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Layer-by-layer capsules as smart delivery systems of CeO_2 nanoparticle-based theranostic agents

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Modern methods of cancer treatment include chemotherapy and radiotherapy, but they are often characterized by low efficacy and high toxicity. The effectiveness of cancer therapy is often limited by a lack of effective systems for drug delivery to the tumor site. Cerium oxide nanoparticles are able to act as radioprotectors and as radiosensitizers exhibiting selective toxicity in the tumor microenvironment, providing for their tremendous potential in treating cancer. However, methods for controlled delivery of CeO_2 nanoparticles to the tumor have not been investigated nor described yet. In this article, we consider different approaches to the development of new ceria nanoparticle-based theranostic agents. Modification of polyelectrolyte microcapsules with nano-ceria appears to be the most promising method. Our design proposals are based on the synergistic pharmacological action of ceria-based nanomaterials and anticancer pharmaceuticals with the ability to control and visualize their sites of localization.

Keywords: cerium oxide nanoparticles, polyelectrolyte microcapsules, theranostics agents, radiation therapy.

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1. Introduction

Radiation therapy is one of the leading methods of cancer treatment [1]. According to WHO recommendations, radiation therapy is advised for more than 70 % of cancer patients within a particular plan of treatment or as part of combined and complex therapy. Treatment of patients with locally advanced tumors corresponding to stages III–IV is particularly difficult due to their sheer numbers of 54–68 % (even when modern diagnostic tools are used) [2]. Radiation therapy is often the only possible means of medical care for these patients. Apart from a purely technical solution to the problem by improving radiotherapy techniques today, much attention is paid to the control of tissue radiosensitivity, i.e. to the development of methods for selective effect on the radiosensitivity of tumor and normal tissue to expand the boundaries of a radiotherapy interval. Prospects for the combination of radiotherapy and chemotherapy for patients with locally advanced tumors are associated with the development of radiochemotherapy. Radiochemotherapy treatment is a method in which radiation and chemical substances are used simultaneously, wherein the special drugs have not only cytostatic effects but also exhibit radiosensitizing properties [3, 4]. The procedure for selecting chemotherapy drugs as photosensitizers, their dosages, optimal modes of administration, as well as the development of adequate dose fractionation schemes of ionizing radiation are still relevant. Methods of administering already known radiomodifiers that increase efficiency and reduce toxic side effects also need improvement.

The present level of nanotechnology development allows the synthesis of new multifunctional nanomaterials with unique physical and chemical properties which are widely used in biomedical applications, including the radiotherapy of tumors. For example, heavy metal nanoparticles (mostly gold nanoparticles) are used in radio-theranostics (radiodiagnostics and radiotherapy) of tumors [5–8]. Bismuth oxide nanoparticles have also been shown to enhance the effect upon irradiation [9] and can replace gold nanoparticles. Multifunctional bismuth sulfide nanocapsules can be used in combined ultrasonic and radiation therapy [10]. The complex therapy uses magnetic iron oxide particles that also have low toxicity [11], and dextran-coated iron oxide nanoparticles decrease tumor growth in a breast cancer model by the combined action of hyperthermia and radiation [8]. Gadolinium oxide nanoparticles (Gd_2O_3) are also considered an alternative to gold nanoparticles. Ultra-small Gd_2O_3 nanoparticles are

accumulated in brain tumors after intravenous injection and can be used for visualization by MRI and subsequent radiation therapy [12]. Hafnium oxide nanoparticles increase the destructive effect of radiation due to the emission of Auger electrons and increase the generation of ROS [13]. The intratumoral injections of 50-nm-sized HfO_2 followed by radiation therapy sessions have shown good results in Phase 1 clinical trials with locally advanced soft tissue sarcoma patients [14].

One of the most promising materials having a multifaceted mechanism of radioprotective action is nanosized cerium oxide [15, 16]. Cerium oxide nanoparticles have SOD-mimetic activity and inactivate superoxide radicals [17], and their ability to inactivate hydrogen peroxide is comparable to that of catalase [18, 19]. Using a variety of surface modifiers and synthetic methods allows one to vary the size, shape, and charge of cerium oxide nanoparticles that affect their physical and chemical characteristics, including the level of antioxidant activity, and consequently intracellular biological effects [16, 20–22]. The presence of oxygen vacancies (defects in a crystal lattice) and auto-regenerative oxidation-reduction cycle ($Ce^{3+} \longleftrightarrow Ce^{4+}$) enable the use of cerium oxide nanoparticles as broad-spectrum antioxidant drugs at the neutral pH found in healthy tissues [23, 24]. Conversely, in the tumor, cerium oxide nanoparticles are able to perform as both peroxidase (effective pro-oxidant) and a radiosensitizer. The key external condition determining the pathway of the biological activity for cerium oxide nanoparticles in cancer therapy is the pH of the medium [16, 25–29] and the power of X-rays used [30]. Previously, it was shown [21] that cerium oxide nanoparticles significantly reduce the level of ROS and increase cell survival in the non-malignant normal cells ($pH \geq 7$) after exposure to ionizing radiation, while emerging as strong pro-oxidants in cancer cells of the pancreas ($pH \leq 7$) increasing cell death. On the other hand, Briggs et al. [30] showed that the use of radiation of different intensities may have a different impact on the radioprotective properties of cerium oxide nanoparticles. When exposed to low-intensity X-rays (150 kVp), cerium oxide nanoparticles do not exhibit radioprotective properties and increase cell death, generating additional Auger electrons that act as radiosensitizers. However, when high-intensity X-ray radiation (10 MV) is used, cerium oxide nanoparticles exhibit a strong radioprotective effect by inactivating a broad range of ROS and free radicals produced by radiolysis, i.e. work as radioprotectors. The key factor determining the effectiveness of radiation therapy of cancer is the localization of cerium oxide nanoparticles while the development of the targeted delivery of cerium oxide nanoparticles is an urgent task of modern biomedicine.

In this article, we propose the use of biodegradable polyelectrolyte microcapsules modified with cerium oxide nanoparticles, other comprising functional components and anticancer pharmaceutical preparations (Fig. 1) for complex therapy of cancer. This microcapsule structure will provide a synergistic effect for the encapsulated anticancer drug and cerium oxide nanoparticles in a combined therapy of oncological diseases. The presence of specific antigens on the surface of the microcapsules will facilitate its targeted delivery to tumor cells.

2. The hypothesis assessment and review

Polyelectrolyte microcapsules are one of the most promising means for effective controlled delivery of substances to target organs and tissues. Previously it was shown that they can be used for encapsulating proteins [20], DNA [31], RNA [32], pharmaceutical formulations [33] and other compounds. A layer-by-layer method of synthesizing polyelectrolyte microcapsules is based on the use of differently charged polyelectrolytes that are alternately adsorbed on an organic (polymeric) or inorganic (oxides, calcium carbonate) substrate [34]. For example, a positively charged substrate is placed in a solution of polyanions, the deposition of which leads to recharging the surface, and the substrate becomes negatively charged preventing further adsorption of polyanions. Adsorptive saturation occurs and the molecular layer is formed with a thickness of about 1 nm. The substrate is then rinsed in water and placed in a solution of positively charged macromolecules. Polycations are deposited, forming ionic bonds between oppositely charged ionic groups, and then they again recharge the surface. These mild synthetic conditions allow the encapsulation of biologically active materials (proteins, peptides, pharmaceuticals, etc.) while retaining their native properties. Thus, a bilayer is formed which can be repeated a number of times. The stratified character of polyelectrolyte microcapsule formation provides ample opportunities for managing their physical and chemical properties. The degradation rate of microcapsules and release of the contents into the cell can be adjusted by varying the type of polyelectrolyte and the number of adsorbed layers. Using a polyelectrolyte matrix can also maintain the physicochemical properties and biological activity of its constituent nanoparticles.

Cerium oxide nanoparticles can be introduced into the microcapsule by a variety of ways (Fig. 1): as a component of the polyelectrolyte shell (A), core (B), or the gap between the core and the shell (C).

The layer-by-layer method allows the integration of CeO_2 nanoparticles by replacing one of the polyanion or polycation layers (Fig. 1, A). In [35], the authors used a similar approach to introduce titanium dioxide into microcapsule shells. Using photoactive TiO_2 nanoparticles allows one to control the release rate of the microcapsules' contents by irradiation. The incorporation of magnetic particles into the shell (e.g. iron oxide) allows control

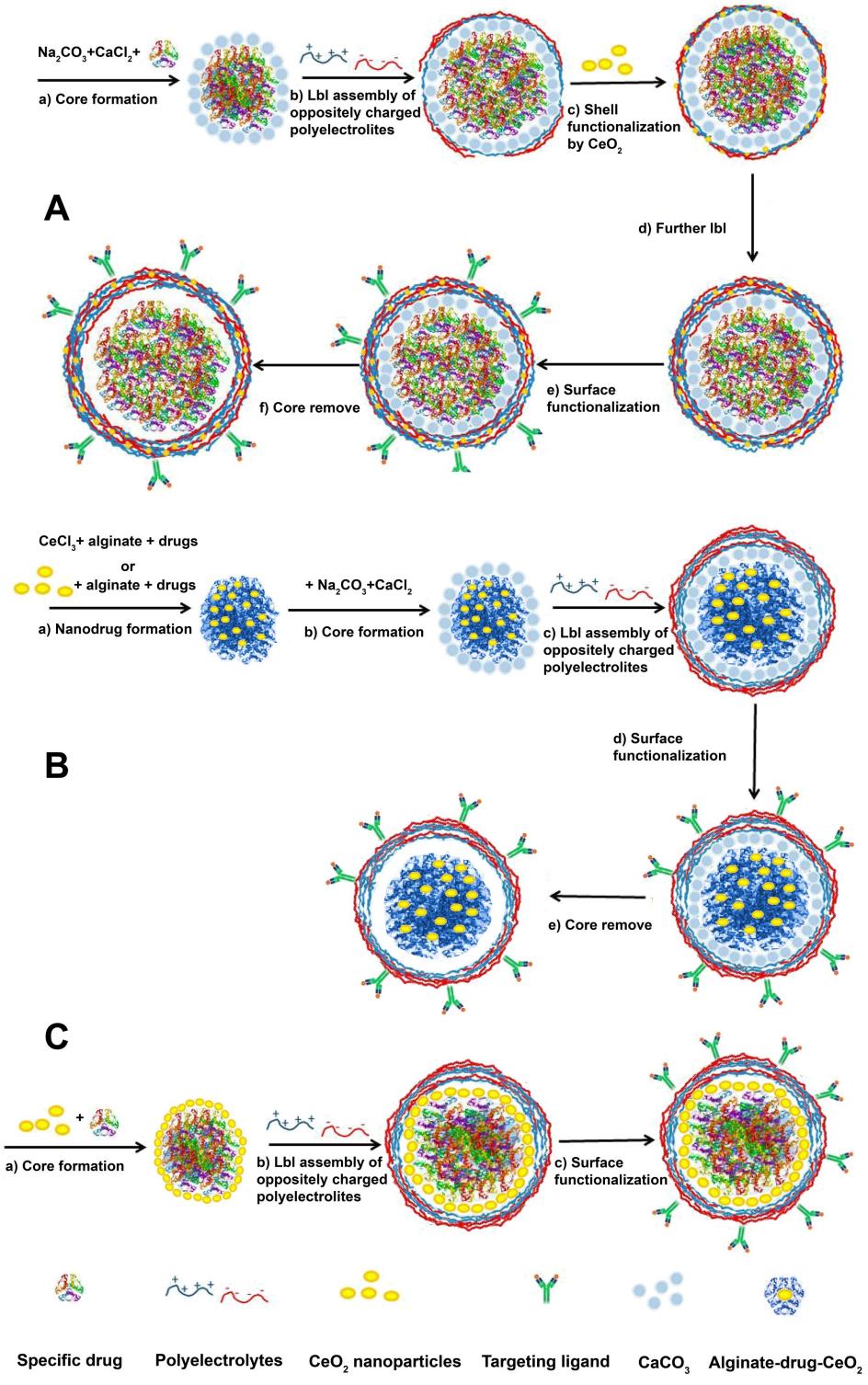

FIG. 1. Possible synthetic scheme of biodegradable polyelectrolyte microcapsules by LbL (layer-by-layer) assembly with cerium oxide nanoparticles: (A) located in shell; (B) located in core and (C) covering the core. A – Encapsulation of anticancer drug (a), step-by-step deposition of differently charged polyelectrolytes (b, d), their modification by cerium oxide nanoparticles (c) functionalization by antibody (e), and removal of the core supporting shell (f). B – Formation of hybrid particles consisting of a drug, cerium oxide nanoparticles and binding polymer (alginate or alginate + chitosan) (a) encapsulation of anticancer drug (b), step-by-step deposition of differently charged polyelectrolytes (s), functionalization by specific antibodies (d) and removal of the core supporting shell (e). C – Encapsulation of anticancer drug with cerium oxide nanoparticles (a), step-by-step deposition of differently charged polyelectrolytes (b) and functionalization by antibodies (c).

over the delivery. In the latter case, the shell modification may be carried out using both previously synthesized magnetite nanoparticles [36] and *in situ* formation of Fe_3O_4 nanoparticles directly on the capsule shell [37, 38]. In the first case, because of the mutual repulsion of charged nanoparticles, their adsorption is limited. In the second case, the nanoparticles formed in the solution are adsorbed on the surface of the polyelectrolyte capsules wherein they are partially stabilized by the shell's polymers. Silver nanoparticles have also been incorporated into microcapsules' shells by the *in situ* method [39]. To introduce CeO_2 nanoparticles into the shell of the microcapsules, both approaches can be used (via pre-synthesized nanoparticles and *in situ* approach). The techniques described herein allow control of the final nanoparticle concentration in each microcapsule up to 1 unit.

Unstabilized ("naked") cerium oxide nanoparticles in solution have a positive ζ-potential (ca. 40 mV) [40], and thus, can replace a polycation layer during microcapsule synthesis. Conversely, polycarboxylic (citric, polyacrylic) acids normally used for the stabilization of cerium oxide nanoparticles provide a negative ζ-potential (ca. -15 mV) [41, 42], and these particles can be incorporated into the microcapsule shell in place of one of the polyanion layers. In terms of electrostatic interaction and the DLVO theory (a physical theory of stability of colloidal systems), with an increase in the particle charge, the rate of adsorption equilibrium increases, but the amount of adsorbed particles per cycle application decreases (fewer particles are required to compensate the charge of a previous layer). Thus, using CeO_2 sols with different ζ-potentials (both in sign and in absolute value) allows one to adjust the loading of a microcapsule with nanoparticles during its synthesis as well as the rate of nanoparticle release during its degradation.

To implement the approach *in situ* after the next polyanionic layer is applied, microcapsules must be transferred into a solution with a predetermined amount of cerium ions in the form of a soluble Ce(III) salt, then, after the adsorption equilibrium is achieved the medium should be made alkaline. At pH $>$ 7, the Ce(III) salts are hydrolyzed and rapidly oxidized by dissolved oxygen to Ce(IV), and cerium oxide nanoparticles are generated on the surface of the microcapsule. Subsequently, microcapsules can be transferred into a solution of polyanion to generate additional layers.

If the therapeutic agent and the cerium oxide nanoparticles are chemically compatible, (as happens in most cases), then, the latter can be introduced into the core of the microcapsule together with the drug (Fig. 1, B). The use of an auxiliary binder polymer allows the formation of the core of hybrid organic-inorganic particles. Thus, alginic acid is often used as a biologically acceptable binding carrier polymer (the compound is a heteropolysaccharide formed by residues of polyuronic acid). The water-soluble alginate forms solid insoluble particles and films in the presence of polyvalent metal ions (calcium salts are most commonly used). Introduction of the cationic polymer (chitosan, poly-L-arginine or poly-L-lysine) can adjust the size of the particles formed. For example, 250–850 nm (depending on the alginate concentration) particles were synthesized as drug carriers; these particles are formed in solution by adding sodium alginate, calcium chloride and then poly-L-lysine [43]. The particle size can also be controlled by the volume of "nanoreactors" (micelles); reverse micelles were successfully used to synthesize nanocarriers (from alginate and calcium salts) with an average size of about 80 nm in diameter exhibiting a high degree of endocytosis by NIH 3T3 cells [44]. It is also possible to combine the surfactant and the cationic polymer to tune the size of alginate particles. In [45], a weakly polar natural polyphenol curcumin (diferulometan) which is widely used in cancer treatment (including radiotherapy) and prevention was encapsulated into 100 ± 20 nm calcium alginate particles. Cationic polymers (chitosan and a non-ionic surfactant (Pluronic)) were used as auxiliary compounds, and their absorption by HeLa cancer cells was recorded using curcumin fluorescence. In a series of preliminary experiments, we found that sols of ceria nanoparticles ("naked" or stabilized by citrate) can be successfully used instead of calcium salts for alginate gelation. In addition, water-soluble salts of cerium may also be used for that purpose. Alginate+CeO_2 nanoparticles systems can serve as a template for the storage and transport of biologically active compounds. Furthermore, the resulting combined nanodrug can be used as a constituent in the formation of an LbL-microcapsule core (Fig. 1, B).

Finally, cerium oxide nanoparticles can be used as a microcapsule core coating and as the basis for the application of polyionic layers (Fig. 1, C). For this purpose, the drug (a part of the microcapsule core) can be treated with a solution of cerium salt or a sol of cerium oxide nanoparticles prior to addition of the polyelectrolyte. Moreover, if the drug has an acidic functional group and is insoluble in water or if the drug is a slightly polar liquid (a slightly polar solid soluble in non-polar or weakly polar liquid), then the particles capable of performing the function of the microcapsule core can be formed directly in the sol of ceria by injection/homogenization (to form a Pickering emulsion [46]). In the literature, there are many examples of the preparation of drug-based sols using nanoparticles. The above mentioned curcumin was successfully stabilized in the aqueous sol by SiO_2 nanoparticles (the sol's stability is 100 times higher than in water) [47]; silica+curcumin composite has great promise in cancer therapy [48]. Our preliminary studies have shown that stability of the aqueous curcumin sols in the presence of

cerium oxide nanoparticles also increases. The resulting hybrid particle may be used as an LbL-microstructure core (Fig. 1, C).

Polyelectrolyte microcapsules may be functionalized by specific surface ligands or antibodies to a particular type of receptor on the surface of cancer cells (Fig. 1, A–C). For example, for the treatment of breast cancer polyelectrolyte microcapsules can be functionalized by selective antibody to the HER2 antigen which is over-expressed on the surface of this type of cancer cells [49]. Antibodies to HORMAD1, CXorf61, ACTL8, PRAME, MAGE and CSAG antigens [50] can be used for treating testicular cancer (those are also over-expressed on the surface of tumor cells of this type). The level of expression varies, depending on the stage of tumor development; however, there is the possibility of selecting both specific antibodies and an encapsulated pharmaceutical preparation at a particular stage of development of the disease.

It was earlier noted that the pro- and antioxidant activity of cerium oxide nanoparticles correlates with the concentration of oxygen vacancies and lattice defects in CeO_2. This parameter can be adjusted, for example, via the introduction of CeO_2 nanoparticles doped with other rare earth elements [51]. The use of gadolinium is quite promising indeed [52–54]. Gadolinium doped cerium oxide nanoparticles not only demonstrate superior antioxidant properties but also can serve as a contrast agent in tumor diagnostics (X-ray CT and enhanced MRI). The microcapsules designed with the use of gadolinium doped cerium oxide nanoparticles could thus serve both therapeutic and diagnostic purposes.

The functionality of microcapsules can be increased by fluorescent label introduction. Organic luminophores or nanoparticles of rare earth elements oxides doped by europium or terbium ions can be used as such a label.

For example, if in a microcapsule design one polyanionic layer is replaced with a fluorescein isothiocyanate-dextran conjugate (FITC-Dextran) or if a layer of polycation is replaced with a rhodamine isothiocyanate-dextran conjugate (RITC-Dextran), these microcapsules will become luminescent. Additionally, the behavior of these microcapsules in the cell can be monitored from the time of administration (accumulation) to degradation. If cerium oxide nanoparticles functionalized with calcein are included in the composition of the microcapsules, these microcapsules will exhibit fluorescent properties only when reacting with active oxygen species [55], which would permit their monitoring during therapy. Moreover, if those luminophores have different emission wavelengths (e.g., calcein in nanoparticles and rhodamine in the shell), this combination would allow monitoring the pharmacokinetics and pharmacodynamics at all stages of the introduction, distribution and degradation of microcapsules.

As nanocrystalline luminophores for microcapsules, it is preferable to use yttrium or gadolinium orthovanadate doped with europium (Gd/YVO_4:Eu) [56,57] or cerium fluoride doped by terbium (CeF_3:Tb) [58]. In the synthesis of "smart" multi-layered microcapsules, it is expedient to replace one ionic nanoparticle layer with CeF_3:Tb [58] or polyacrylic acid with YVO_4:Eu nanoparticles synthesized in [56] to visualize the nanoparticles of cerium oxide doped with gadolinium. In addition to the fluorescent properties, these compounds exhibit an independent antioxidant and radioprotective activity [57–59]. Similar to CeO_2, nanocrystalline CeF_3 is involved in redox processes (and in some cases is even superior to cerium oxide nanoparticles in its protective effect [58]). Cerium fluoride is one of the most efficient scintillators [60]. The use of CeF_3 (and CeF_3:Tb) nanoparticles in radiological diagnostics and therapy has great promise. For example, in microcapsule construction, a photosensitizer (of porphyrin or phthalocyanine series) can be placed near to cerium fluoride nanoparticles so that during radiotherapy under the influence of light emitted by the scintillator the photosensitizer will generate oxygen radicals and singlet oxygen. Reactive oxygen species will accelerate the degradation of the microcapsule shell, releasing its contents during radiotherapy, as well as provide additional damaging factors in tumor cells through photodynamic (radio dynamic) action.

Figure 2 shows one possible mode of action for smart polyelectrolyte microcapsules in tumor cells. Due to the presence of surface ligands (antibodies), microcapsules can be selectively accumulated at the site of oncogenesis, making it possible to define the size and location of the tumor (A) and to select a subsequent procedure of radiotherapy (B) using diagnostic methods (CT and MRI). Once inside the tumor cell, the microcapsules will be destroyed releasing the anti-cancer drug and cerium oxide nanoparticles into the cytoplasm of a cancer cell. Further irradiation of the cells by low-intensity X-rays will cause the surface of ceria oxide nanoparticles to generate secondary Auger electrons, and the anti-cancer drug will provide a specific effect inhibiting the metabolism of cancer cells. The acidic pH of "tumor microenvironment" promotes the pro-oxidant activity of cerium oxide nanoparticles and the generation of reactive oxygen species. This multifaceted effect of all components of the polyelectrolyte microcapsules should result in a rapid accumulation of reactive oxygen species in cancer cells and in their DNA damage that ultimately leads to the destruction of malignant tumors.

This article describes possible methods for the synthesis and functionalization of the polyelectrolyte microcapsules by cerium oxide nanoparticles to form novel drug delivery and theranostic systems. However, detailed

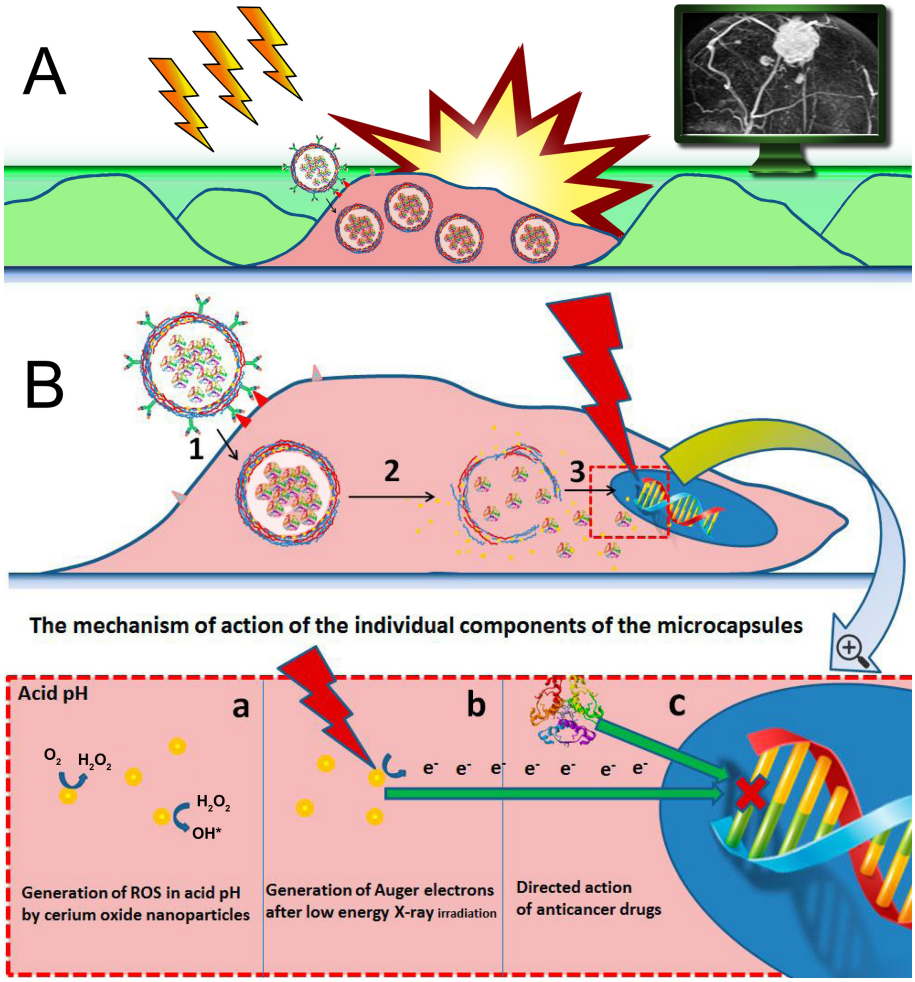

FIG. 2. Role of "smart" polyelectrolyte microcapsules in a cancer cell in radiation diagnostics (A) and treatment (B). Targeted entry into the cell (1), degradation of the microcapsules, and release of cerium oxide nanoparticles and encapsulated anticancer drug (2), the effect of low-intensity X-rays (3). The mechanism of action of polyelectrolyte microcapsules in a cancer cell: a – pro-oxidant properties of cerium oxide nanoparticles in the site of carcinogenesis; b – generation of Auger electrons by cerium oxide nanoparticles; c – chemotherapy by anti-cancer drug.

research is required to determine cytotoxicity and effectiveness *in vitro* and *in vivo* as well as confirm the mechanism of action.

3. Conflict of interest

The authors declare no conflict of interest.

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