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ROS-Mediated Photodynamic Cancer Therapy by Nanoparticle

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Abstract

Photodynamic therapy (PDT) offers great promise for cancer treatment in the presence of photosensitizer and molecular oxygen. Because of their biocompatibility, metal-based nanoparticles (NPs) are promising materials for applications as photosensitizers of PDT. The ROS-based therapeutic mechanism of NPs toward cancer cells has been elucidated. The influence factors of ROS production by NPs, including physicochemical properties of NPs (e.g. particle size and surface coating), solution chemistry (e.g. aqueous media) and experimental conditions (e.g. humic acid and light conditions), have been summarized. In addition, the ROS generation mechanism of metal-based NPs is elucidated. Finally, key challenges facing cancer therapy by metal-based NPs are listed and the directions for further research are pointed out.

Keywords: Nanoparticles; Cancer therapy; ROS; Impact factors

Abbreviations: PDT: Photodynamic Therapy; ROS: Reactive Oxygen Species; NPs: Nanoparticles; •OH: Hydroxyl Radical; $^1O_2$: Singlet Oxygen; O_2•−: Superoxide Radical; H_2O_2: Hydrogen Peroxide; DOM: Dissolved Organic Matter; HA: Humic Acid; SPR: Surface Plasmon Resonance; NHE: Normal Hydrogen Electrodes

Introduction

Traditional cancer treatment technologies such as chemotherapy and surgery have some limitations, including poor patient compliance and adverse drug reaction [1]. In recent years, photodynamic therapy (PDT) has received extensive attention for cancer treatment in the presence of photosensitizer and molecular oxygen due to its minimal invasiveness, nondrug resistance, low poison, and accurate tumor therapy [1-3]. PDT depends on the photochemical reaction between light and the photosensitizer to produce reactive oxygen species (ROS) that eventually leading to cancer cell death [4,5]. Since metal-based nanoparticles (NPs) are biocompatible, they are promising materials that can be used as photosensitizer for PDT [6,7]. It has been demonstrated that metal oxide or metallic NPs exposed to light can produce ROS that induce cancer cell damage [7,8]. In this review, we will summary the therapeutic mechanism of metal-based NPs toward cancer cells, influence factors of ROS production, and ROS production mechanism of metal-based NPs.

Therapeutic mechanism of metal-based nanoparticles

The main therapeutic mechanism of metal-based NPs to cancer cells is associated with the production of ROS and subsequent ROS-induced apoptosis in cancer cells [7,8]. Three types of ROS (hydroxyl radical (•OH), singlet oxygen ($^1O_2$) and superoxide radical (O_2•−) jointly contribute to the death of tumor cells [9]. Among them, •OH has the ability to non-specifically *oxidize many* any types of macromolecules, such as nucleic acids, carbohydrates, and DNA [8]. $^1O_2$ is the most detrimental ROS to tumor cells because it reacts extensively with amine acids, proteins unsaturated fatty acids and steroids [8]. This can lead to oxidation and degradation of bio membrane in cancer cells. O_2•− reacts with macromolecules slowly. However, O_2•− can produce hydrogen peroxide (H_2O_2) by disproportionate reaction [9]. H_2O_2 can be converted to •OH and $^1O_2$. Consequently,$^1O_2$, •OH and O_2•− may coexist and contribute to cancer therapy by NPs.

Effect factors of ROS production by metal-based nanoparticle

ROS production of metal-based NPs could be influenced by many factors, such as physicochemical properties of NPs (e.g. particle size and surface coating), solution chemistry (e.g. aqueous media), and environmental conditions (e.g. dissolved organic matter (DOM) and light conditions) [8,10]. The role of these parameters in ROS production is discussed below.

Effect of particle size

In general, when the particle size reduces, ROS production concentrations increase due to the larger surface areas and more reactive sites of NPs [11]. Previous study has shown that ROS production by Au (5-250 nm) under UV or X-ray irradiation linearly increased with the decrease of NPs diameters [6]. Metal-oxide NPs have been found to produce more ROS than their bulk counterparts because larger surface areas of NPs provide more reaction sites for light absorption and oxygen exposure [8].

Effect of surface coating

Surface coating can change the light absorption characteristics of metal-based NPs and will eventually affect their ROS production profile. In the field of biomedicine, surface coating was decorated on the metal-based NP surface to enhance ROS generation for photodynamic treatment of cancer [12]. However, Wang et al. demonstrated that ginger and mint decreased ROS production by Ag NPs in cells of Hep G2 and He La [7]. This is mainly because biocapping agents on the surface of Ag NPs have antioxidant activity [8].

Effect of aqueous medium

The ability of ROS production by metal-based NPs is significantly impacted by the physicochemical properties of the aqueous medium [13,14]. Previous studies have found that ZnO NPs generated O_2•−, •OH and $^1O_2$ in deionized water, sodium chloride solution, phosphate-buffered saline and minimal Davis medium, but only formed $^1O_2$ and O_2•− in Luria-Bertani medium [14]. ROS production ability could be decreased by the organic components (e.g., yeast extract glucose, tryptone and citrate) in the aqueous media [14].

Effect of DOM

No consistent conclusions on the role of DOM in ROS production by metal-based NPs exist. For example, researchers have shown that intracellular ROS production by TiO_2 NPs was promoted by humic acid (HA) in aquatic environment under natural sunlight irradiation. However, Lin et al. have demonstrated that HA inhibited ROS production by TiO_2 NPs under natural sunlight irradiation, which was mainly because HA acted as ROS quenchers [15]. The metal ions released by metal-based NPs could disable the triplet states of HA, resulting in their reduced sensitization ability for ROS production [16]. Moreover, DOM may serve as a UV filter and finally reduced ROS generation by NPs [17].

Effect of light condition

Light exposure plays an important role in ROS production of metal-based NPs in natural condition [14,18,19]. Previous studies have shown that light exposure, such as irradiation by xenon lamp, UV lamp, X-ray, and solar, could enhance ROS production by metal-based NPs [14,18,19]. $^1O_2$, •OH and O_2•− cannot be detected by all metal-oxide and metallic NPs in the dark, but at least one type of ROS was detected when exposed to UV light. This was because the light irradiation induces surface plasmon resonance (SPR) production in the surface of metallic NPs and electron-hole pairs in metal-oxide NPs, which will be elucidated in the following section.

Production mechanism of ROS

The generation mechanism of ROS in metal-oxide NP suspensions was clarified by comparing the band edge energy levels of metal oxides with the redox potentials of various ROS production [20,21]. For example, the E_c value of TiO_2 is -0.28 eV relative to normal hydrogen electrodes (NHE; all E_c and E_v values are relative to NHE) [22], which is lower than -0.2 eV (E_H of O_2/O_2•−). This demonstrate that the electrons in TiO_2 NPs have enough reductive power to reduce O_2 and result in O_2•− production. The reductive ability of the electrons in CuO conduction band (Ec value of 0.69 eV) is not enough to reduce O_2 [22], thus no measurable amount of O_2•− was detected in CuO suspension.

Metallic NPs can interact with light by scattering or absorbing the photons [6,18]. When excited by light, the oscillating electric field of the incoming radiation leads to coherent collective oscillation of the free mobile electrons on the surface of metallic NPs [6,18]. When the frequency of surface electron oscillation equals to that of the photon, SPR is produced [6,18]. A strong absorption of incident photon energy is induced by SPR, which can be transferred to O_2 and result in $^1O_2$ production [6,12]. The photoelectrons transferred to O_2 are responsible for the production of O_2•− [6], which can further enhance •OH production under light irradiation [6,12]. Research has showed that Ag NPs generated O_2•− and •OH [23]. $^1O_2$ was not discovered, which was primarily due to the consumption of $^1O_2$ by the released Ag^+ [23].

Conclusion and Perspectives

The applications of metal-oxide NPs for PDT are limited because the high band gap of NPs allows ROS production in the presence of UV light, which has poor penetration into biological tissue and can cause DNA damage. Efforts should be made to develop NPs capable of response to visible light or X-ray. In addition, further work should be done to combine with other therapies, such as photo acoustic and photo catalytic, to decrease the doses of NPs and overcome the drug resistance problem.

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