoate) and loaded with doxorubicin presented a drug encapsulation performance of above 80% [27].

Furthermore, in vitro assays exhibited a release profile of the anticancer drug of approximately 50% in the first five days, and in vivo assays showed that the system displayed enhanced therapeutic efficiency in limiting the tumor growth when compared to controls [27]. Additionally, PLGA nanoparticles loaded with methotrexate–transferrin conjugates and coated with Polysorbate 80, a water-soluble surfactant, were investigated as vehicles for brain cancer treatment. Polysorbate 80 is known to enhance the transport of nanoparticles across the blood–brain barrier (BBB) [32][33]. According to Jain and al., the continuous delivery of methotrexate–transferrin conjugates was attained by virtue of the overexpressed transferrin receptors on the surface of tumor cells, and the results of both in vivo and in vitro assays highlighted the efficiency of the conjugated system when compared to controls [34].

The surface functionalization of nanoparticles with polyethyleneglycol (PEG), also termed PEGylation, is a widely used strategy for extending their blood circulation, thereby improving therapeutic outcomes in vivo. However, PEGylation compromises the uptake and endosomal escape efficiency (PEG dilemma). To overcome this dilemma, several strategies were introduced regarding the surface of nanoparticles to improve cancer treatment and diagnosis. For example: a polyion complex micelle was developed by self-assembling ethylenediamine-based polycarboxybetaine polymers with pDNA [35]. This micelle switched its surface charge to a positive charge in response to a tumorous (pH 6.5) and endolysosomal acidic milieu (pH 5.5) from its original neutral charge at pH 7.4 (bloodstream), thereby promoting the cellular uptake and endosomal escape toward efficient gene transfection. The cargo pDNA of this micelle encodes a soluble form of soluble fms-like tyrosine kinase-1, a potent antiangiogenic exogenous protein, which captures vascular endothelial growth factor (VEGF), thereby significantly suppressing the growth of hard-to-treat solid tumors.

In another example, ligands targeting tumor neovasculature endothelial cells (for example, cyclic Arg-Gly-Asp) are strategically appended to the distal end of the PEG shell for promoting tumor cell uptake of nanoparticles via specific integrin-mediated uptake [36].

Recent results challenge the transport of nanoparticles through interendothelial gaps of the tumor blood vessels, which is a central paradigm in cancer nanomedicine. Sindhwani et al. found that up to 97% of nanoparticles enter tumors using an active process through endothelial cells, unlocking strategies to enhance tumor accumulation [37][38].

Additionally, among the polymeric nanoparticles, dendrimers stand as a unique class of macromolecules with narrow molecular weight distribution, comprising an almost monodispersed nanosystem for target drug delivery. They are composed of a hyperbranched polymeric mantle, a central core, and corona and have numerous branches that can carry a variety of drugs [39]. The molecular size of dendrimers of a certain family is very often identified by its generation, which increases as the molecular weight of the dendrimer increases. The particle size

and shape of dendrimers can be adjusted via chemical synthesis, thus providing branched macromolecules with diverse chemical groups that can be explored for target applications. This is of uttermost relevance for drug delivery because the loading of guest species (e.g., drug molecules) depends on the nature and number of chemical groups in the branched architecture. Due to their single surface, dendrimers have made a great contribution to the design of nanosystems but cytotoxicity has been a critical issue in these systems; the toxicity of these nanocarriers has been related, namely, to surface terminal groups [40]. The most valuable ability of these nanoparticles is the active and passive tumor targeting.

4. Quantum Dots

Quantum dots are semiconducting nanocrystals whose charge carriers are confined in the three dimensions, thus showing quantum size effects in their optical properties [41][42]. These inorganic nanoparticles have been prepared by a variety of chemical methods, however, those relying on colloidal synthesis offer several advantages for nanomedicines such as their easy biofunctionalization, namely, for bioimaging diagnosis. Among the biomarkers used for these purposes, quantum dots stand out for their size-dependent photoluminescence, narrow and tunable emission bands, photostability, and pronounced Stokes shift. Furthermore, the observation of size-tuned photoluminescence in quantum dots under irradiation using a single light source makes these particles suitable for multiplexing methods of analysis. Seminal research on colloidal quantum dots involved mainly the synthesis of Cd-containing materials using hot injection methods, whose surfaces could be subsequently modified with biomolecules. Currently, alternatives to toxic Cd-containing quantum dots are available and have been a subject of interest for bioimaging, such as zinc-sulfide-coated indium phosphide quantum dots or other types of fluorescent nanoparticles, including silica nanocomposites [43][44].

The present imaging techniques available such as X-ray scan, MRI, and computer tomography have serious limitations when it comes to cancer diagnosis and the main limitation is that those techniques cannot recognize small numbers of malignant cells in primary or in metastatic sites [45]. Because quantum dots have improved signal brightness, synchronous excitation of multiple fluorescence colors, and size-tunable light emission, they have been explored as biofunctionalized labels for cancer imaging [2]. However, besides the requirements for cytotoxicity assessment, quantum dots still pose challenges concerning their use in bioimaging, such as the observation of tissue autofluorescence and photon scattering.

5.4. Gold Nanoparticles

Throughout history, gold has consistently held its place as one of the most prized metals on Earth. Gold nanoparticles have been widely investigated for cancer therapies, due to their high chemical stability, well-established synthetic and surface modification methods, shape and size tunability, and biocompatibility [46][47][48][49]. In addition, gold nanoparticles show strong absorption in the visible spectrum due to localized surface plasmon resonances (LSPRs); this means that in the presence of light (an oscillating electromagnetic field), the free electrons from these plasmonic nanoparticles will oscillate and resonate at a particular frequency of light [50]. In fact, gold nanospheres absorb light up to 10^5 times stronger than most efficient light-absorbing dye molecules [51],

which is a clear advantage in comparison to the conventional drugs. The LSPR oscillation can decay by non-radiative processes and convert energy to heat, which makes gold nanoparticles particularly important for plasmonic photothermal therapy (PPTT) applications [52]. Furthermore, anisotropic gold nanostructures (e.g., gold nanorods or gold nanostars) can be synthesized to show resonances in the near-infrared windows (650–950 nm; 1000–1700 nm), a spectral range that allows maximum depth of penetration of incident light in a tissue. Hence, a gold nanorod shows two LSPR bands, associated with two dipole oscillations along its axis, the transverse and longitudinal modes. The latter originates strong absorption in the NIR spectrum, whose exact location can be adjusted by controlling the particle's aspect ratio during the synthesis. The ability for controlling the plasmonic behavior of gold nanoparticles via chemical and surface modification methods makes these nanosystems of great relevance in a number of cancer therapies, including PPTT and surface-enhanced Raman scattering bioimaging [53][54][55][56][57][58].

Considering the capability to thermally destroy the cancerous cells, the photothermal heating capacity, and ease in surface functionalization, gold nanoparticles stand out for their application in multiple cancer therapies. According to Lungu et al., hyperthermia, a common approach in terms of cancer treatment, consists in heating the tumor site up to 40 °C using microwaves and radiowaves as heat generators [6]. Nonetheless, gold nanoparticles can be used as heat sources, showing many advantages over conventional hyperthermia, such as the ability to affect only the adjacent sites, without damaging healthy cells, leading to efficient targeted action [59][60]. The gold nanoparticles start heating up the adjacent locations when an external radiofrequency electric field acts upon them. However, radiofrequency hyperthermia has some serious inconveniences, such as high levels of pain for the patient [59].

It has been reported that gold nanoparticles generate local dose augmentation at the cancerous location by virtue of their properties, such as strong optical absorption in the LSPR region. Furthermore, a system consisting of gold nanoparticles and organic molecules, such as bovine serum albumin (BSA), results in a higher agglomeration of nanoparticles in the tumor site [6]. Also, this system exhibits better features, such as uniform dimensions, ease in synthesis, and stability under physiological conditions [6]. According to Chen et al., both in vitro and in vivo assays using BSA-modified gold nanoparticles showed auspicious results, such as inhibition of cloning formation and cancerous cell death and did not present destructive consequences on healthy tissues and cells [40].

The basis of using gold nanoparticles in cancer radiotherapy is to inject them into the tumor location, then the external X-ray source will act upon them, and it will produce radicals that will damage the cancerous cells and promote their death [6]. When it comes to radiotherapy, assays were made by injecting gold nanoparticles in mice with the EMT-6 cancerous cell line. The mice were exposed to X-ray therapy and the survival rate considerably increased compared to mice that were subjected to conventional treatment, such as irradiation [6].

As mentioned above, colloidal Au nanoparticles can be synthesized with distinct particle size distributions and specific particle shape, such as nanospheres and anisotropic particles. As such, the optical behavior of such colloids can be judiciously tuned by controlling their morphological characteristics. Additionally, the surfaces of such nanoparticles can be functionalized envisaging specific bioapplications. Hence, Au nanoparticles coated with cysteamine and thioglucose were synthesized by Kong et al. and applied to healthy and cancerous breast cell lines

[61]. It was reported that the gold nanoparticles coated with glucose were internalized by the tumor cells, while the ones coated with cysteamine were essentially disposed on the surface. The assays showed that the number of internalized functionalized nanoparticles was substantially higher than that of the unfunctionalized ones. Nonetheless, when the irradiation acted upon the nanoparticles, it was noticed that the cytotoxic effect of the functionalized nanoparticles was considerably higher than the one arising from the unfunctionalized ones.

6. Iron Oxide Nanoparticles

Iron oxide nanoparticles, namely of magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), have garnered significant attention in cancer therapies, due to their unique properties, such as small size, high surface-to-volume ratio, and magnetic properties (which differ from their bulk counterparts) [62][63]. Often, the surface of these magnetic nanoparticles is coated with a material that increases the biocompatibility and stability in physiological media, such as a polysaccharide or smaller carbohydrates, endowing the final material with a hard-core/soft-shell structure [64].

One of the primary applications of these nanoparticles is their use as contrast agents for MRI scans (such as ferumoxsil, Lumirem®, or Gastro MARK®), enabling accurate tumor localization, staging, and monitoring of treatment response [65]. For example, Han et al. developed multifunctional iron oxide nanoparticles with a carbon-based shell, whose magnetic and fluorescence properties allowed the detection and imaging of cancer cells [66]. To provide an optimal balance of sensitivity and selectivity, MRI-based approaches can be combined with other imaging techniques, such as computerized tomography, which relies on the application of X-rays to generate two-dimensional images of the body. Within this context, Deng et al. [67] reported the synthesis of radiolabeled superparamagnetic iron oxide nanoparticles functionalized with a small peptide, as selective dual-modality agents for imaging of breast cancer.

Another well-documented application is the use of magnetic iron oxide nanoparticles in hyperthermia therapy, where these systems are exposed to alternating magnetic fields (typically ranging from ~100–300 kHz) and generate heat, mostly via magnetic hysteresis loss [64][68]. Due to hyperthermia, the temperature of cancer tissues might be raised up to 41–46 °C, triggering various paths as necrosis, apoptosis, protein denaturation, and immune system reactions [69]. Still, a is to ensure true tumoral tissue specificity, without damaging surrounding healthy tissues. Currently, several iron oxide nanoparticles have been approved for use in hyperthermia-based cancer therapy, such as NanoTherm® and ThermoDox® [64].

It has been described that that this class of nanoparticles can stimulate proinflammatory immune cell phenotypes, facilitating the recognition of tumors to enhance cancer therapies [64][70]. For example, Korangath et al. [71] recently reported the coupling of amine-functionalized starch-coated ferrite nanoparticles with a monoclonal antibody (HER2/neu), which has been clinically approved in therapies for breast cancer. After exposing cancer cells to these nanoparticles, the authors observed an infiltration of T cell populations (part of the immune system) into tumors, followed by tumor growth suppression. Similarly, the exposure of cancer cells to ferumoxytol [72], an example of an FDA-approved iron oxide nanoparticle, triggers an inflammatory response that leads to the prevention of metastases.

The functionalization of iron oxide nanoparticles with targeting ligands, antibodies, or peptides might enhance their selectivity towards cancer cell receptors or markers, facilitating targeted delivery of drug molecules (as doxorubicin and paclitaxel) [73][74] and short ribonucleotides (e.g., miRNAs, siRNAs) [75][76].

7. Carbon Nanomaterials

Carbon nanostructures are an important class of materials in the field of cancer therapies, including, for example, graphene-based structures, carbon nanotubes (CNTs), fullerenes, and carbon dots (CDs) [77]. These carbonaceous structures have found applications as drug carriers and photoactive and diagnostic agents in several cancer theranostics [77][78]. A significant advantage of these systems lies in their large surface-area-to-volume ratios, which allows for enhanced loading and delivery of anticancer drugs towards the target cells, thus minimizing off-target effects. Moreover, because of their easy functionalization possibilities, the surface of these nanomaterials can be tailored to achieve different types of interactions (covalent and/or non-covalent) with drug molecules and ensure their controlled release to tumor sites [77].

The two-dimensional nature of graphene-based nanomaterials and their sp^2 hybridization endow them with a unique honeycomb lattice structure to act as nanovehicles of anticancer drugs [79][80]. Within this context, oxidized derivatives of graphene, such as graphene oxide (GO), play a key role due to their higher dispersibility in physiological media and ability for chemical functionalization [81][82]. For example, Zhang et al. [83] loaded doxorubicin and camptothecin (CPT) onto GO to simultaneously explore the cytotoxic effect arising from DNA intercalation and topoisomerase inhibition in MCF-7 breast cancer cells. Moreover, due to their strong absorbance in the NIR region, it has been reported [84] that graphene derivatives can be stimulated by light to produce hyperthermia [85]. Additionally, these nanomaterials can aid typical photodynamic therapy due to their ability to carry multiple PSs that generate reactive oxygen species (ROS) under light irradiation.

CNTs assume special relevance in cancer treatment and diagnosis, namely when chemically functionalized with biocompatible molecules that increase their inner stability in physiological media. For example, Oh et al. [86] developed a delivery system that carried doxorubicin with PEGylated single-wall CNTs (SWNTs), which showed potential in chemotherapy and in combined NIR-irradiated PTT against human breast cancer cells [87]. Wen et al. [88] followed a similar rationale to load another anticancer drug (Sor) and EGFR onto multiwall CNTs (MWNTs): the results showed that this nanocomposite could decrease tumor growth in liver cancer cells, mostly by apoptosis. While attempting to target mitochondria, Yoong et al. [89] functionalized multiwall CNTs (MWNTs) with fluorescent rhodamine molecules to encapsulate a chemo-potentiator 3-bromopyruvate (BP) and platinum prodrug; the as-developed system led to mitochondrial malfunction, causing apoptosis of cancer cells.

The unique geometry and molecular topology of fullerene C_{60} consists of a round cage-type structure bearing 60 carbon atoms arranged in 12 pentagons and 20 hexagons [90]. Other fullerenes exist with other numbers of C atoms arranged in fused rings of five to seven atoms or with the surfaces functionalized with a variety of chemical groups. The abundant π–π conjugation of these nanomaterials endows them with important optical and

thermodynamic properties, suitable for use as a photosensitizing agent in PDT, hyperthermia, imaging, and photoacoustic-assisted theranostics [91].

As a more recent member of this carbonaceous nanomaterial family, fluorescent CDs have been acquiring increasing importance in cancer therapies, namely in bioimaging [92][93]. Targeted staining of specific cancer cells using CDs typically relies on the attachment of special ligands, such as transferrin, folic acid, and hyaluronic acid [94][95][96]. These materials can also be used as delivery systems [97][98].

Despite these encouraging breakthroughs, the biocompatibility of carbon nanomaterials remains challenging: surface functionalization, modification, and encapsulation strategies have been employed to enhance biocompatibility, biodegradability, and control immune responses [99]. For example, CNTs have raised nanotoxicological concerns which prompt the necessity of more studies, namely associated with surface functionalization and biological impact. Hence, rigorous preclinical and clinical studies are still required to evaluate the safety and efficacy of carbon-nanomaterial-based cancer therapies.

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