Advances in Biological Science Research

A Practical Approach

Edited by
Surya Nandan Meena and Milind Mohan Naik

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Surya Nandan Meena
Biological Oceanography Division, National Institute of Oceanography, Dona Paula, Goa, India

Milind Mohan Naik
Department of Microbiology, Goa University, Goa, India

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Chapter 21

Role of nanoparticles in advanced biomedical research

R.K. Kunkalekar[1], Umesh B. Gawas[2]
[1]*Department of Chemistry, Goa University, Taleigao Plateau, Goa, India;* [2]*Department of Chemistry, Dnyanprassarak Mandal's College and Research Centre, Assagao, Goa, India*

21.1 Introduction

Nanotechnology refers to the branch of science and engineering dedicated to materials with dimensions in the range 1−100 nm. Nanoparticles (NPs) are of great scientific interest as they are effectively a bridge between bulk materials and atomic or molecular structures. Morphological and topographical features of NPs play important roles in their potential applications in various fields like biomedical, optical, storage system, magnetic separation, targeted drug delivery, electronics, etc. Consequently, with a wide range of applications available, NPs have the potential to make a significant impact on society. The characteristic feature of NPs is that the physical and chemical properties are significantly different from bulk counterparts [1]. In the case of magnetic nanomaterials, the quantum size effects and large surface area dramatically changes their magnetic behavior and they exhibit superparamagnetic phenomena with quantum tunneling of magnetization because at nanodimensions below a critical size each particle behaves as a single magnetic domain [2]. The research associated with nanomaterials in the biological field is mostly directed toward their use in medical diagnosis and treatment of cancer-related ailments. The potential for drug delivery systems involving NPs offers several advantages such as (1) the ability to target specific locations in the body; (2) reduction of the drug quantity needed to attain a particular concentration in the vicinity of the target cells; and (3) reduction of the concentration of the drug in the normal cells to minimize the severity of size effects [3]. This chapter gives an overview of NPs in advanced biomedical research. The biomedical roles of metallic, nonmetallic (metal oxide NPs), and carbon-based nanomaterials with special reference to cancer diagnosis and treatment have been discussed.

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21.2 Cancer therapy

Cancer refers to a group of diseases characterized by abnormal cell growth with the potential to invade or spread to other parts of the body with the exception of benign tumors which do not spread to other parts of the body. With severe health consequences, cancers are a major cause of death worldwide [4,5]. According to the World Health Organization, worldwide deaths due to cancer are estimated to be 8.2 million, which is about 13% of the total deaths, and this is expected to rise to 22 million by 2030 [6,7]. In the United States alone, 1,735,350 new cancer cases and 609,640 deaths due to different types of cancers are projected to occur in 2018. In India, the estimated number of people living with cancer is around 2.5 million, and every year over seven lakhs are diagnosed for cancer out of which 5,56,400 deaths occur due to cancer-related diseases [8]. The most common types of cancer include breast cancer affecting females, which is the leading cause of cancer mortality next to lung cancer [9]. There is no single cause for cancer; it is caused due to the interaction of many factors together, which may be genetic, environmental, or constitutional characteristics of individuals. The treatments for cancer depend on its type, advancement in the body, all of which have some limitations and side effects [10]. The commonly used cancer treatments include: surgery, radiation therapy, chemotherapy, immunotherapy, hormone therapy, stem cell transplant, and precision medicine. The major disadvantage of the existing cancer therapies is their inability to deliver specific drugs to the target, causing drugs to act on both cancerous and healthy cells, leading to systemic toxicity, which also prevents sufficient drug concentration to be delivered to tumor sites, thus making the cancer treatment deemed to be ineffective. Most of anticancer agents used in conventional methods for cancer treatment are hydrophobic with low solubility and high metabolism, consequently, the bioavailability of drug decreases [11]. Furthermore, the available conventional chemotherapeutic treatments are limited in their solubility, selectivity toward tumor cells and are increasingly multidrug resistant (MDR), and hence, the resistance of tumors against anticancer drug increases [12]. This has generated the necessity for alternative methods for cancer treatment, and one approach that has evolved in the recent past is targeted drug delivery. It works selectively on cancer cells with minimum side effects on normal cells, tissues, and the body as a whole. For an effective cancer treatment, it is desirable to increase the efficacy of anticancer drugs, which can be achieved by specific targeted drug delivery, thereby minimizing the side effects. The recent development of nanomedicines offers tremendous opportunities in specific targeted drug delivery for anticancer therapy. The binding ability and specificity of NPs to bind malignant tumor cells can be enhanced by conjugation with suitable biomolecular ligands and high surface area that may be utilized as carriers for therapeutic and diagnostic agents [13]. Among metallic NPs, colloidal silver, in addition to its antitumor activity exhibits excellent in vivo

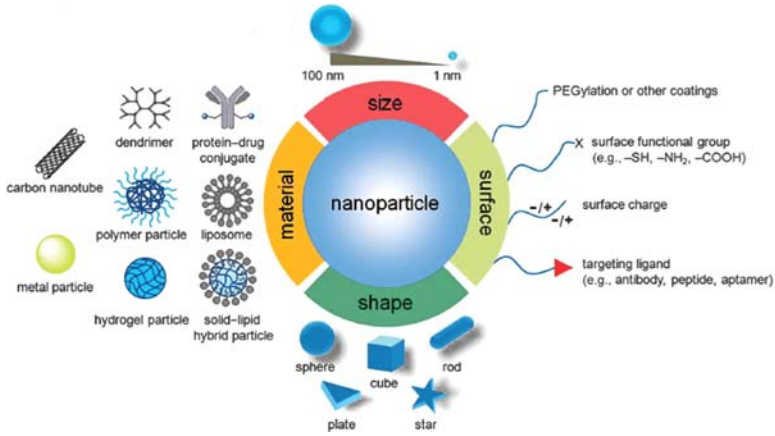

FIGURE 21.1 Physicochemical properties of nanomaterials.

distribution and very low toxicity [14,15]. The in vitro antiproliferative activity of silver NPs (AgNPs) is reported on breast cancer cell lines (MCF-7, MDA-MB-231) [16]. Gold NPs (AuNPs) display unique physicochemical properties that can be utilized in building multifunctional platforms for transport of low solubility and poor pharmacokinetic profile therapeutics to the tumor target as well as to sensitize cells and tissues to the treatment [17]. Superparamagnetic iron oxide nanoparticles (SPIONs), due to their low in vivo toxicity and high tolerability, offer great advantage in cancer diagnosis as well as anticancer therapy by hyperthermia [18]. Carbon-based nanomaterials such as graphene oxide (GO), reduced graphene oxide (rGO), and carbon nanotubes (CNTs) have been explored as promising drug carriers for targeted drug delivery systems [19]. GO has attracted more attention due to its effective endocytosis, biocompatibility, and large surface area for drug loading. Furthermore, GO and rGO display good dispersing capability in water and physiological environments because of the surface functionalities that may help in forming hydrogen bonds with the associated drug molecules [20,21]. This hydrogen bonding, in addition to the π-π stacking and hydrophobic interaction, can assist drug loading on the nanocarriers [22]. Physicochemical properties of various nanomaterials are illustrated in Fig. 21.1.

21.3 Metal nanoparticles as drug delivery and anticancer agents

Metal nanoparticles (MNPs) have enthralled researchers for over a century and are now profoundly utilized in material science, catalysis, fuel cells, biomedical sciences, electrochemical sensors, and biosensors. MNPs' surface can be suitably modified with different functional groups that help them to

conjugate with antibodies, ligands, and drugs of interest and thus open a wide range of potential biomedical applications. The size- and shape-controlled synthesis of MNPs with high surface area is important in present-day cutting-edge materials. NPs of noble metals such as Pt, Au, Ag, and Cu have potential applications in catalysis and other fields [23–27]. Biomedical functions and applications of noble metals like Au and Ag are presented in the following section.

21.3.1 Gold nanoparticles

Gold nanoparticles are being looked upon as an ideal candidate for various biomedical applications because of their characteristic properties such as small size, unique photophysical features, easy surface functionalization, and biocompatibility (Fig. 21.2). These properties render AuNPs as a versatile nanoplatform for emerging biomedical applications like cell imaging, ultrasensitive detection, transfection, drug transport and delivery system, antiviral agent, efficient material for photothermal ablation, etc. [28,29]. X. Zheng et al. [30] have obtained the renal clearable ~2 nm glutathione-coated AuNPs. The zwitterionic coating was found to minimize nonspecific MPS uptake in balb/c mice. Further, the pharmacokinetic measurements in animal model have indicated rapid distribution and circulation with a blood-elimination half-life

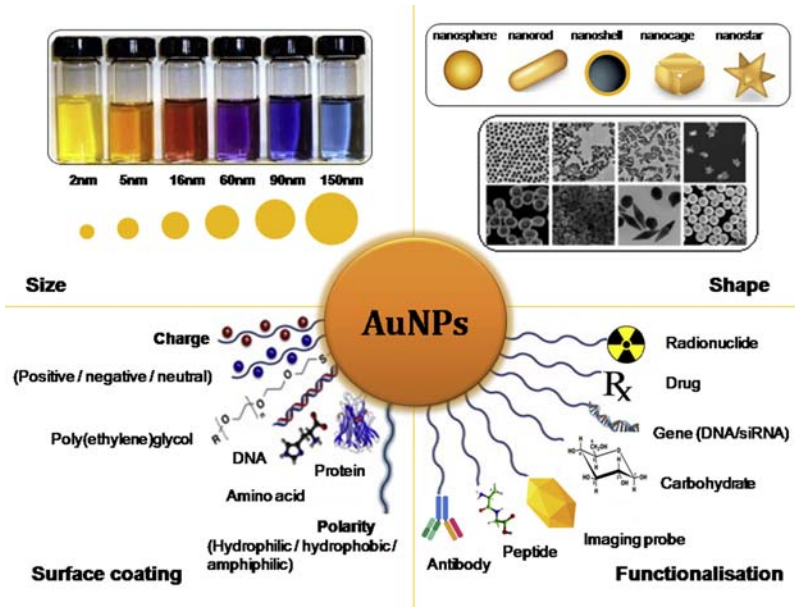

FIGURE 21.2 Schematic representation of AuNP characteristics in biomedical research.

of 12.7 hr. The long blood retention time signifies the ability of these coated AuNPs to passively target tumor-bearing nude mice [31]. K. Huang et al. [32] observed superior cancer cell penetration and in vivo tumor accumulation for N-(2-mercatopropionyl)glycine-coated ultrasmall AuNPs (2 nm) as compared with 6 and 15 nm particles. P. Xu et al. [33] have studied remote control drug release employing supramolecular assembly system and synergistic chemo-photothermal therapy for cancer treatment. They have used cucurbit (CB) [7] uril-stabilized gold nanostar (GNS) to encapsulate anticancer drug camptothecin (CPT) via host-guest chemistry. Importantly, the drug release was triggered using near infrared (NIR) light and CB [7] performs a dual role, that is, acting as surfactant to improve stability of GNS in aqueous solution and as cage for intermolecular assembly of CPT molecules. S. Gulla et al. [34] have evaluated the bioactivity of novel tumor vasculature targeting noncytotoxic Au-CGKRK nanoconjugates. They observed >70% enhancement in overall survivability in melanoma-bearing mice by intraperitoneal administration of the Au-CGKRK NPs complexed with both PD-L1siRNA and STAT3siRNA; while, the biodistribution study using NIR dye-loaded Au-CGKRK nanoconjugates has revealed the accumulation of dye in tumor site in the mice. S. Ke et al. [35] have observed higher potency in promoting apoptosis for AuNPs combined with tumor necrosis factor—related apoptosis-inducing ligand (TRAIL) in nonsmall-cell lung cancer cells. The AuNPs-TRAIL combination causes excessive mitochondrial fragmentation in cancer cells, which is accompanied by dramatic increase in mitochondrial recruitment of dynamin-related protein 1 (Drp1), mitochondrial dysfunction, and enhancement of autophagy induction resulting in increased apoptosis in exposed cells.

21.3.2 Silver nanoparticles

Silver NPs are one of the most vital and fascinating nanomaterials extensively explored in biological and medical research. AgNPs are being employed in various fields such as medical, food, health care, consumer, as well as industrial purposes due to their unique optical, electrical, thermal, and biological properties [36]. Commercially, AgNPs find use as antibacterial agents in industrial, household, health care—related products, in consumer products, medical device coatings, optical sensors, and cosmetics. As well, AgNPs also find biomedical applications such as drug delivery and anticancer agents in targeted drug therapy [37,38]. P. Roychoudhary et al. [39] investigated the antiproliferative activity of AgNPs against leukemic cell lines (K562, MOLT-3, REH) through MTT assay. AgNPs synthesized by *Lyngbya majuscula* displayed dose- and time-dependent activity in REH cells and 4′,6-diamidino-2-phenylindole (DAPI) staining clearly revealed the fragmentation of cancer cells due to treatment of AgNPs. J. Blanco et al. [40] have investigated effects of AgNPs on a human lung carcinoma cell line (A549). They have observed decrease in p53, p21, MDM2, and caspase-3 expression after

low dosage daily and high single dosage exposure to AgNPs; the opposite effect was noticed with changed frequency of doses/administration, which clearly indicate time- and dose-dependent antiproliferative activity. M. Khan et al. [41] observed smallest IC_{50} values for A549 with higher cytotoxic activity than the reference tamoxifen for AgNPs decorated with highly reduced graphene oxide. Further, the cytotoxic effect was found to be proportional to the concentration of AgNPs and cell death mechanism due to cell cycle arrest at G0/G1 phase and apoptosis induction. P. Yuan et al. [42] reported the synthesis and cytotoxic studies of GO-AgNPs nanocomposite against human neuroblastoma cancer cells (SH-SY5Y). The GO-AgNPs nanocomposite displayed significant cytotoxicity at lower concentrations. Further, they have established the molecular mechanism of cytotoxicity. P. Netchareonsirisuk et al. [43] have reported the antiproliferative activity of AgNPs capped with sodium alginate and poly(4-styrensulfonic acid-comaleic acid) sodium salt (PSSMA) against human normal skin fibroblast (CCD-986SK) and malignant melanoma (A375). The sodium alginate−capped AgNPs displayed high selectivity against A375 cell line through apoptosis and necrosis, while PSSMA-capped AgNPs exhibited nonselective toxicity. R. Bhanumathi et al. [44] investigated drug discharge capacity and anticancer effect of folic acid (FA) and berberine (BBR), an isoquinoline alkaloid−loaded AgNPs. They have used BBR encapsulated on citrate-capped AgNPs in conjugation with polyethylene glycol (PEG)-functionalized FA. The in vivo antitumor efficiency of NP-encapsulated drug showed significant restraint of tumor progression. The toxicities behavior of FA-PEG@BBR-AgNPs against different organs was established by histopathological observations.

21.4 Metal oxide nanoparticles as drug delivery and anticancer agent

Metal oxide nanoparticles (MONPs) are important compounds in the materials chemistry field, attracting considerable interest due to the potential technological applications of these compounds. The importance of these materials in different areas such as medicine, information technology, catalysis, energy storage, piezoelectric devices, corrosion protection coatings, and sensing, etc. has driven much research in developing synthetic pathways to such nanostructures. MONPs with different morphological features such as nanorods, nanotubes, nanospheres, nano-hollow spheres, and nanofibrous materials can be conveniently synthesized using different techniques such as hydrothermal, precursor, sol-gel, etc. MONPs have a unique structure, high surface area, unusual redox properties, good mechanical stability, and biocompatibility. For these reasons, MONPs have attracted considerable interest in the fields of biomedical therapeutics, bioimaging, and biosensing and are important components in medical implants, cancer diagnosis and therapy, and in neurochemical monitoring [45−50].

21.4.1 Iron oxide nanoparticles

Iron oxide NPs (IONPs) have been investigated for magnetic properties, which find several important applications such as magnetically mediated hyperthermia for cancer treatment [51], contrast agent MRI [52], treatment of anemia [53], etc. However, the recent studies have indicated that the ability of NPs to generate reactive oxygen species (ROS) can be used in cancer therapy [54,55]. Among iron-based NPs, SPIONs are being explored extensively, especially for their therapeutic and diagnostic applications. SPIONs, in particular magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), are considered as means of transport for targeted drug delivery as they can be guided to the tumor site through an external magnetic field and this prevents drug diffusion to the rest of the body. Due to their superparamagnetic nature, SPIONs lose their magnetism and enter the blood circulation when the external magnetic field ceases [56,57]. The effectiveness of NPs in diagnostic or therapeutic applications can be increased by surface coating, which enhances the physicochemical and biological properties of nanomaterials by providing protection against corrosion and environmental degradation. Also, the biocompatibility and colloidal stability of NPs increases, thereby enhancing the drug release at therapeutic site [58]. N. Mallick et al. [59] have investigated the chondroitin-4-sulphate (CS)-capped SPIONs for loading of the anticancer agent doxorubicin hydrochloride (DOX). The in vitro drug release profile indicated 96.77% of DOX release within 24 hr and MTT assay in MCF7 cells has revealed significantly higher toxicity for CS-SPIONs-DOX with IC_{50} value 6.294 ± 0.4169. S. Mondal et al. [60] have investigated hydroxyapatite (HAp)-coated IONPs synthesized using solvothermal and chemical precipitation for magnetic hyperthermia-mediated cancer therapy. The nontoxic nature of IONPs-HAp was established by trypan blue and MTT assay. The hyperthermia study performed on osteosarcoma cells (MG-63) displayed excellent hyperthermia effect with specific absorbance rate value 85 W/g. They have achieved hyperthermia temperature of about 45°C within 3 min, which could kill nearly all the studied cancer cells within 30 min. C. Saikia et al. [61] have studied FA-tagged aminated starch/ZnO-coated SPIONs for targeted delivery of anticancer drug, curcumin. The cytotoxicity study of the drug-loaded NPs was analyzed by MTT assay in human lymphocytes, liver cancer cells (HepG2), and MCF7, wherein NPs were found to be compatible with human lymphocyte cells and reduce the cell viability up to 61% with 0.5% ZnO concentration in HepG2 and MCF7 cells. The cell uptake efficiency and ROS generation was studied using HepG2 cell lines. The ROS generation was found to enhance with increasing ZnO concentration in the system. N. Moghadam et al. [62] reported improved antiproliferative effect of the nevirapine (Nev) on cancer cell line (Hela) by loading onto chitosan-coated magnetic iron oxide nanoparticles (MIONPs). The in vitro ct-DNA-binding study has revealed DNA aggregation on Nev-loaded MIONPs through groove-binding mode.

21.4.2 Miscellaneous

Photocatalyzed titanium dioxide NPs (TiO_2NPs) have been shown to eradicate cancer cells. However, the required in situ introduction of UV light limits the use of such therapy in humans. Hydrophilized TiO_2 NPs ($HTiO_2$NPs) produce ROS in vivo when activated by ultrasound to eradicate tumor. $HTiO_2$ NPs-based sonodynamic therapy generates a high level of ROS both in vitro and in vivo that can cause destruction of the tumor [63]. Cerium oxide NPs (CONPs) are a novel and very interesting material for radiation therapy, possessing the "smart" capacity to selectively induce the death of irradiated cancer cells by increasing oxidative stress and apoptosis, while protecting the surrounding tissue from radiation-induced damage and oxidative stress. Therefore, CONPs have the unique feature of acting as radio-protecting, as well as radio-sensitizing agents simultaneously [64]. Application of zinc oxide NPs (ZnONPs) has shown that they are most efficacious on cancer cells (T98G), moderately effective on tumor cell line (KB), and least toxic on normal human (HEK) cells. These results demonstrated that treatment with ZnONPs sensitizes T98G cells by increasing both mitotic (linked to cytogenetic damage) and interphase (apoptosis) death [65]. Copper oxide NPs can be used to kill human liver cancer cells. The small spherical NPs generate ROS (such as superoxide anions, hydroxyl radical, and hydrogen peroxide) that damages the membranes and the DNA of the cancer cells, eventually inducing their death. ROS also turned on several death-triggering genes, driving the cancer cells to commit mass suicide. Also, these NPs have shown cytotoxic effects on A549 cells [66]. A. Wani et al. [67] reported that PEGylation of mesoporous silica nanorods (MSNRs) prevented dose-dependent hemolysis in concentration range 0−10 mg/L, improved colloidal stability of MSNR, and increased mitoxantrone (MTX) release. Also, decrease in the IC_{50} of MTX and MTX-loaded MSNR was observed under hypoxic conditions.

21.5 Carbon-based nanoparticles as drug delivery and anticancer agents

Graphene, carbon nanotubes, and fullerenes are important classes of carbon-based nanoparticles. They have a unique pore structure, adsorptive capacity, electronic properties, and acidity. This has generated tremendous interest in these nanomaterials for applications in fields such as physics, chemistry, biology, and medicine. The basic building blocks of all the carbon nanostructures are a single layer of graphite that consists of hexagonally aligned sp^2 hybridized carbon atoms forming a hexagonal honeycomb-like lattice. Graphene is the thinnest two-dimensional single layer of hexagonal packed carbon atoms that has attracted researchers all over the world [68−71]. Graphene oxide is a product of chemical exfoliation of graphite. It is typically synthesized by reacting graphite powders with strong oxidizing agents such as

$KMnO_4$ in concentrated sulfuric acid. GO is described as a graphene sheet modified with different types of organic functionalities such as carboxyl (-COOH), carbonyl (-CO), hydroxyl (-OH), and epoxy (C—O—C). The presence of these functionalities renders GO hydrophilicity and the potential to improve the solubility of some water-insoluble drugs. Hence, GO is preferred over pristine graphene for drug delivery application [72]. Reduced GO is another most commonly explored graphene material for biomedical applications. It is generally obtained by chemical, thermal, and electrochemical reduction of GO [73]. Both GO and rGO hold great potential in biomedicine such as polymer composites, biological sensors, bioimaging, targeted drug delivery, and photothermal therapy (PTT) [74]. CNTs are allotropes of carbon, which consist of hexagonally aligned sp^2 hybridized carbon atoms interlinked with each other to form a tubular shape with an outer diameter ranging from 4 to 30 nm. Structurally, they are similar to graphite sheets that are rolling upon themselves. The rolled sheets can be single, double, or many walls, and therefore they are named as single-walled, double-walled, or multiwalled carbon nanotubes (MWNTs), respectively. Due to their unique physical, chemical, and mechanical characteristics, these materials have wide applications in various areas including polymer science, biomedical research, energy storage, electrodes, gas sensors, catalyst support, etc. [75,76].

21.5.1 Graphene oxide/reduced graphene oxide for drug delivery

Functionalized GO has been extensively investigated for anticancer therapy because of its high water solubility and biocompatibility. Z. Rao et al. [77] investigated complex of amino-modified GO with carboxymethycellulose as a carrier of DOX. A cumulative drug release of 65.2% was observed at pH 5. The cytotoxicity studies on Hela cell and mouse fibroblasts (NIH-3T3) cells by MTT assay have indicated good biocompatibility with no cytotoxicity. N. Duran et al. [78] have developed hybrids by coupling small interfering RNA (siRNA)-GO-PEG (6ARM-poly(ethylene glycol)amine-PEI (polyethylenimine) as a carrier to administer DOX in nonmuscle invasive bladder cancer (NMIBC) treatment. In vivo studies revealed 60% normal bladder diagnosis for the association of GO-COOH-DOX and GO-PEG-PEI/siRNA. A. Deb et al. [79] demonstrated use of the anticancer drug camptothecin (CPT) loaded onto GO nanomaterial with PEG and FA against MCF-7 by MTT assay. They observed higher cytotoxicity to the cancer cell with CPT loaded onto GO-PEG-FA in comparison with free drug. Also, the nontoxic nature of the drug composite was confirmed by cell viability assay wherein 95% of cell count was observed after 24 hr incubation. N. Hussien et al. [80] investigated aptamer-conjugated magnetic graphene oxide (MGO) nanocarrier for targeted drug delivery cancer treatment. They used nanosize magnetite particles on GO layer with aptamer as a targeting moiety and paclitaxel (PAC) as an anticancer agent. In vitro results have indicated 95.75% entrapment efficiency and

pH-sensitive drug release. Cytotoxicity studies have shown biocompatibility of MGO nanocarrier with over 80% cell viability for fibroblast cell line (L-929) with high cytotoxic effect of PAC-loaded MGO on MCF-7. S. Kiew et al. [81] studied dextrin-conjugated GO nanocarrier as drug delivery system to respond to a tumor-associated stimulus, α-amylase. They observed 1.5-fold higher release and 2-fold increase in the cytotoxic effect of DOX in dextrin-conjugated GO. Also, higher permeabilities through fenestrated endothelial barrier were observed for GO-based nanocarrier. R. Sousa et al. [82] developed hyaluronic acid (HA) functionalized-rGO for cancer PTT. The rGO was obtained by greener route employing L-ascorbic acid as reducing agent and functionalized using hyaluronic acid−based amphiphilic polymer. The functionalization with amphiphile improved its thermal stability, cytocompatibility, and internalization by CD44 overexpressing cells, which indicates its potential for targeted cancer therapy.

21.6 Conclusions

Nanotechnology has provided novel and powerful materials that may be used in the treatment and diagnosis of cancer. However, there are still limitations due to the heterogeneity of the cells used for each tumor model in vitro and/or in vivo, which make it difficult to do a comparison between the different studies. Another limitation is the formation of protein corona when NPs reach the blood and interact with the plasma proteins, affecting in vivo distribution and clearance. Nonetheless, the majority of products, reagents, and drugs being used for the development of these nanoscale theranostic agents have still to be approved by the main supervising agencies, such as the FDA and EMA. Research continues in this area, and more information about the distribution, biocompatibility, and low toxicity for normal tissues is necessary prior to clinical trials. Thus far, there are some questions whose answers still provide no clear understanding about the design and application of NPs, such as pharmacokinetics, biodistribution, and side effects of the nanotherapies, and safety profile of NPs before and after conjugation and toxicity. Even though there is no general mechanism for making NPs universally “nontoxic” to all living cells and all organisms, there are important findings that can be applied for increasing nanoparticle biocompatibility and reducing cytotoxic interactions in vivo and in vitro. Although both metallic and nonmetallic NPs have shown potential to be powerful tools against cancer, they still need further optimization and characterization for complete understanding of therapeutic mechanisms. It is now time to start translating these promising nanoplatforms to the clinical settings toward widespread effective therapy strategies in the fight against cancer.

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References

[1] Babes L, Denizot B, Tanguy G, Jeune L, Jallet P. Synthesis of iron oxide nanoparticles used as MRI contrast agents: a parametric study. J Colloid Interface Sci 1999;212:474–82.

[2] Goya GF, Berquo TS, Fonseca FC, Morales MP. Static and dynamic magnetic properties of spherical magnetite nanoparticles. J Appl Phys 2003;94(5):3520–8.

[3] Arruebo M, Pacheco RF, Ibarra MR, Santamaría J. Magnetic nanoparticles for drug delivery. Nano Today 2007;2:22–32.

[4] Madani SY, Naderi N, Dissanayake O, Tan A, Seifalian AM. A new era of cancer treatment: carbon nanotubes as drug delivery tools. Int J Nanomed 2011;6:2963–79.

[5] Wicki A, Witzigmann D, Balasubramanian V, Huwyler J. Nanomedicine in cancer therapy: challenges, opportunities, and clinical applications. J Contr Release 2015;200:138–57.

[6] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2018;68(1):7–30.

[7] GBD 2015 mortality and causes of death collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the global burden of disease study 2015. Lancet 2016;388:1459–544.

[8] Reddy KS. Global burden of disease study 2015 provides GPS for global health 2030. Lancet 2016;388:1448–9.

[9] DeSantis C, Siegel R, Bandi P, Jemal A. Breast cancer statistics, 2011. CA Cancer J Clin 2011;61(6):409–18.

[10] Nandakumar A. National cancer registry programme. Indian council for medical research, consolidated report of the population based cancer registries 1990–96. New Delhi: Indian Council of Medical Research; 2009.

[11] Probst CE, Zrazhevskiy P, Bagalkot V, Gao X. Quantum dots as a platform for nanoparticle drug delivery vehicle design. Adv Drug Deliv Rev 2013;65(5):703–18.

[12] Chidambaram M, Manavalan R, Kathiresan K. Nanotherapeutics to overcome conventional cancer chemotherapy limitations. J Pharm Pharmaceut Sci 2011;14:67–77.

[13] Nguyen VL, Cao MT, Masayuki N. The recent patents and highlights of functionally engineered nanoparticles for potential applications in biology, medicine, and nanomedicine. Curr Phys Chem 2014;4:173–94.

[14] Stensberg MC, Wei Q, McLamore ES, Porterfield DM, Wei A, Sepúlveda MS. Toxicological studies on silver nanoparticles: challenges and opportunities in assessment, monitoring and imaging. Nanomedicine 2011;6:879–98.

[15] Munger MA, Radwanski P, Hadlock GC, Stoddard G, Shaaban A, Falconer J. In vivo human time-exposure study of orally dosed commercial silver nanoparticles. Nanomedicine 2014;10:1–9.

[16] Rao PV, Nallappan D, Madhavi K, Rahman S, Wei LJ, Gan SH. Phytochemicals and biogenic metallic nanoparticles as anticancer agents. Oxid Med Cell Longev 2016. https://doi.org/10.1155/2016/3685671.

[17] Dreaden EC, Austin LA, Mackey MA, El-Sayed MA. Size matters: gold nanoparticles in targeted cancer drug delivery. Ther Deliv 2012;3:457–78.

[18] Gobbo OL, Sjaastad K, Radomski MW, Volkov Y, Prina-Mello A. Magnetic nanoparticles in cancer. Theranostics 2015;5:1249–63.

[19] John AA, Subramanian AP, Vellayappan MV, Balaji A, Mohandas H, Jaganathan SK. Carbon nanotubes and graphene as emerging candidates in neuroregeneration and neurodrug delivery. Int J Nanomed 2015;10:4267–77.

[20] Zhou T, Zhou X, Xing D. Controlled release of doxorubicin from graphene oxide based charge-reversal nanocarrier. Biomaterials 2014;35:4185−94.

[21] Yang X, Wang Y, Huang X, Ma Y, Huang Y, Yang R, Duan H, Chen Y. Multifunctionalized graphene oxide based anticancer drug-carrier with dual-targeting function and pH-sensitivity. J Mater Chem 2011;21:3448−54.

[22] Goenka S, Sant V, Sant S. Graphene-based nanomaterials for drug delivery and tissue engineering. J Contr Release 2014;173:75−88.

[23] Wei D, Qian W. Facile synthesis of Ag and Au nanoparticles utilizing chitosan as a mediator agent. Colloids Surf B Biointerfaces 2008;62:136−42.

[24] Nadagouda MN, Varma RS. Green synthesis of Ag and Pd nanospheres, nanowires, and nanorods using vitamin b_2: catalytic polymerisation of aniline and pyrrole. J Nanomater 2008;1−8.

[25] Fkiri A, Mezni A, Robert C, Caps V, Smiri LS. Synthesis of monodisperse gold octahedral in polyol: selective oxidation of stilbene. Colloids Surf, A 2017;530:85−92.

[26] Hatakeyama Y, Morita T, Takahashi S, Onishi K, Nishikawa K. Synthesis of gold nanoparticles in liquid polyethylene glycol by sputter deposition and temperature effects. J Phys Chem C 2011;115(8):3279−85.

[27] Panda BR, Chattopadhyay A. Synthesis of Au nanoparticles at "all" pH by H_2O_2 reduction of $HAuCl_4$. J Nanosci Nanotechnol 2007;7(6):1911−5.

[28] Giljohann DA, Seferos DS, Daniel WL, Massich MD, Patel PC, Mirkin CA. Gold nanoparticles for biology and medicine. Angew Chem Int Ed 2010;49:3280−94.

[29] Dreaden EC, Alkilany AM, Huang X, Murphy CJ, El-Sayed MA. The golden age: gold nanoparticles for biomedicine. Chem Soc Rev 2012;41:2740−79.

[30] Zhang XD, Chen J, Luo Z, Wu D, Shen X, Song SS. Enhanced tumor accumulation of sub-2 nm gold nanoclusters for cancer radiation therapy. Adv Healthc Mater 2014;3:133−41.

[31] Zhang XD, Luo Z, Chen J, Song S, Yuan X, Shen X. Ultrasmall glutathione-protected gold nanoclusters as next generation radiotherapy sensitizers with high tumor uptake and high renal clearance. Sci Rep 2015;5:8669.

[32] Huang K, Ma H, Liu J, Huo S, Kumar A, Wei T. Size-dependent localization and penetration of ultrasmall gold nanoparticles in cancer cells, multicellular spheroids, and tumors in vivo. ACS Nano 2012;6:4483−93.

[33] Xu P, Feng Q, Yang X, Liu S, Xu C, Huang L, Chen M, Liang F, Cheng Y. Near infrared light triggered cucurbit [7] uril-stabilized gold nanostars as a supramolecular nanoplatform for combination treatment of cancer. Bioconjug Chem 2018;29:2855−66.

[34] Gulla SK, Kotcherlakota R, Nimushakavi S, Nimmu NV, Khalid S, Patra CR, Chaudhuri A. Au-CGKRK nanoconjugates for combating cancer through t- cell-driven therapeutic RNA interference. ACS Omega 2018;3:8663−76.

[35] Ke S, Zhou T, Yang P, Wang Y, Zhang P, Chen K, Ren L, Ye S. Gold nanoparticles enhance TRAIL sensitivity through Drp1-mediated apoptotic and autophagic mitochondrial fission in NSCLC cells. Int J Nanomed 2017;12:2531−51.

[36] Li WR, Xie XB, Shi QS, Zeng HY, Ou-Yang YS, Chen YB. Antibacterial activity and mechanism of silver nanoparticles on *Escherichia coli*. Appl Microbiol Biotechnol 2010;8:1115−22.

[37] Chernousova S, Epple M. Silver as antibacterial agent: ion, nanoparticle, and metal. Angew Chem Int Ed 2013;52:1636−53.

[38] Gurunathan S, Park JH, Han JW, Kim JH. Comparative assessment of the apoptotic potential of silver nanoparticles synthesized by Bacillus tequilensis and Calocybe indica in

MDA-MB-231 human breast cancer cells: targeting p53 for anticancer therapy. Int J Nanomed 2015;10:4203−22.

[39] Roychoudhury P, Gopal PK, Paul S, Pal R. Cyanobacteria assisted biosynthesis of silver nanoparticles-a potential antileukemic agent. J Appl Phycol 2016;28:3387−94.

[40] Blanco J, Lafuente D, Gómez M, Garcıá T, Domingo JL, Sánchez DJ. Polyvinyl pyrrolidone-coated silver nanoparticles in a human lung cancer cells: time- and dose-dependent influence over p53 and caspase-3 protein expression and epigenetic effects. Arch Toxicol 2016;91(2):651−66.

[41] Khan M, Khan M, Al-Marri AH, Al-Warthan A, Alkhathlan HZ, Siddiqui MR. Apoptosis inducing ability of silver decorated highly reduced graphene oxide nanocomposites in A549 lung cancer. Int J Nanomed 2016;7:873−83.

[42] Yuan YG, Wang YH, Xing HH, Gurunathan S. Quercetin-mediated synthesis of graphene oxide-silver nanoparticle nanocomposites: a suitable alternative nanotherapy for neuroblastoma. Int J Nanomed 2017;16:5819−39.

[43] Netchareonsirisuk P, Puthong S, Dubas S, Palaga T, Komolpis K. Effect of capping agents on the cytotoxicity of silver nanoparticles in human normal and cancer skin cell lines. J Nanoparticle Res 2016;18:322.

[44] Bhanumathi R, Manivannan M, Thangaraj R, Kannan S. Drug-carrying capacity and anticancer effect of the folic acid- and berberine-loaded silver nanomaterial to regulate the akt-erk pathway in breast cancer. ACS Omega 2018;3:8317−28.

[45] Kunkalekar RK, Prabhu MS, Naik MM, Salker AV. Silver-doped manganese dioxide and trioxide nanoparticles inhibit both gram positive and gram negative pathogenic bacteria. Colloids Surf B Biointerfaces 2014;113:429−34.

[46] Kunkalekar RK, Naik MM, Dubey SK, Salker AV. Antibacterial activity of silver-doped manganese dioxide nanoparticles on multidrug-resistant bacteria. J Chem Technol Biotechnol 2013;88:873−7.

[47] Shen W, Li Z, Wang H, Liu Y, Guo Q, Zhang Y. Photocatalytic degradation for methylene blue using zinc oxide prepared by codeposition and sol−gel methods. J Hazard Mater 2008;152:172−5.

[48] Wang LC, He L, Liu YM, Cao Y, He HY, Fan KN, Zhuang JH. Effect of pretreatment atmosphere on CO oxidation over α-Mn_2O_3 supported gold catalysts. J Catal 2009;264:145−53.

[49] Gawas SG, Gawas UB, Verenkar VMS, Kothawale MM, Pednekar R. Structural and magnetic studies of cu-substituted nanocrystalline ni−zn ferrites obtained via hexamine−nitrate combustion route. J Supercond Nov Magnetism 2017;30:1447−52.

[50] Gawas UB, Verenkar VMS, Meena SS, Bhatt P. Influence of Mn substitution on mössbauer and magnetic properties of ni-zn ferrites nanoparticles. J Supercond Nov Magnetism 2017;30:3241−6.

[51] Abenojar EC, Wickramasinghe S, Bas-Concepciona J, Samia. Structural effects on the magnetic hyperthermia properties of iron oxide nanoparticles. Prog Nat Sci 2016;26:440−8.

[52] Savla R, Minko T. Nanoparticle design considerations for molecular imaging of apoptosis: diagnostic, prognostic, and therapeutic value. Adv Drug Deliv Rev 2017;113:122−40.

[53] McCormack PL. Ferumoxytol in iron deficiency anaemia in adults with chronic kidney disease. Drugs 2012;72:2013−22.

[54] Hauser AK, Mitov MI, Daley EF, McGarry RC, Anderson KW, Hilt JZ. Targeted iron oxide nanoparticles for the enhancement of radiation therapy. Biomaterials 2016;105:127−35.

[55] Zou Z, Li H, Wang S. Induction of reactive oxygen species: an emerging approach for cancer therapy. Apoptosis 2017;22(11):1321−35.

[56] Li W, Zaloga J, Ding Y, Liu Y, Janko C, Pischetsrieder M, Alexiou C, Boccaccini AR. Facile preparation of multifunctional superparamagnetic PHBV microspheres containing SPIONs for biomedical applications. Sci Rep 2016;6:23140.

[57] Lee KJ, An JH, Shin JS, Kim DH, Chung KH. Tumor-targeting hederagenin-loaded magnetic nanoparticles for anticancer drug delivery. Adv Mater Lett 2016;7:366−70.

[58] Malekzadeh AM, Ramazani A, Tabatabaei Rezaei SJ, Niknejad H. Design and construction of multifunctional hyperbranched polymers coated magnetite nanoparticles for both targeting magnetic resonance imaging and cancer therapy. J Colloid Interface Sci 2017;490:64−73.

[59] Mallick N, Anwar M, Asfer M, Mehdi SM, Rizvi MMA, Panda AK. Chondroitin sulfate-capped super-paramagnetic iron oxide nanoparticles as potential carriers of doxorubicin hydrochloride. Carbohydr Polym 2016;151:546−56.

[60] Mondal S, Manivasagan P, Bharathiraja S, Moorthy MS, Nguyen VT, Kim HH, Nam SY, Lee KD, Oh J. Hydroxyapatite coated iron oxide nanoparticles: a promising nanomaterial for magnetic hyperthermia cancer treatment. Nanomaterials 2017;7:426.

[61] Saikia C, Das MK, Ramteke A, Maji TK. Evaluation of folic acid tagged aminated starch/ZnO coated iron oxide nanoparticles as targeted curcumin delivery system. Carbohydr Polym 2017;157:391−9.

[62] Moghadam NH, Salehzadeh S, Rakhtshah J, Tanzadehpanah H, Moghadam AH, Hajibabaei F, Sharifinia S, Asl SS, Saidijam M. Improving antiproliferative effect of the nevirapine on Hela cells by loading onto chitosan coated magnetic nanoparticles as a fully biocompatible nano drug carrier. Int J Biol Macromol 2018;15:1220−8.

[63] Zhang AP, Sun YP. Photocatalytic killing effect of TiO_2 nanoparticles on Ls- 174-t human colon carcinoma cells. World J Gastroenterol 2004;10(21):3191−3.

[64] Colon J, Hsieh N, Ferguson A, Kupelian P, Seal S, Jenkins DW, Baker CH. Cerium oxide nanoparticles protect gastrointestinal epithelium from radiation-induced damage by reduction of reactive oxygen species and upregulation of superoxide dismutase 2. Nanomedicine 2010;6(5):698−705.

[65] Wahab R, Kaushik NK, Kaushik N, Choi EH, Umar A, Dwivedi S, Musarrat J, Al-Khedhairy AA. ZnO nanoparticles induces cell death in malignant human T98G gliomas, KB and non-malignant HEK cells. J Biomed Nanotechnol 2013;9(7):1181−9.

[66] Sankar R, Maheswari R, Karthik S, Shivashangari KS, Ravikumar V. Anticancer activity of *Ficus religiosa* engineered copper oxide nanoparticles. Mater Sci Eng C 2014;44:234−9.

[67] Wani A, Savithra GHL, Abyad A, Kanvinde S, Li J, Brock S, Oupický D. Surface PEGylation of mesoporous silica nanorods (MSNR): effect on loading, release, and delivery of mitoxantrone in hypoxic cancer cells. Sci Rep 2017;7(1):2274.

[68] Bhuyan MSA, Uddin MN, Islam MM, Bipasha FA, Hossain SS. Synthesis of graphene. Int Nano Lett 2016;6:65−83.

[69] Bagotia N, Choudhary V, Sharma DK. A review on the mechanical, electrical and EMI shielding properties of carbon nanotubes and graphene reinforced polycarbonate nanocomposites. Polym Adv Technol 2018;29:1547−67.

[70] Power AC, Gorey B, Chandra S, Chapman J. Carbon nanomaterials and their application to electrochemical sensors; a review. Nanotechnol Rev 2017;7(1):1−48.

[71] Khan I, Saeed K, Khan I. Nanoparticles: properties, applications and toxicities. Arabian J Chem 2018. https://doi.org/10.1016/j.arabjc.2017.05.011.

[72] McCallion C, Burthem J, Rees-Unwin K, Golovanov A, Pluen A. Graphene in therapeutics delivery: problems, solutions and future opportunities. Eur J Pharm Biopharm 2016;104:235−50.

[73] Stobinski L, Lesiak B, Malolepszy A, Mazurkiewicz M, Mierzwa B, Zemek J, Jiricek P, Bieloshapka I. Graphene oxide and reduced graphene oxide studied by the XRD, TEM and electron spectroscopy methods. J Electron Spectrosc Relat Phenom 2014;195:145–54.
[74] Davami K, Jiang Y, Cortes J. Tuning the mechanical properties of vertical graphene sheets through atomic layer deposition. Nanotechnology 2016;27(15):155701.
[75] Popov VN. Carbon nanotubes: properties and application. Mater Sci Eng 2004;43:61–102.
[76] Mishra NS, Kuila A, Nawaz A, Pichiah S, Leong KH, Jang M. Engineered carbon nanotubes: review on the role of surface chemistry, mechanistic features, and toxicology in the adsorptive removal of aquatic pollutants. Chem Select 2018;3:1040–55.
[77] Rao Z, Ge H, Liu L. Carboxymethyl cellulose modified graphene oxide as pH-sensitive drug delivery system. Int J Biol Macromol 2018;107:1184–92.
[78] Durán N, Fávaro W. Nanopharmaceuticals and their applications in bladder cancer therapy: a mini review. J Braz Chem Soc 2018;29(5):973–85.
[79] Deb A, Vimala R. Camptothecin loaded graphene oxide nanoparticle functionalized with polyethylene glycol and folic acid for anticancer drug delivery. J Drug Deliv Sci Technol 2018;43:333–42.
[80] Hussien NA, Işıklan N, Türk M. Aptamer-functionalized magnetic graphene oxide nanocarrier for targeted drug delivery of paclitaxel. Mater Chem Phys 2018. https://doi.org/10.1016/j.matchemphys.2018.03.015.
[81] Kiew SF, Ho YT, Kiew LV, Kah JCY, Lee HB, Imae T, Chung LY. Preparation and characterization of an amylase-triggered dextrin-linked graphene oxide anticancer drug nanocarrier and its vascular permeability. Int J Pharm 2017;534:297–307.
[82] Sousa RL, Melo-Diogo D, Alves CG, Costa EC, Ferreira P, Louro RO, Correia IJ. Hyaluronic acid functionalized green reduced graphene oxide for targeted cancer photothermal therapy. Carbohydr Polym 2018;200:93–9.