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Metal-Based Hybrid Nanoparticles as Radiosensitizers in Cancer Therapy

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ABSTRACT

Radiation therapy is one of the most commonly used interventions in cancer therapy. However, innate or acquired radioresistance in several cancers, and toxicity to normal tissues are still serious concerns. In order to enhance radiation response in cancer therapy, metal-based nanoparticles have been widely studied as the radiosensitizers. Recently, more and more studies have demonstrated the potential value of metal-based hybrid nanoparticles (MHNs) as novel radiosensitizers. In this review, we have summarized the applications of MHNs in optimization of radiosensitization, and in combinatorial therapeutic regimes for improving treatment outcomes in cancer therapy.

1. Introduction

Cancer is one of the most lethal diseases among humans. Traditional clinical methods including surgery, chemotherapy and radiation therapy (RT), have been widely adopted to treat cancer patients [1,2]. As a widely-used method to treat cancer patients, RT utilizes high-energy radiation, such as X-rays and gamma-rays, which causes lethal effects in cancer cells by enhancing reactive oxygen species (ROS) [3]. However, the damages to normal tissues, caused by the non-specific killing effect of radiation and resistance effect from hypoxic areas of tumor tissues, have raised public concern. An increased dose of radiation must be used to address the resistance effect of tumor tissues, which further causes more surrounding healthy tissues exposed in radiation. The balance between lethal effects on tumor tissues and protection of normal tissues is hard to maintain. As a result, one of proper strategies to keep the balance is to make the lethal radiation energy focus on tumor tissues. The discovery of radiosensitizers offered a possible choice to realize this strategy [4]. However, conventional radiosensitizers have cytotoxic effects and other side effects. In the past decade, the rapid development of nanotechnology offered opportunities for designing novel radiosensitizers [5–8]. Many studies have found that nanoparticles synthesized with high atomic number (high-Z) elements lead to efficient lethal effects on tumors [9–13]. When the X-rays or gamma-rays function on metal nanoparticles, a series of effects occur, *i.e.* photoelectron scattering creates special particles and enhance the activity [14]. In specifically, the energy which kill cancer cells is delivered from radiation waves to the particles, and functions on subcellular structures to finally cause lethal effects. Additionally, metal nanoparticles also show a tendency to alter hypoxia environment in tumor tissue [15].

In recent years, metal-based hybrid nanoparticles (MHNs) have been investigated for RT [16–18]. MHNs, by combining with high-Z elements and extra functional components such as noble metal and organic material, not only exhibit radiation enhancement properties, but also act as important biomedical agents in photothermal therapy (PTT) [19–26], photodynamic therapy (PDT) [27], and chemotherapy [16,28]. The MHNs provide many attractive possibilities for RT. For example, the tumor hypoxia microenvironment can be modulated by MHNs to overcome hypoxia-associated radiation resistance and enhance RT efficacy. Additionally, the possibilities to synthesis MHNs have led to innovative designs for various therapeutic strategies, such as RT-PTT and RT-PDT. Such combination of two different techniques

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can compensate the inherent limitations of each single therapeutic strategy. What's more, MHNs can increase the stability of sensitive materials and decrease the potential toxicity of certain materials (*e.g.*, Bi, Ag, Gd, and Pt) through specific hybrid structures. Although the applications of nanomedicine in RT have already been proposed for over a decade, there have been tremendous new progresses in past few years, particularly in the development of MHNs to promote RT *via* a number of different innovative mechanisms. In this review, the current literatures on cancer therapy with MHNs as radiosensitizers have been evaluated. We also conclude with an outlook of future prospects in this area, and point out the urge for MHNs-based RT.

2. Metal-Based Nanoparticles and Radiosensitization

Gold nanoparticles (AuNPs) are noble metal nanoparticles with advantages of small size, good biocompatibility and ease in chemical modification [29]. Due to such advantages, AuNPs have been widely used and analyzed in the field of biochemistry and biomedical engineering [30]. Specifically, the unique physicochemical characteristics of AuNPs make them an ideal candidate for application in cancer therapy [9,31,32]. AuNPs used in radiosensitization can increase photoelectric absorptions and lower electron beam range. *In vivo* researches show that X-rays cancer treatment with AuNPs as the radiosensitizer could extend the survival of the mice [12,33]. The radiosensitization is also observed in ratio-resistance cancer cells. Radiation with AuNPs increases ROS formation within cancer cells, and plays an important role in cell cycle. The lethal effect caused by AuNPs radiosensitizer is size-dependent [34]. According to the previous report, AuNPs with a diameter about 13 nm may cause the best lethal effect (Fig. 1) [34]. Size-dependent effects are seen when irradiation dose from 4 Gy to 8 Gy. At the dose of 6 Gy, AuNPs provide the most lethal effects on inhibiting tumor growth to negative control groups. Radiosensitization treatments only have lethal effects on tumor tissue, providing no obvious injury to normal tissues. AuNPs larger than 30 nm show the similar effect to that of 13 nm, but perform more serious cytotoxicity issues. Polyethylene glycol (PEG)-coated AuNPs with a diameter of ~13 nm are used to enhanced CT imaging and radiosensitization with an optimized results. AuNPs can also be further modified with different kinds of ligands to acquire functions for drug therapy or gene therapy.

In addition to AuNPs, other metal nanoparticles are also widely applied in radiosensitization. Silver nanoparticles (AgNPs) mediated cell death activities, including apoptosis, oxidative stress activation, and membrane fluidity [35]. Tantalum-based nanoparticles, like TaO_x covered by PEG and perfluorocarbon, are efficient oxygen carriers, thus improving cancer cellular concentration of oxygen [36]. So the oxygen loaded particles such as TaO_x not only enhance radiosensitization but also reduce hypoxia-associated radio-resistance. By synergistically working with X-ray, the amorphous PEG-Selenium nanoparticles significantly enhance inhibition of cell growth by mechanism of DNA double strand breaks and activation of capases-3, which functions in cell apoptosis [37].

3. Functional MHNs and Combination Application with Radiosensitization

RT is a therapy that uses ionizing radiation, which typically controls or kills malignant cells as part of the cancer treatment. Ionizing radiation works by damaging the DNA of tumor tissue leading to cell death. Traditionally single cancer treatment methods comprise of chemotherapy, RT and PTT, and they all have their own limitations. Therefore, the combination of two therapies can take the advantages of both therapies, while reducing their respective shortcomings has

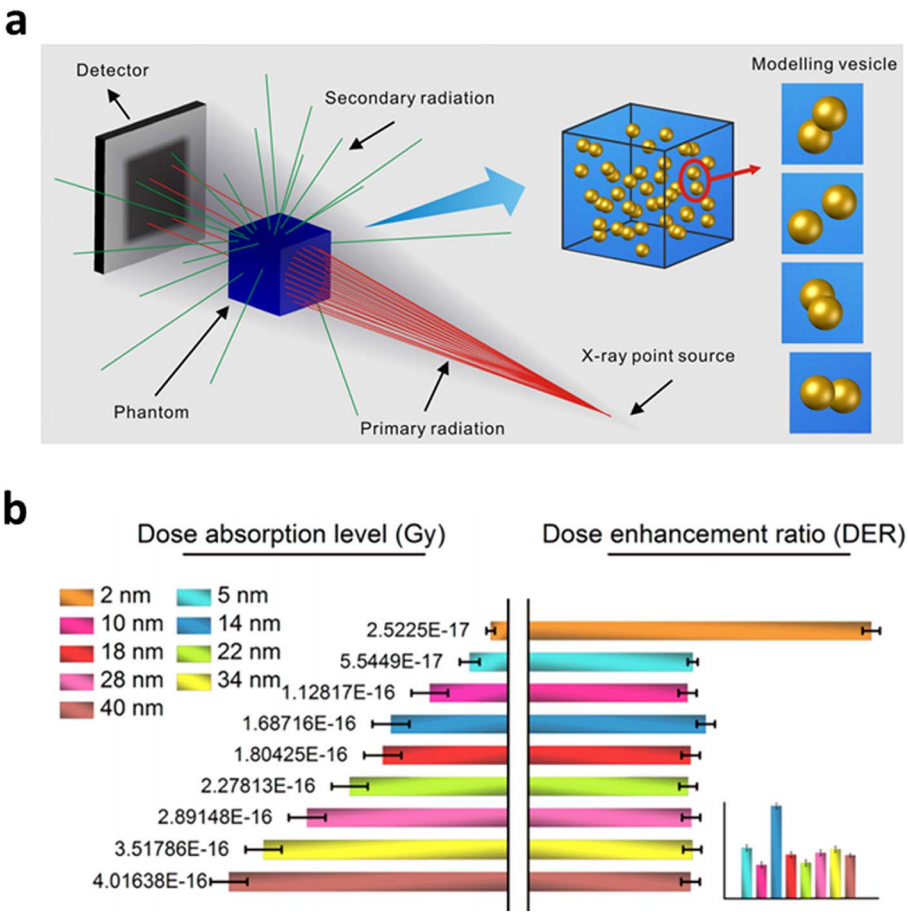

Fig. 1. Monte Carlo simulations to evaluate size-dependent enhancements. (a) Schematic showing a phantom filled with a AuNPs aqueous suspension that may trigger completely different secondary radiation depending on primary radiation energies irradiated from the X-ray point source for CT detection or RT. (b) Dose absorption levels (left) and dose enhancement ratios (DER) (right) of simulated particle sizes. [Reprinted with permission from Ref 34. Copyright ©2016 American Chemical Society].