Nanotheranostics

Subjects: Others

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Several nanotheranostics are used in medical imaging and radiation therapy for tumor detection and treatment.

metal nanoparticles nanotheranostics medical imaging

1. Gold-Based Nanoparticles

Many studies have used gold nanoparticles (AuNPs) for therapeutic applications in cancer treatments [1]. High atomic number, relatively strong photoelectric absorption coefficient, good renal clearance, and biocompatibility are the features that make AuNPs a good, promising choice for use in radiotherapy [2][3]. Studies have often investigated the radiation sensitization and synergistic effects of AuNPs alone or in combination with other materials or treatment modalities. One pioneering in-vivo study was conducted by Herold et al. [4] in 2000 when it was first reported that gold microspheres could produce radiation dose enhancement against tumors using kilovoltage X-rays. Tudda et al. reported that 15 nm AuNPs could produce biologically effective dose enhancement in rotational radiotherapy of breast cancer using kilovoltage X-rays [5]. Luan et al. [6] described an improvement in the radio-therapeutic efficiency in the treatment of esophageal tumor-bearing mice following the delivery of AuNPs to tumors. Particle type, radiation parameters, and cell type are the main factors that affect the radio-sensitization efficiency of AuNPs. The sensitizing or synergistic effects of AuNPs in radiation therapy have been investigated using in vitro studies with X-rays, γ-rays, electron beams, and high-energy charged protons/carbon ions. In a study, the results showed that AuNPs could produce sensitization and synergistic effects in radiotherapy using different types of radiation [7][8][9][10]. In a major advance in 2022, Mzwd et al. [11] used a green technique for nanoparticle synthesis. They formed and used stable AuNPs in gum arabic (GA) solution via laser ablation technique as a computed tomography (CT) contrast agent. They claim that the image CT numbers increased with the concentration of GA-AuNPs. It has been suggested that the GA-AuNPs can be used as a CT contrast agent. Moreover, in another study that set out to determine the effect of glucose-modified dendrimer-entrapped gold nanoparticles (Au DENPs) labeled with radionuclide ^{68}Ga for positron emission tomography (PET)/ CT dual-mode imaging, Li et al. [12] found that ^{68}Ga labeled with 2-amino-2-deoxy-D-glucose (DG) DG-Au DENPs can be used for PET/CT imaging and immunotherapy of different tumor types. In this line [13], the researcher investigated the multi-modality imaging and photothermal effect of gold-doped upconverting nanoparticles (UCNPs). Zhang et al. [14] pointed out that due to photothermal stability, low cytotoxicity, and high biocompatibility, Au-UCNPs-DSPE-PEG$_{2k}$ may be utilized as magnetic resonance imaging (MRI) and CT contrast agents for both in vivo and in vitro, and may also be used for photothermal treatment.

2. Gadolinium-Based Nanoparticles

Gadolinium (Gd, rare earth (lanthanide) metal, Z = 64)-based nanoparticles have been used as multifunctional theranostic (diagnostic and therapeutic) agents in MRI-guided radiotherapy. Hence, Gd chelates have been applied for a more precise, accurate, and enhanced dose delivery in radiotherapy [15][16]. A study in 1996 [17] was conducted on the radio-sensitizing effect of Gd (III) texaphyrin (Gd-tex^{2+}). Results of this study showed that Gd-tex^{2+} was established to be an efficient radiation sensitizer in in-vitro and in-vivo experiments carried out with HT29 cells and a murine mammary carcinoma model, respectively. Motexafin gadolinium (MGd), a metallotexaphyrin, is a compound of gadolinium and an expanded porphyrin that can enhance the cytotoxic effects of radiation through several mechanisms relying on the additional generation of reactive oxygen species (ROS) that catalyze the oxidation of intracellular-reducing metabolites and interference with repair mechanisms of radiation-induced damage, which lead to increased cell death. Motexafin gadolinium showed great promise for multifunctional theranostic applications, especially for glioma treatment, and so far, two-phase clinical studies combined with standard radiation treatment have been established [18]. The research results indicated that, in addition to exploiting GdNPs as a positive MR imaging T_1 contrast agent, they had been identified as valued theranostic sensitizers for radiation therapy [19][20]. Being a toxic lanthanide heavy metal, free GdNPs are not used clinically; instead, it is used as an organic chelating agent compound. The GdNP “Activation and Guidance of Irradiation by X-ray,” or AGuIX, is a polysiloxane nanoparticle with chelated gadolinium that exhibits no toxicity in preclinical and early-stage clinical studies in humans at medically used concentrations and is eliminated rapidly via the kidneys [21][22][23]. The radiation dose enhancement and synergistic effects of GdNPs have also been proven in combination with other ionizing radiation types, such as γ-rays, X-rays, and charged particles [24][25][26]. At kilovoltage X- and γ-ray energies, interactions with high-Z GdNPs produce photoelectrons and numerous Auger electrons, which short-ranged electrons may improve the killing effects of radiation in a highly localized region, on the order of a few cell diameters or less [27][28]. With the increase in energy in megavoltage energies (MV), the physical mechanisms of radiation sensitization become less important and give way to biological mechanisms such as immune responses, oxidative stress, DNA damage, and repair responses [29][30]. The investigation into the combination of cell therapy and nanotechnology found that gadolinium-neutron capture therapy (Gd-NCT) can be used for glioblastoma multiforme (GBM) treatment [31]. More recent evidence [32] highlights that the Au@DTDTPA(Gd) NPs, in combination with conventional external X-ray irradiation, may be used as a radio-sensitizer for GBM treatment.

3. Iron-Based Nanoparticles

Iron-based NPs that include inorganic paramagnetic iron oxide (or magnetite) nanoparticles or superparamagnetic iron oxide nanoparticles (SPIONs) have been investigated as theranostic magnetic nanoparticles and are ideal agents for theranostic applications, especially cancer treatment due to their excellent properties, such as facile synthesis, biocompatibility, and biodegradability [33]. Iron NPs are useful as excellent MRI agents, photothermal therapy (PTT), photodynamic therapy (PDT), magnetic hyperthermia, radiation therapy, and chemo/biotherapeutics presented in varied investigations [34]. Iron NPs could be used as radio-sensitizers/enhancers. Although radio-sensitization is usually proposed for high Z-metals, and the atomic number of iron (Fe, Z = 26) is relatively low, IONs are primarily used in combination with low-linear energy transfer (LET) keV and MV X-rays. Iron oxide nanoparticles increased ROS production in cancer cells when combined with radiation therapy, compared to the

treatment with radiation therapy alone [35]. The efficiency of the radio-sensitization potential of silica-coated iron oxide magnetic nanoparticles (SIONPs) when exposed to an X-ray beam was studied in MCF-7 cells. MCF-7 cells tend to show increased radio-sensitization enhancement; meanwhile, with 0.5 Gy dose, dose enhancement factor (DEF) values of cells treated with 5 and 10 μg/mL of SIONPs were 1.21 and 1.32, respectively. Results demonstrated that SIONPs potentially improve the radio-sensitivity of breast cancer [36]. Guerra et al. [37] studied the radio-sensitization effects produced by gold and dextran-coated superparamagnetic iron oxide nanoparticles (SPION-DX) in M059J and U87 human glioblastoma cell lines irradiated by 6 MV photons beam. For U87 cells, SPION-DX nanoparticles with a core diameter of 21.1 nm showed a maximum sensitization enhancement ratio (SER10%) = 1.61 in the group exposed to 50 μg/mL of nanoparticles. For the radio-sensitive M059J cells, sensitization assisted by both types of nanoparticles was much less efficient. Furthermore, they found that sensitization mechanisms occurring through GNPs mostly follow the promotion of lethal complex damage, but SPION-DX repairable damage dominates. Other studies also reported the enhancement of radio-sensitization and synergistic effects on tumor cells in vitro and in vivo using X-rays accompanying with SPIONs and IONs [38][39][40]. Recently, in several studies, iron-based nanoparticle-mediated radio-sensitization was observed in combination with low-energy X-ray and monoenergetic γ-ray radiation [41][42][43]. Most of them reported that IONs enhanced the efficacy of X-ray energies above Fe K-edge more significantly than conventional broadband high-energy X-rays. Although the FDA has approved several ION formulations, specific unwanted toxicity issues reported in many studies that could be overcome by functionalization and surface modification with various coverage and ligands would be helpful to improve their circulation time, clearance, and evasion by reticuloendothelial system, as well as improving tissue targeting, biocompatibility, and stability [44][45][46][47][48]. It has now been demonstrated that [49] the doxorubicin (DOX)-loaded liposomal iron oxide NPs (IONP) (Lipo-IONP/DOX) might serve as a safe and effective agent for combined chemo/photothermal cancer therapy. Currently, iron oxide NPs are the ideal agents for cancer theranostics.

4. Tungsten-Based Nanoparticles

Tungsten (W, Z = 74) can produce photoelectrons, Compton electrons, scattered photons, high-energies characteristic X-rays, positron and negative electron pairs, and Auger electrons under high-energy irradiation that result in direct and indirect interactions (free radicals) with tumor cells [10][50][51][52]. Qin et al. [53] revealed that tungsten nanoparticles could be used for photothermal therapy (PTT) and RT combination treatment. Chen et al. [54] designed a novel theranostics nanoplatform (Au NPs/UCNPs/WO_3@C) comprising tungsten trioxide (WO_3) that loaded gold nanoparticles (Au NPs) and up-conversion nanoparticles (UCNPs). The nanosystem exhibited superior oxygen-generation effects and doxorubicin loading capacity, thus serving as an efficient radio-sensitizer for radio-chemo anticancer therapy. Niknam et al. discussed tungsten disulfide (WS2)-based nanomaterial as a PTT agent. In combination with X-ray irradiation, the nanocomposite could catalyze the high expression of H_2O_2 to produce cell membrane disruption, mitochondrial dysfunction, reactive oxygen species (ROS) production, and oxidative stress. The results showed that local RT/PTT could efficiently inhibit tumor metastasis, ablate local tumors, and prevent the recurrence of tumors. At the same time, the nanocomposite could also induce high temperatures under near-infrared irradiation to enhance RT results [51]. A large and growing body of literature [55][56][57][58] has

investigated tungsten nanoparticles' radiation protection and shielding effect in medical imaging. Surveys such as that conducted by Wu et al. [59] have shown that ultrasmall metal cores and metal-oxide shell nanoparticles, such as CoFe-WO_x ($CoWO_4$-Fe_2WO_6-WO_3), can be used as theragnostic nanoprobes for visible/infrared/MRI/CT imaging and photothermal/photodynamic and magnetothermal/magneto-dynamic therapies. The first study of two-dimensional (2D) PEGylated $WO_{2.9}$ (a substoichiometric form of WO_3) nanosheets for multimodal imaging was reported by Zhang et al. [60] in 2022. In another major study, Chen et al. [54] found that Au NPs and up-conversion NPs (UCNPs) loaded with tungsten trioxide (WO_3) produce novel theragnostic NPs, Au NPs/UCNPs/WO_3@C, which improved PA imaging performance. The research of Li et al. [61] showed that it is possible to use thermo-responsive polyethylene glycol-coated tungsten-doped vanadium dioxide (W-VO_2@PEG) NPs as nanoprobes for depth PA imaging.

5. Platinum-Based Nanoparticles

Platinum nanoparticles (PtNPs) are relatively new agents that have been extensively used as part of anticancer drug formulation (cisplatin, carboplatin, and oxaliplatin, etc.) in chemotherapy and chemoradiotherapy [62]. Considering the effective antioxidant property and anti-tyrosinase activity of PtNPs, developing these nanoparticles as anticancer agents can be one of the most valuable approaches for clinical use [63][64]. In order to improve therapeutic efficacy, functionalization of the surface of PtNPs could help to increase biodistribution, accumulation, cell-specific targeting, and controlled release, and reduce side effects to human beings. Though numerous studies highlight the chemotherapeutic effect of platinum-based anticancer drugs, there are relatively few published studies about the radio-sensitizing and synergistic effects of PtNPs for radiation therapy. Hullo et al. [65] showed that PtNPs could induce the radio-enhancement effect in breast cancer cell lines after internalization and accumulate in lysosomes and multivesicular bodies. Likewise, the lysosome-localized PtNPs could absorb radiation energy and focus more on the cancer site, damaging DNA and killing tumor cells. Zhang et al. [66] found that the radiation doses could be physically enhanced when combining the platinum nanoparticles coated with bovine serum albumin (BSA), Pt@BSA NPs, for use in radiotherapy. Also, studies showed that the presence of platinum nanoparticles when cell cultures were irradiated could result in strongly enhanced breaks in DNA, especially DSBs, mediated by water radicals which may originate from the inner-shell excitation of platinum atoms [25][67][68]. In other studies, Gutiérrez et al. [69] discussed the enhanced effect of radiation on cervical–uterine cancer cells (HeLa) when the cancer cells were treated with PEGylated PtNPs functionalized with a fluorescent marker in combination with γ-rays. Results showed that as the radiation dose increased, the number of survived cells decreased in the presence of the nanoparticles. Yang et al. [70] reported that Pt nanoenzyme-functionalized nanoplatform BP/Pt-Ce6@PEG NPs improved the cellular uptake and decomposed endogenous H_2O_2 into O_2 in situ to relieve tumor hypoxia, affording enhanced reactive oxygen species (ROS) production and causing the intratumoral oxygen level to surmount tumor hypoxia for efficient tumor treatment in an in vivo and in vitro study.

6. Bismuth-Based Nanoparticles

Meng et al. [71] developed bismuth and gadolinium-codoped carbon quantum dots (Bi, Gd-CQDs) for fluorescence imaging, CT imaging, and MRI imaging. They demonstrated that, due to the high X-ray attenuation coefficient, short T1 relaxation time, and robust and steady fluorescence characteristics of Bi, Gd-CQDs, we could use Bi, Gd-CQDs as a good nanoprobe for CT, MRI, and fluorescence imaging.

It was reported in the literature [72] that triptorelin peptide-targeted multifunctional bismuth nanoparticles (Bi_2S_3@BSA-Triptorelin NPs) might be used as a CT contrast agent.

In an investigation into introducing photoacoustic imaging (PAI) contrast agents for deep tissue imaging, Zhao et al. [73] used DNA-templated ultrasmall bismuth sulfide (Bi_2S_3) NPs for myocardial infarction imaging. For NPs synthesis, they employed a simple strategy for ultrasmall NPs via self-assembly of single-stranded DNA (ssDNA)/metal ion complexes. Zhao et al. [73] suggested that ultrasmall DNA-Bi_2S_3 NPs can be used as a PAI contrast agent for myocardial infarction imaging, and the ssDNA template could be used for ultrasmall PAI contrast agent preparation.

It has now been suggested that polymer-coated bismuth oxychloride (BiOcl) nanosheets can be used as CT contrast agents for gastrointestinal (GI) imaging [74].

In their groundbreaking paper, Zaho et al. [75] developed Bi@mSio_2@Mno_2/DOX as a powerful theragnostic agent for CT/MR imaging and photothermal therapy (PPT)/chemodynamic therapy (CDT)/chemotherapy cancer treatment. More recent evidence [76] shows the effect of reducing T_1 and T_2 relaxation times and increasing CT image contrast of Bi_2S_3@BSA-Fe_3O_4 nanoparticle as a dual contrast agent for MRI and CT imaging modalities.

7. Tantalum-Based Nanoparticles

Lakshmi et al. [77] investigated the impact of tantalum oxide NPs (TaOx NPs) and the Au-decorated tantalum oxide (TaOx-Au NPs) as imaging contrast agents on cancer diagnostics. As Lakshmi et al. [4] noted, TaOx-Au NPs, due to higher X-ray attenuation in a low-energy X-ray, is far more attractive than TaOx NPs and, therefore, can be used for cancer diagnosis with a CT imaging modality. A recent study [78] involved PEG-Ta_2O_5@Cus multifunctional NPs for diagnosing hepatocellular carcinoma (HCC) with CT/PA imaging. The application of poly-coated tantalum NPs (Ta@PVP NPs) in medical imaging was first demonstrated by Ji et al. [79]. In their seminal study, Ta@PVP NPs were used as radiotherapy/photothermal therapy (PTT) and CT/PA imaging agents in breast carcinoma.

8. Ytterbium-Based Nanoparticles

It has now been proposed that [80] glutathione functionalized ytterbium/iron oxide NPs as a dual-modality contrast agent for MRI/CT imaging. In a major advance, Dong et al. [81], for the first time, developed an ultrasmall ytterbium NPs (YbNPs) contrast agent for CT/spectral photon-counting computed tomography (SPECT) imaging. They pointed out that, in the clinical X-ray energy range, the YbNPs attenuation is significantly higher than the AuNPs. Many attempts have been made [82] to introduce multi-modality MRI/PA/near-infrared (NIR)-II fluorescence contrast

agents. They have focused on using calcium fluoride co-doped with rare-earth ions such as ytterbium, gadolinium, and neodymium (CaF_2: Yb, Gd, Nd) NPs. It has conclusively been shown that [83] Yb^{3+} concentration in $LaNbO_4$ nanoparticles affects the luminescent properties of NPs for medical imaging applications, and the intensity of emissions is directly related to Yb^{3+} concentration. Recently, an in-vivo study has shown that $BaYbF_5$-SiO_2 NPs can be used as contrast agents for imaging the osteochondral interface with micro-CT imaging with high-resolution images [84].

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