

Cerium oxide nanoparticles in cancer

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Abstract: With the development of many nanomedicines designed for tumor therapy, the diverse abilities of cerium oxide nanoparticles (CONPs) have encouraged researchers to pursue CONPs as a therapeutic agent to treat cancer. Research data have shown CONPs to be toxic to cancer cells, to inhibit invasion, and to sensitize cancer cells to radiation therapy and chemotherapy. CONPs also display minimal toxicity to normal tissues and provide protection from various forms of reactive oxygen species generation. Differential cytotoxicity is important for anticancer drugs to distinguish effectively between tumor cells and normal cells. The antioxidant capabilities of CONPs, which enable cancer therapy protection, have also resulted in the exploration of these particles as a potential anticancer treatment. Taken together, CONPs might be a potential nanomedicine for cancer therapy and this review highlights the current research into CONPs as a novel therapeutic for the treatment of cancer.

Keywords: cerium oxide nanoparticles, cancer treatment, radioprotection, radiosensitization

Introduction

Nanotechnology has become a main focus of biomedical research in recent years. Nanomaterials show many useful and unique properties and can be applied in the areas of medicine, biology, and life science research.¹⁻⁶ Nanoparticle applications include drug delivery systems, luminescent biomarkers, and tissue engineering, among others.⁷ Many nanomedicines have been designed for tumor therapy with the rapid development of nanoscience and nanotechnology. Nanomedicines are emerging as one of these new treatment options^{8,9} since it is necessary to explore novel drugs^{10,11} when the conventional therapies, including surgical interventions, radiation, and cytotoxic chemotherapies, are ineffective in curing cancer.⁸⁻¹² In particular, cerium oxide nanoparticles (CONPs), which consist of a cerium core surrounded by an oxygen lattice, have shown promise in a number of applications. The tissue or cell environmental conditions appear to play an important role in the determination of activity, as CONPs also possess direct oxidant behavior despite the fact that CONPs have been shown to display a number of antioxidant behaviors.¹³⁻¹⁷ To date, pH is one of the few factors shown to drive whether CONPs act as oxidants or antioxidants.^{18,19}

The reactive oxygen species (ROS) can drive both the initial development and progression of cancer, as well as downregulate antioxidant enzymes that normally combat radical production.²⁰ In normal, healthy cells, the cellular levels of ROS are tightly controlled.²¹ The ability to modulate the redox status of cells has applications in diseases in which ROS levels have become deregulated or are altered by treatment. Some studies have shown CONPs to possess innate cytotoxicity to cancer cells,

anti-invasive properties, and the ability to sensitize cancer cells to radiation-induced cell death, while protecting the surrounding normal tissues.^{18–21} Therefore, CONPs have extensive potential as a therapeutic agent for the treatment of cancer, as well as other diseases in which ROS have been implicated.²² Potential applications and prospects of CONPs in cancer are summarized herein.

Antitumor aspects

Cerium oxide is prepared by the supercritical synthesis method. There are two main ways of making the particles – chemical or flame spray pyrolysis.²³ It has been reported that many nanomedicines with chemical modifications can kill tumor cells by increasing ROS level in tumor cells or by targeting the nucleus or other organ cells.^{12,24–56} As for CONPs, a study has demonstrated their toxicity to cancer cells and inhibition of the metastasis and polymer-coated CONPs to manipulate tumor–stroma interactions to the detriment of tumor progression and invasion.²⁸ Another study found that CONPs caused cytochrome c release and activated caspase-3 and caspase-9, which demonstrates that CONPs induced the apoptosis of tumor cells by initiating a mitochondrion-mediated apoptosis signaling pathway without chemical modification, specifically targeting the mitochondria.¹²

Polymer coating of CONPs increases aqueous solubility,¹⁸ but it does not appear to impact CONP redox activities.^{13,28} Myofibroblasts largely mediate epithelial/stromal signaling. They play a key role in the expression of extracellular matrix components, including alpha-smooth muscle actin and collagen, to facilitate tumor invasion and angiogenesis.²⁹ Data show that CONPs possess the ability to modulate myofibroblast formation with the transition from fibroblast to myofibroblast driven by TGF- β 1-induced ROS-dependent expression of smooth muscle actin. Pretreatment with CONPs mitigated both the corresponding myofibroblast transition and TGF- β 1-induced alpha-smooth muscle actin expression in fibroblasts.^{7,28} As some myofibroblasts localize to the invasion front of tumors, CONP treatment diminished the ability of myofibroblasts to induce invasion by squamous tumor cells.²⁸ In addition, CONPs are also able to decrease the intrinsic ability of cultured squamous tumor cells to invade, even in the absence of any myofibroblast stimulation. To sum up, these results demonstrate the direct negative effects of CONPs on cancer cells, as well as their ability to modulate the tumor environment and indirectly inhibit tumor cell invasion. These data also suggest that CONPs as a new type

of antitumor nanomedicine can be applied to the treatment of cancer ultimately.²⁸

Radioprotection and radiosensitization

In addition to surgery and chemotherapy, radiation therapy (RT) remains a mainstay in the treatment of cancer.²⁹ However, the side effects of RT remain the most challenging issue for cancer treatment. Many harmful side effects are associated with RT, including nausea, fatigue, and dermatitis,^{30,31} but few radiation adjuvants are available to mitigate these painful outcomes. At present, the clinically available radioprotectant drugs are not ideal. These include amifostine, which remains the radioprotectant, and which is itself associated with nausea and hypotension.^{32,33} Thus, it is necessary to explore novel drugs. The ability of CONPs to modulate ROS has led to their exploration for the improvement of RT. The dual capabilities of CONPs to act as an oxidant in cancer cells, yet antioxidant in normal cells, supports the role of CONPs as an adjuvant for RT that could significantly impact patient quality of life. Several publications have shown that treatment with CONPs prior to RT exposure decreases the RT-induced cell damage and death in normal tissues in line with the protection from other methods of inducing oxidative stress.^{34–37} One study suggests that CeO₂ may be radioprotective for salivary production and reduce grade III dermatitis and skin hyperpigmentation incidence.³⁷ CeO₂ as radioprotectant may be a feasible concept during radiotherapy.³⁷ CONP radical scavenging was found to inhibit the resulting caspase-3 activation in irradiated colonic crypt tissue, as well as caspase-3 and -7 activation mechanistically in irradiated lung fibroblasts in culture.^{34,35} In addition, CONPs increased super oxide dismutase 2 (SOD2) expression up to twofold in a dose-dependent manner in normal human colon cells in vitro, while increasing SOD2 expression by 40% in colonic crypt cells from mice treated with CONPs.³⁴ The aquatic environment and the size of CONPs are important. pH, and phosphate ligands might play important roles in controlling the solubility of CeO₂.³⁸ pH is one of the few factors shown to drive whether CONPs act as oxidants or antioxidants.^{18,19} The antioxidant capabilities of CONPs have also resulted in the exploration of these particles as a potential treatment for other disorders characterized by ROS accumulation, which enables radiation protection. Thus, pH is an important factor for CONPs' appearance as nontoxic in normal cells because of a different pH in normal cells compared to tumor cells.¹⁹ In addition, the size and size distribution of the major components of the CONP solution are the most dominant factors for determining the dispersibility of

CONPs in solution.³⁹ Taken together, CONPs display minimal toxicity to normal tissues and provide protection from various forms of ROS generation.¹⁹ They may protect normal cells indirectly by priming cells to respond to ROS insult or directly by scavenging cellular ROS.

In contrast, CONPs have been found to be toxic to cancer cells, inhibit invasion, and sensitize cancer cells to RT. Pre-treatment with CONPs has been shown to enhance the ability of RT to induce cell death in cancer cells with acidic pH.⁷ Some studies showed that CONP treatment prior to RT markedly potentiated the cancer cell apoptosis, both in culture and in tumors, and the inhibition of the pancreatic tumor growth without harming the normal tissues or host mice.^{7,19} The results identify CONPs as potentially novel RT sensitizers as well as protectants for improving pancreatic cancer treatment. It has been suggested that CONPs in cancer cells are only capable of catalyzing the conversion of highly unstable superoxide to far more stable H₂O₂, as acidic pH has been shown to inhibit the catalase activity of CONPs.^{7,28} CONPs actually enhance the toxicity of RT in cancer cells by encouraging the accumulation and stability of ROS in the cell without the ability to act as a catalase mimetic and remove H₂O₂. These effects resulted in the radiosensitization of pancreatic cancer, significantly decreasing cell viability *in vitro*.¹⁹ In a pancreatic tumor-bearing mouse model that received the combination therapy of CONPs prior to RT, significant decreases in tumor weight and volume occurred with an increase in the number of apoptotic cells in the tumors.¹⁹

In all, these data demonstrate that CONPs modulate ROS in cancer cells such that, not only are there direct toxic effects, but the therapeutic properties of CONPs potentially extend to radioprotection and radiosensitization of cancer therapies.

CONP prospects in cancer treatment

CONPs are widely reported to be noncytotoxic and modulate intracellular ROS. The level of nanoceria surface functionalization with heparin determines the intracellular localization and ROS scavenging ability of these particles. Heparin–nanoceria was effective in reducing endothelial cell proliferation, indicating that they may have application in the control of angiogenesis in cancer in the future.⁴⁰ It has been shown that CONPs have a unique property of inducing angiogenesis, which is critical for many physiological and pathophysiological processes and promotes the formation of new blood vessels from existing blood vessels.⁴⁰ In particular, CONPs trigger angiogenesis by modulating the

intracellular oxygen environment and stabilizing hypoxia, inducing factor 1 α endogenously. Additionally, correlations between angiogenesis induction and CONP physicochemical properties, including surface Ce³⁺/Ce⁴⁺ ratio, surface charge, size, and shape, have also been explored. Increased Ce³⁺/Ce⁴⁺ ratio and high surface area make CONPs more catalytically active toward regulating intracellular oxygen, which in turn leads to more robust induction of angiogenesis. Atomistic simulation was also used to reveal that the surface reactivity of CONPs and facile oxygen transport promotes angiogenesis.⁴¹

Furthermore, various nanoparticle-based approaches to overcome efflux-mediated resistance have been investigated,⁴² such as the use of formulation excipients that inhibit transporter activity and co-delivery of the anticancer drug with a specific inhibitor of transporter function or expression. However, the effectiveness of nanoparticles can be diminished by poor transport in the tumor tissue. Hence, to overcome that, adjunct therapies that improve the intratumoral distribution of nanoparticles may be vital to the successful application of nanotechnology. Coadministration of the chemotherapeutic and efflux inhibitor in nanoparticles may allow temporal colocalization of some unfavorable molecules, limiting their nonspecific distribution and hence their toxicities.⁴² In addition, another study has shown that some of the excipients used in the construction of nanoparticles are capable of inhibiting efflux transporters.⁴³ Taken together, nanotechnology offers a promising approach for overcoming efflux pump-based drug resistance.

Curcumin has been used in the treatment of inflammatory disorders and cancer for many years.^{38,44–47} Curcumin may inhibit tumor growth via multiple mechanisms, including antitumor angiogenesis, suppression of proliferation, induction of apoptosis, and prevention of metastasis.^{48–53} There is some evidence suggesting that curcumin is an ideal chemosensitizer for chemotherapy and that it helps to protect patients from the side effects of treatment.^{54–58} Curcumin chemosensitizes because it is a highly effective scavenger of ROS and also inhibits the c-Jun NH₂-terminal kinase pathway.⁵⁹ Both ROS and activation of the c-Jun NH₂-terminal kinase pathway are crucial elements in the success of chemotherapy.⁵⁶ However, the clinical applications of curcumin remain limited because of its short biological half-life, poor solubility resulting in poor absorption, and low bioavailability via the oral route.^{60–62} Recently, many novel chemotherapeutic formulations have been developed. These formulations contain chemotherapeutic agents inside the vehicle, resulting in

better drug penetration into tumor tissue and less toxicity. Biodegradable polymeric nanoparticles are often used to achieve controlled release of drugs in advanced anticancer drug delivery systems.^{63–66} Further, some biodegradable polymer-derived drug delivery systems, such as nanoparticles delivering anticancer agents, are commercially available.⁶⁷ Despite overcoming drug resistance to chemotherapy and the development of chemosensitizers from nanoparticles, there is still little research concerning CONP in this context. Future studies involving CONP application in chemotherapy are anticipated.

Some studies have shown that CONPs can selectively induce apoptosis and suppress the proliferation of tumor cells. Wang et al showed that nanoparticles can target specific organs, have a lower toxicity against the whole organism, and have good dissolubility in water.¹ In their study, low concentrations of CONPs selectively killed tumor cells; the inability to clear CONPs might be one of the mechanisms that caused the CONPs to show selective cytotoxicity against tumor cells.¹ Other results demonstrated that CONPs not only significantly delayed the growth of subcutaneous melanoma, but also increased the survival rate of tumor-bearing mice without damage to the organs.¹² Importantly, the results also indicated that CONPs were rapidly cleared from the organs and that these particles exhibited little systemic toxicity.¹² In addition, published data indicate that CONPs are toxic to bronchial epithelial lung fibroblasts in culture, but nontoxic to mammary epithelial cells, macrophages, immortalized keratinocytes, or immortalized pancreatic epithelial cells.⁷ The physiological pH in normal cells, to which CONPs are not toxic, enables canonical radical scavenging by CONPs.^{19,23,68,69} Therefore, CONPs introduced prior to ROS insult confer protection from the effects of oxidative stress in vitro and in vivo.^{70–73}

On the other hand, CONPs are toxic to several types of human cancer cells.^{19,28,74} Cellular toxicity is attributed to the generation of ROS and the induction of oxidative stress, at least in part by the inherent oxidase activity of the nanoparticle core at acidic pH similar to that of cancer cells.^{13,19,28,69} CONPs can also produce ROS and initiate lipid peroxidation of the liposomal membrane, thereby regulating many signaling pathways and influencing the vital movements of cells. In particular, CONP treatment has been shown to induce glutathione oxidation, lipid peroxidation, and membrane damage in lung cancer cells.⁷⁴ The generation of CONPs with a negative surface charge can induce preferential accumulation in acidic lysosomes within the cell, resulting in increased toxicity in cancer cells.

Conclusion

Differential cytotoxicity is important because one of the greatest challenges in chemotherapy is the inability of anticancer drugs to distinguish effectively between tumor cells and normal cells. Taken together, despite the fact that the number of potential applications for CONP-based therapies appears countless, given that ROS and oxidative stress linked to so many conditions, these results demonstrate that CONPs have selective cytotoxicity toward tumor cells, and indicate that CONPs might be a potential nanomedicine for cancer therapy and results pertaining to the potential application of CONPs for the treatment of numerous diseases are overwhelmingly positive thus far.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No 81301937) and by the International Cooperation Foundation of Shaanxi Province of China (No 2013KW-27-03).

Disclosure

The authors report no conflicts of interest in this work. This paper has not been published previously. This study will not be published elsewhere in the same form, in English or in any other language, without consent of the publisher.

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