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Cerium-based nanoparticles for cancer photodynamic therapy

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Metal- and metal-oxide-based nanoparticles have been widely exploited in cancer photodynamic therapy (PDT). Among these materials, cerium-based nanoparticles have drawn extensive attention due to their superior biosafety and distinctive physicochemical properties, especially the reversible transition between the valence states of Ce(III) and Ce(IV). In this review, the recent advances in the use of cerium-based nanoparticles as novel photosensitizers for cancer PDT are discussed, and the activation mechanisms for electron transfer to generate singlet oxygen are presented. In addition, the types of cerium-based nanoparticles used for PDT of cancer are summarized. Finally, the challenges and prospects of clinical translations of cerium-based nanoparticles are briefly addressed.

Keywords: Photodynamic therapy; photosensitizer; cerium; reactive oxygen species.

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1. Introduction

Cancer is a life-threatening disease with an incidence that increases significantly with age, resulting in the deaths of millions of people.[1] Conventional therapy, including surgery, chemotherapy, and radiotherapy,[2] can efficaciously treat some cancers and inhibit cancer metastasis. Nevertheless, these treatments have inevitable drawbacks, such as a high recurrence rate for surgical resection and severe damage to the whole body from chemotherapy and ionizing radiation. Photodynamic therapy (PDT) is a phototherapy technique that takes advantage of light sources to selectively eliminate primary and recurrent cancers,[3] thereby avoiding damage to normal tissue, achieving noninvasive treatment, and improving the quality of life of patients.[4] PDT has been gradually applied in different fields of biotechnology over the past few years because of its high efficiency, high selectivity, and noninvasiveness.[5–7]

PDT is a local therapeutic modality that is implemented via photoelectron energy transfer and conversion.[8] Under excitation by an appropriate light source, a photosensitizer (PS) interacts with oxygen to generate cytotoxic reactive oxygen species (ROS) for the treatment of various diseases. During this process, the conversion of triplet oxygen molecules ($^3O_2$) into singlet oxygen ($^1O_2$) is accompanied by oxygen consumption. The production of ROS by a PS can efficaciously and precisely destroy malignant tissues with minor side effects.[9–11]

With the continuous development of nanoscience, nanotechnology has been widely used for biomedical applications, such as in drug delivery, imaging, and biological detection, which has significantly revolutionized biomedical technology.[12–14] Recently, metal-based nanoparticles (NPs), such as manganese dioxide,[15,16] iron oxide,[17] and cerium oxide,[18] have been widely boosted for PDT with therapeutic effects.[1,19] In general, ideal PSs for PDT have outstanding photodynamic properties along with low or even no toxicity toward normal cells in the absence of light irradiation.[20,21] Among these PSs, cerium and its oxidant-based nanoparticles have received extensive attention because of its low cytotoxicity and unique physicochemical characteristics,[22] especially the reversible transition between the valence states of Ce(III) and Ce(IV).[23]

The ion diagram of CeO_2 (Fig. 1) depicts the tetrahedron of Ce atoms centered on the O atom as well as the charges on these atoms. In Fig. 1 (from left to right), while reducing two Ce ions to the trivalent valence state, the reduction process forms a neutral oxygen vacancy (hollow circle) in the interior of the tetrahedron. With Ce(IV) occupying the octahedral interstitial sites and O^{2-} occupying the tetrahedral interstitial sites, CeO_2 exhibits a face-centered cubic (FCC) fluorite crystal structure. One of the most fundamental features of CeO_2 is the production and migration of oxygen vacancies, which allows for reversible conversion between antioxidants Ce(III) and prooxidants Ce(IV). The marvelous oxygen storage properties.[23] of CeO_2 NPs have been demonstrated in photocatalysis,[24] magnetic semiconductors,[8] and oncotherapy.[25,26]

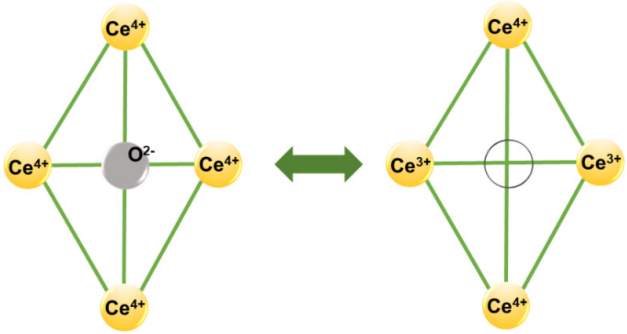

Fig. 1. Diagrammatic representation of charge redistribution that occurs after the oxygen vacancy formation in CeO_2.

CeO_2 NPs are one type of low-toxicity rare-earth nanoparticles[27] that have attracted extensive attention in the field of biomedicine because of multienzyme mimicking activities.[28] In general, the PDT properties of nanoparticles are highly dependent on their structures and physicochemical properties. Chemical doping, surface functionalization, and other strategies have been utilized for modulating the physicochemical properties and morphology of CeO_2 NPs to enhance photodynamic performance.

Herein, we summarize advances in the applications of cerium and its oxidant-based nanoparticles to cancer PDT (Fig. 2). The underlying working mechanisms of Ce-based PDT were first revealed with representative examples. Next, we focus on the design and synthesis of cerium-based nanoparticles. Finally, the challenges and prospects of cerium and cerium-oxide-based materials for PDT are presented.

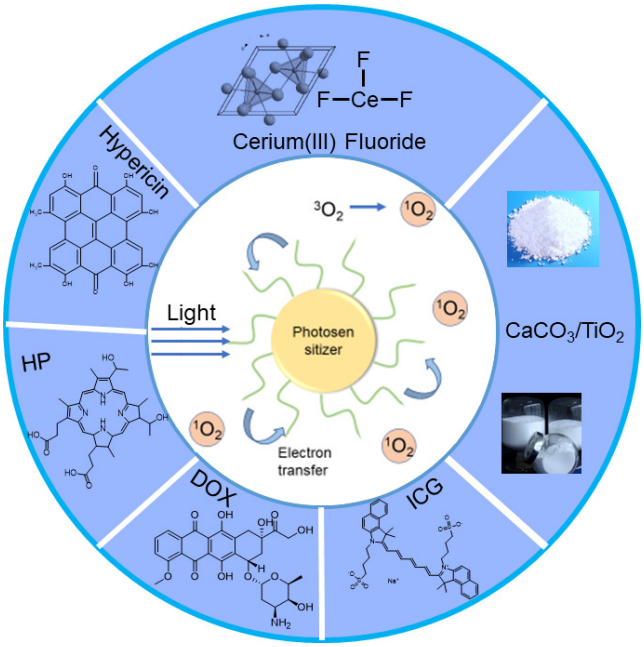

Fig. 2. Cerium-based hybrid nanoparticles for cancer PDT.

2. Therapeutic Mechanism of Cerium-Based Nanoparticles

Cerium-based nanoparticles have a unique mechanism for conversion between valence states and have therefore been verified as effective and durable anticancer agents.[29,30] PSs based on cerium and its oxidant-based nanoparticles have received considerable attention, and numerous studies have confirmed that cerium-based nanoparticles can be used for oncotherapy,[31] as will be discussed in detail later. A schematic of the PDT mechanism of cerium-based nanoparticles is shown in Fig. 3.

PS absorbs photon energy and then is activated, transitioning from the electronic ground state to the excited state.[32] The excited PS reaches the T_1-state through the intersystem crossing and then generates ROS through electron transfer and energy transfer.[33] ROS include $^1O_2$, superoxide ions ($\bullet O^{2-}$), hydroxyl radicals ($\bullet$OH), etc. that can cause lipid peroxidation or protein inactivation and result in cell necrosis or apoptosis [Fig. 3(a)]. Figure 3(b) shows that a PS absorbs photon energy to reach the S_n-state and then returns to S_1 through internal conversion and vibrational relaxation. In this case, the excited state of PSs may undergo different experiences: intersystem crossover to the triplet excited state (T_1) by changing the electron spin orientation, decay to the ground state to produce fluorescence, or vibration relaxation to generate heat.[34,35] Following intersystem crossing, molecular PSs in the T_1-state can either exhibit PDT effects by interacting with adjacent triplet state molecules, in particular with triplet oxygen ($^3O_2$), to produce ROS, or they can return to the ground state by emitting phosphorescence.[1]

As one of the most significant functional rare-earth nanomaterial, CeO_2 with ample oxygen vacancies and defects possesses a high potential to improve photocatalytic capability, thereby increasing the generation of ROS,[36] which provides a chance for PDT in cancer therapy. Oxidative damage is the most direct manifestation of PDT.[36] Generally, the oxidative stress induced by the PDT-generated ROS can be exacerbated because ROS production can be promoted by reversible conversion between antioxidants Ce(III) and prooxidants Ce(IV). *In-vitro* cell experiments have indicated that PDT-generated ROS interact with phospholipids, cholesterol, membrane proteins, and other biomolecules of cell components,

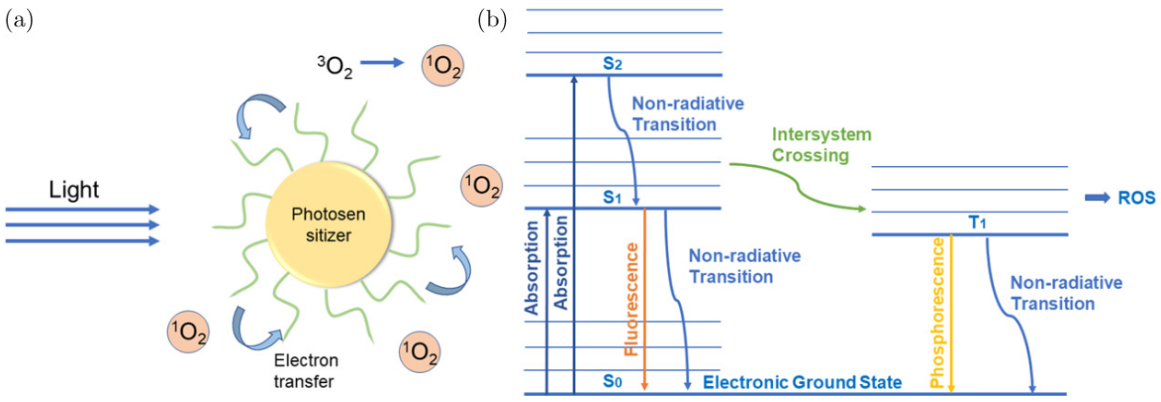

Fig. 3. (a) Cerium and its oxidant-based nanoparticles acting as PSs for electron transfer to generate $^1O_2$. (b) Jablonski diagram of PDT describing the excitation and relaxation process in photosensitive molecules.

resulting in the loss of cell function and even cell death.[37]

3. Compounds Containing Cerium or Cerium Oxide for PDT

With the study of cerium or cerium oxide nanoparticles, more and more cerium-based nanomaterials have been used for cancer therapy and their therapeutic mechanisms have been deciphered. In this section, we list the representative compounds containing cerium or cerium oxide that act on more than one substrate or activate under a distinct environment (Table 1).

3.1. *Cerium-containing compounds*

The PDT effect of pure cerium-containing compounds was verified by Clement *et al.* CeF_3 NPs can generate $^1O_2$ under irradiation by UV light or 8-keV X-rays. The $^1O_2$ quantum yield of CeF_3 NPs was determined to evaluate the photodynamic performance. The calculated $^1O_2$ generation from CeF_3 under X-ray exposure is 1000 ± 170, in which case the X-ray $^1O_2$ quantum yield is around 0.13 ± 0.02.[38] The complementary mechanisms of cell death between photodynamic (membrane damage) and ionizing radiation (DNA damage) therapies are hypothesized to enable CeF_3 NPs to improve the radiotherapeutic effectiveness.

In 2022, Li *et al.* reported the second near-infrared region (NIR-II) light-induced nanoparticles for photoacoustic (PA) image-guided sonodynamic amplified PDT/photothermal synergistic therapy (PTT), utilizing cerium oxide (CeO_{2-x}) with ample oxygen vacancies (Fig. 4).[39] The introduction of oxygen vacancies is beneficial to minimizing the bandgap, providing a broad absorption performance in the ultraviolet–visible–NIR region for PTT. In addition, the vacancies of oxygen could allow electrons (e^-) and holes (h^+) to be separated from the band structure with electron trapping sites by ultrasound irradiation, promoting ROS production.[40] Given this, the SDT of CeO_{2-x} is capable to amplify the effect of PDT/PTT to eliminate cancer cells. Meanwhile, the bandgap was narrowed (from 2.74 eV to 1.66 eV), allowing the absorbance of NIR laser irradiation for PDT/PTT. Oxygen vacancies could inhibit the hole–electron recombination, as well as transfer energy as heat effectively. The photogenerated electrons could catalyze molecular oxygen to generate $O_2^{\bullet-}$, whereas the holes in the valence band oxidized H_2O to generate •OH. Besides, hyaluronic acid (HA) was coated on the surface of CeO_{2-x} to endow it with a higher affinity for CD44 receptor overexpressed on the surface of cancer cells. This research remarkably broadened the application of NIR-II-responsive CeO_{2-x} for PA imaging-guided SDT-enhanced PDT to the elimination of cancer cells.

3.2. *Cerium/cerium-oxide-doped nanoparticles*

Ionizing radiation known as X-rays interacts with molecules to produce ROS and free radicals that can

Table 1. Typical compounds containing cerium or cerium oxide for PDT.

Types of the nanomaterials	Name	Cell/tumor modal	Exogenous activators	Source
Cerium-containing compounds	CeF_3	PANC-1	X-ray	Ref. 38
	CeO_{2-x}	4T1	NIR-II	Ref. 39
Cerium/Cerium-oxide-doped nanoparticles	TiO_2:Ce	A549	X-ray	Ref. 42
	Ce:$CaCO_3$	A549	X-ray	Ref. 44
	GAG@mSiO_2@RB	MDA-MB-231	X-ray	Ref. 45
	$Mn_xCe_{1-x}O_2$	MCF-7	630-nm laser	Ref. 46
Cerium-oxide-based inorganic composite nanoparticles	CeONR@PDA–Gal/Hyp	HepG2	590-nm laser	Ref. 51
	MSN–HP–DOX@CeO_2	293 T	630-nm laser	Ref. 52
	DOX–Pt@CeO_2@MnO_2	HepG2	808-nm laser	Ref. 53
	ICG@PEI–PBA–HA/CeO_2	MCF-7	808-nm laser	Ref. 56
	USCGP	4T1	808-nm laser	Ref. 57
Cerium-oxide-based organic composite nanoparticles	CPs	H22	808-nm laser	Ref. 58
	SPNs	4T1	808-nm laser	Ref. 62

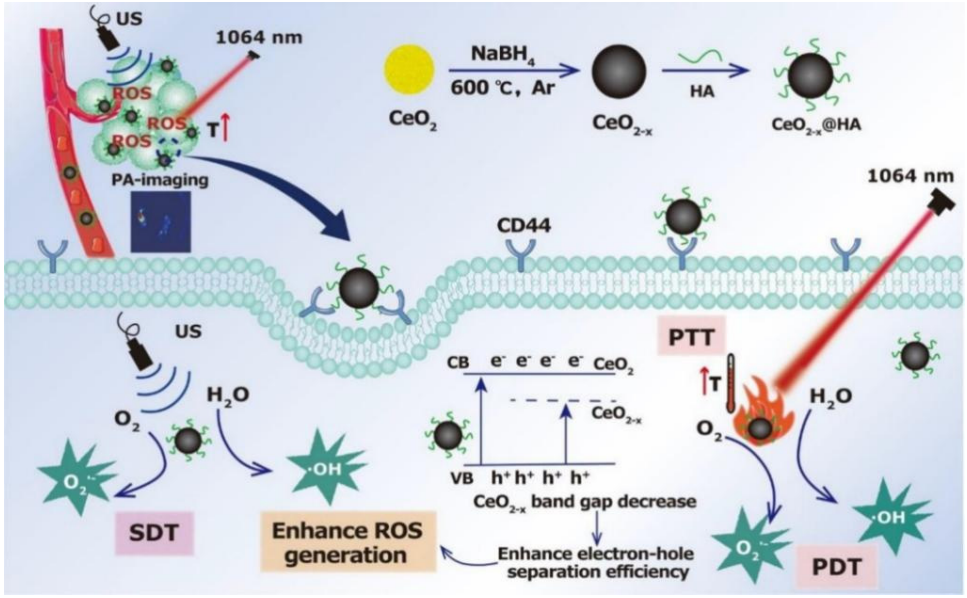

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Fig. 4. Schematic diagram of Ce_{2-x}@HA for co-enhancing PDT/PTT with SDT guided by NIR-II PA imaging.

harm DNA or organelles. Thus, X-rays can be utilized as an alternative light source for deep penetration (8–14 cm) into tissues.[41] Cerium-based doped nanoparticles have considerable application potential. Recently, researchers have doped Ce into $CaCO_3$, TiO_2, etc., to build *in-vitro* and *in-vivo* models and activated PDT by using X-rays to generate ROS.

In 2017, Yang *et al.* reported that X-rays could activate Ce-doped TiO_2 to act as a PS for PDT [Fig. 5(a)]. TiO_2 possesses the characteristics of low toxicity, good chemical stability, and high photocatalytic activity.[42] However, as a PS for cancer treatment, TiO_2 still suffers from insufficient ROS production and a high required X-ray dose, resulting in a poor therapeutic effect. Doping Ce into TiO_2 effectively narrows the energy gap and facilitates ROS generation.[43]

$CaCO_3$ is one of the main inorganic substances found in nature and has been utilized in medication delivery systems due to its excellent biocompatibility characteristics and low manufacturing cost.[47] In 2019, Yang *et al.* used coprecipitation to synthesize Ce:$CaCO_3$ for use in oncotherapy [Fig. 5(b)].[44] The synthesized particles had a diameter of 100–300 nm and could be ingested by A549 cells through the endocytosis pathway. The {110} facet of cerium provided a strong photon interaction to absorb X-ray radiation, leading to the overproduction of ROS.[48] A high ROS concentration can induce oxidative damage to mitochondrial proteins, DNA, and lipids, culminating in mitochondrial damage and death. Under acidic conditions, $CaCO_3$ degraded and produced CO_2, which had an explosive effect that led to physical cell damage and even cell death.

The ability of X-rays to penetrate deeply into tissues has been boosted in deep-lying PDT cancers. For example, Wang *et al.* used mesoporous silica preloaded with $SrAl_2O_4$:Eu^{2+} NPs and an MC540 to perform X-PDT on H1299 cancers without side effects on normal tissues.[49] Among the numerous reports on the development of X-PDT nanocomposite systems, most use porphyrin derivatives for PDT, which often have limited spectral overlap with the donor (rare-earth-doped nanoscintillator) and reduce PDT efficacy. Jain *et al.* [Fig. 5(c)] reported a brand new multifunctional magnetic-luminescent $Gd_{2.98}Ce_{0.02}Al_5O_{12}$@$mSiO_2$@RB (GAG@$mSiO_2$@RB).[45] Upon X-rays excitation, GAG@$mSiO_2$@RB NPs produced ROS efficaciously, demonstrating the development of a novel magnetic-luminescent nanoplatform that holds considerable promise for simultaneous detection and PDT of deeply buried cancers.

Furthermore, $Mn_xCe_{1-x}O_2$ nanoparticles were synthesized to explore their phototoxicities and antibacterial activities [Fig. 5(d)]. It was verified

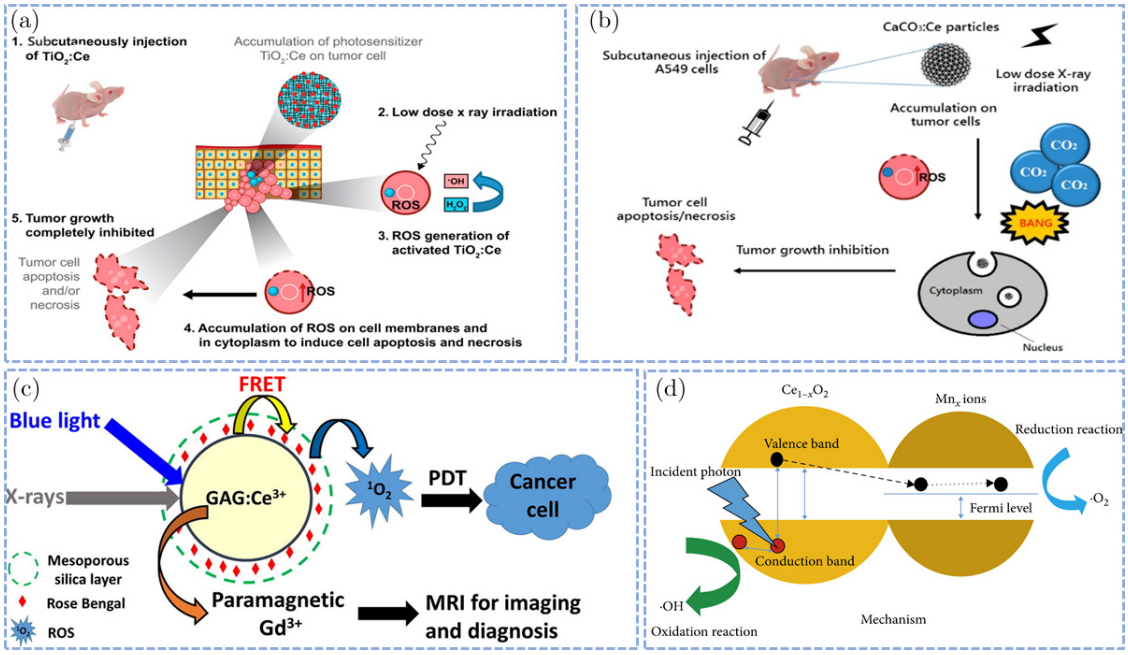

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Fig. 5. (a) The process of TiO_2:Ce nanomaterial for tumor inhibition under low-dose X-ray irradiation. (b) $CaCO_3$:Ce for synergistic CO_2 gas/X-ray-excited photodynamic therapy. (c) GAG@mSiO_2@RB NPs for magnetic resonance imaging-guided deep PDT. (d) The interaction between $Ce_{1-x}O_2$ and Mn_x.

that 9% doped with CeO_2 exhibited a 40% inhibition of the bacterial growth of *Staphylococcus aureus*, a 46% inhibition against *Escherichia coli*, and a 44% inhibition against *Pseudomonas aeruginosa*. In addition, the survival rate of MCF-7 cancer cells decreased to 7.33% after PDT.[46]

3.3. *Cerium-oxide-based inorganic composite nanoparticles*

Chemotherapy remains the main treatment method for cancer. Despite numerous efforts, the performance of chemotherapy is hampered by poor drug accumulation at the cancer site and the prominent adverse effects of anticancer medicine on normal tissues. Therefore, it is necessary to develop targeted therapeutic nanoparticles to achieve cancer-specific enrichment while minimizing the adverse effects of anticancer drugs.

Previous studies indicated that CeO_2 can be cytotoxic to cancer cells through cell membrane damage and lipid peroxidation.[50] In addition, Ce(IV) can revert to Ce(III) in the acidic cancer microenvironment accompanied by ROS generation to achieve a synergistic therapeutic effect. For example, a delivery mechanism based on polydopamine (PDA)-coated cerium oxide was developed for targeted PDT of human hepatoma HepG2 cells.[51]

A dense PDA layer was formed on cerium oxide nanorods (CeONR) by a dopamine self-polymerization process under alkaline circumstances. The surface of CeONR was then modified with thiolated galactose (Gal-SH) and hypericin (Hyp) to create CeONR@PDA–Gal/Hyp. The hypericin drug delivery system demonstrated excellent biocompatibility and selective targeting capabilities, with galactose units specifically recognizing overexpressed asialo-glycoprotein receptors (ASGP-R). MTT assay showed that the HepG2 viability was dropped (10–20%) at the concentration investigated under a dark condition, while the cell viability of 293T remained almost unchanged, indicating the negligible dark toxicity of CeONR@PDA–Gal/Hyp. After being taken up by HepG2 cells, CeONR@PDA–Gal/Hyp was able to execute PDT when exposed to a 590-nm laser.

In addition, cerium oxide can be converted into Ce ions under reducing conditions.[52] CeO_2 NPs possess a strong fluorescence quenching capability that can be used to construct a "turn-on" fluorescent probe for real-time monitoring of drug release. For example, CeO_2-coated mesoporous silica NPs

(MSN–HP–DOX@CeO_2) were designed and prepared for combined chemotherapy and PDT [Fig. 6(a)].[52] Both hematoporphyrin (HP) and doxorubicin (DOX) possess conjugated structures that can be combined through π–π interactions to facilitate DOX loading. Ingestion of MSN–HP–DOX@CeO_2 by cancer cells results in the reduction of CeO_2 NPs to Ce ions in an intracellular microenvironment with a high concentration of glutathione (GSH) and low pH. Figure 6(b) is a SEM image showing the spherical structure of MSN–HP–DOX@CeO_2. Figure 6(c) shows XRD patterns confirming that CeO_2 was successfully coated on mesoporous silica nanoparticles (MSN). The release of DOX and the production of $^1O_2$ led to a decrease in cell viability upon exposure to a 650-nm laser [Figs. 6(d) and 6(e)].

In another study, Xu *et al.* developed a novel therapeutic nanoplatform (DOX–Pt@CeO_2 @MnO_2) for combined photothermal therapy/PDT/chemotherapy.[53] After Pt@CeO_2@MnO_2 preloaded with DOX accumulated in a tumor, the protective layer of MnO_2 catalyzed intratumoral hydrogen peroxide to produce oxygen to enhance PDT and was degraded in the acidic environment to realize cancer-microenvironment-responsive release of DOX. Moreover, the introduction of Pt enhanced the separation of photogenerated electrons and holes, which facilitated $^1O_2$ generation. HepG2 cells treated with DOX–Pt@CeO_2@MnO_2 and 808 laser exhibit a remarkable decrease in cell activity. *In-vivo* anticancer evaluation indicated that Pt@CeO_2 @MnO_2 produced an excellent anticancer effect through multimodal therapy with synthetic effects.

Currently, a variety of strategies have been explored to elevate the concentration of O_2 to improve PDT efficacy. For example, Liu *et al.* fabricated a multifunctional CeO_2–PEG–Ce6–GoX (CPCG) to generate O_2: high levels of hydrogen peroxide (H_2O_2) in the cancer microenvironment were converted to oxygen by making a great deal of the catalase-mimicking activity of CeO_2, where PEG denotes phosphoethanolamine-polyethylene glycol with hydrophobic and hydrophilic and fragments,[55] Ce6 denotes Chlorin e6, GoX denotes glucose oxidase[54,55] Similarly, Zeng *et al.* reported[56] a double-targeted cancer medication delivery system (ICG@PEI–PBA–HA/CeO_2) based on an inorganic nanozyme (CeO_2), where PEI denotes polyethylenimine, PBA denotes 4-carboxylphenylboronic acid inacol ester, and HA denotes hyaluronate. Figure 7(a) is a schematic of the drug-loaded complex, showing the transition between the valence states of Ce(III) and Ce(IV), as well as the regenerable cycle of the cerium oxide nanozyme. The valence transition of cerium ions manifests as a change in the solution color [Fig. 7(b)]. ICG@PEI–PBA–HA/CeO_2 can catalyze H_2O_2 to O_2 at various concentrations [Figs. 7(c) and 7(d)]. ICG@PEI–PBA–HA/CeO_2 significantly relieved hypoxia inside cancer *in vivo*, thereby efficiently enhancing PDT.

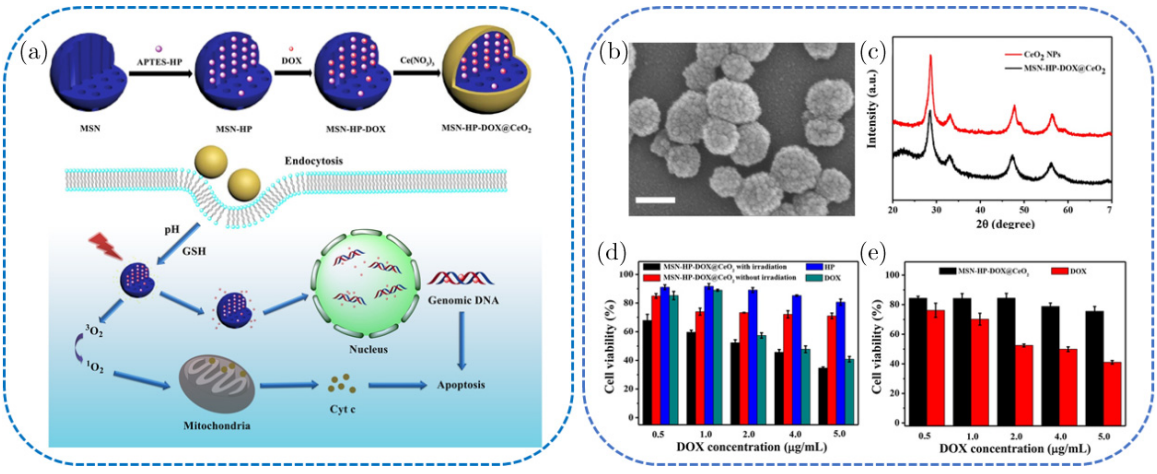

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Fig. 6. (a) Schematic illustration of a synthetic methodology for a triple-stimulus-responsive medication delivery system. (b) SEM images of MSN–HP–DOX@CeO_2. Scale bar: 100 nm. (c) XRD patterns of CeO_2 NPs, as well as MSN–HP–DOX@CeO_2. (d) MSN–HP–DOX@CeO_2 cytotoxicity values on HeLa cells for 24 h with and without radiation and with HP and DOX at varying doses. (e) Cytotoxicity values for 24 h of MSN–HP–DOX@CeO_2 and DOX at various doses on 293T cells.

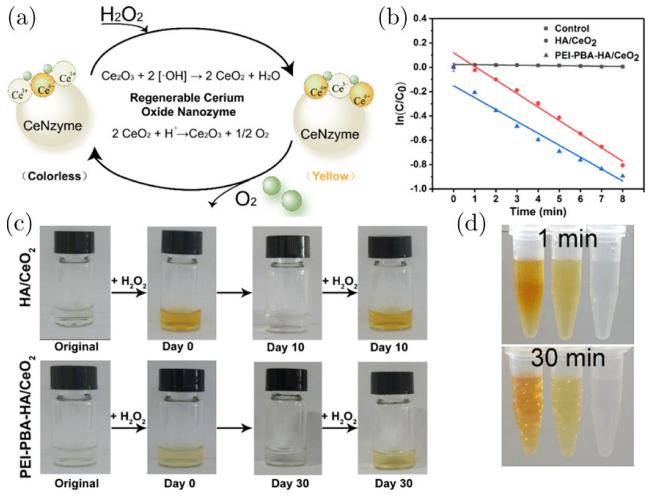

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Fig. 7. (a) Diagram illustrating the catalase activities of HA/CeO_2 and PEI–PBA–HA/CeO_2, as well as the regeneration cycle of CeO_2 and the crossover between its valence states. (b) Evaluation of the cerium oxide nanozyme's catalytic activity. (c) Cerium oxide regeneration cycle: temporal color shift in the samples reveals the transformation between Ce(III) and Ce(IV). (d) Oxygen generation caused by the catalysis of H_2O_2 at different HA/CeO_2 concentrations.

In 2022, Gao *et al.* designed a multilayered porous biocatalyst to realize cascade synergistic cancer therapy.[57] First, the researchers synthesized OA-stabilized core–shell–shell-structured $NaYF_4$:Yb,Tm@$NaLuF_4$:Yb,Nd@$NaLuF_4$ NPs (UCNPs). And then MSN, CeO_2, and glucose oxidase (GOD) were modified in turn on the exterior of UCNPs to construct UCNPs@mSiO_2@CeO_2–GOD (USCG). Finally, USCGP was harvested after using PEG–cRGDfK to modify the surface of USCG. In this system, GOD catalyzes the decomposition of glucose and simultaneously regulates the tumor environment (TME), activating the catalysis of USCGP (Fig. 8). Moreover, the cascade interactions between GOD and CeO_2 accelerate the generation of •OH and accelerate nutrient depletion in TME. Experimentally, USCGP with good biocompatibility exhibited efficient elimination of cancer cells by a combination of PDT, chemodynamic therapy, and starvation therapy.

3.4. *Cerium-oxide-based organic composite nanoparticles*

The ROS production levels of most PDT nanoparticles do not change with the disease microenvironment, which may limit selective treatment

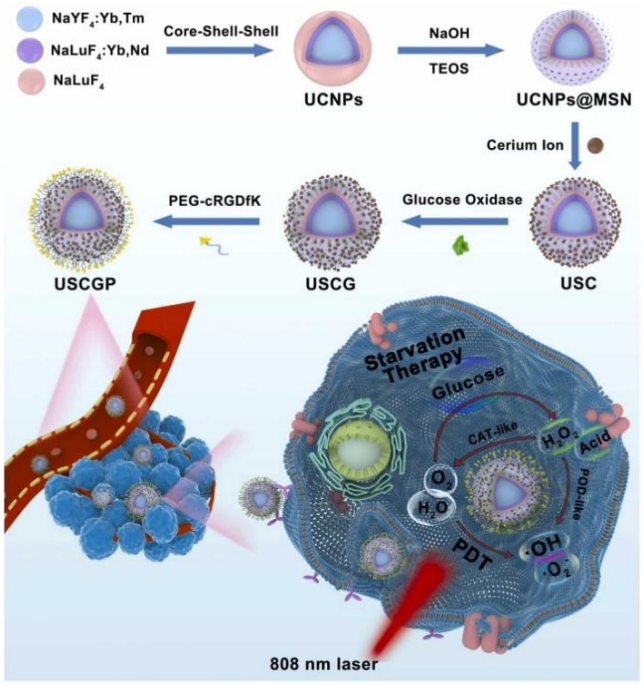

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Fig. 8. The preparation and cascade-reaction process of USCGP biocatalyst for synergistic starvation/PDT cancer treatment.

using these nanoparticles due to potential damage to normal tissues. Recently, Hu and Ding reported a simple pH/H_2O_2-activatable, O_2-evolving, and ROS-regulating DOX and ICG co-loading PEGylated polyaniline (PANI)-coated CeO_x@polyacrylic acid (PAA) nanoclusters, PAA–CeO_x@PANI–PEG nanoclusters (CPs), for cancer combination treatment.[58] Depending on the dual-mode catalytic characteristics of Ce at varying pH, it operates as catalase-like catalytic agents (pH = 7.4–6.5, $Ce^{4+}/Ce^{3+} = 3.46$), and as oxidase-like catalytic agents (pH = 5.4–6.5, $Ce^{4+}/Ce^{3+} = 0.58$),[59,60] which is able to increase the intracellular O_2 and ROS levels in cancer region. In addition, due to the protective effect of PAA, PANI, and PEG, the catalase activity of CeO_x would be activated upon irradiation with NIR light after accumulation at the tumor site.

Semiconducting polymer nanoparticles (SPNs) are a novel type of molecular imaging and PDT nanoagent that circumvents the potential toxicity of metal ions and possesses intrinsically good biocompatibility.[61] Zhu *et al.* reported a hybrid approach for modulating the PDT properties of SPNs to optimize cancer therapy.[62] SPNs have two active components (Fig. 9): CeO_2 NPs and poly

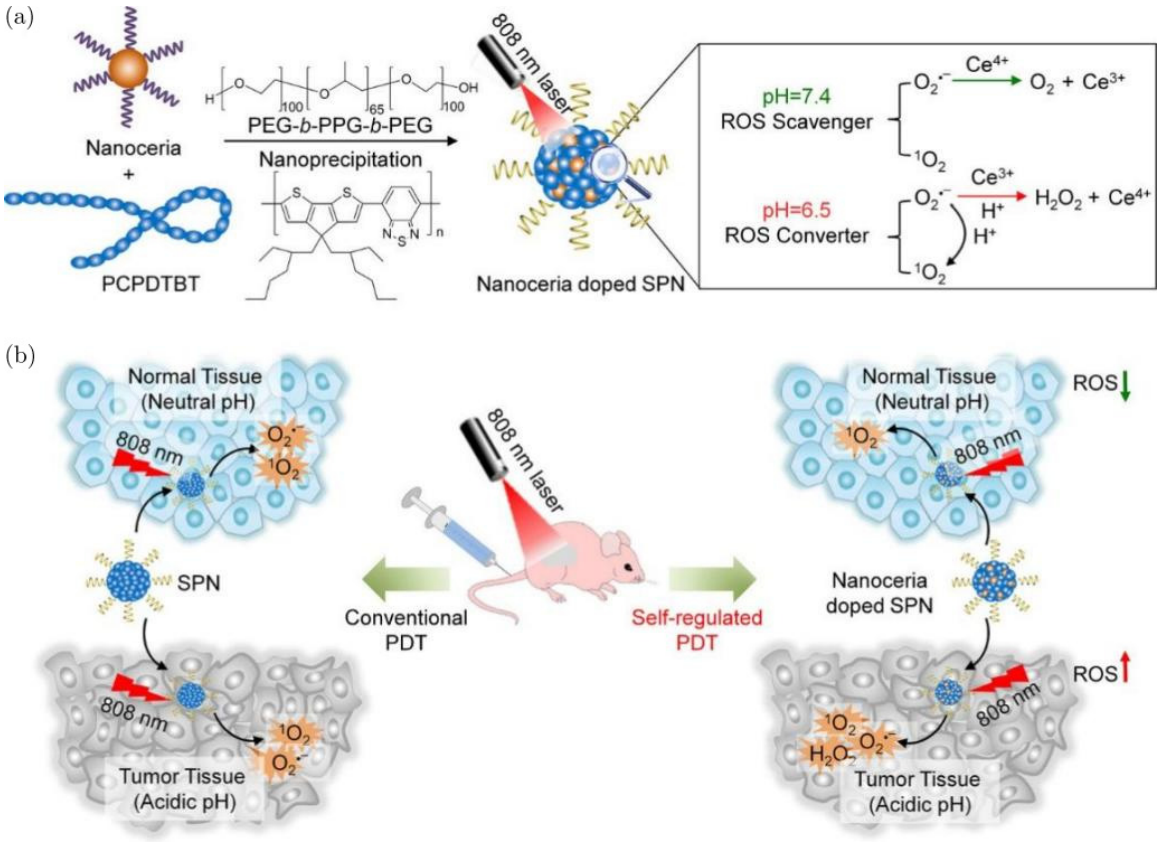

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Fig. 9. Schematic diagrams of (a) the formation of nanoceria-doped SPNs, as well as the self-regulating PDT properties of SPNs in physiologically neutral and pathologically acidic environments, and (b) nanoceria-doped SPNs versus nondoped SPNs as mediators of self-regulated and conventional PDT.

(cyclopentadithiophene-alt-benzothiadiazole) (PCPDTBT). CeO_2 NPs were easily doped into PCPDTBT nanoparticles by nanoprecipitation. PCPDTBT has triple energy of 1 eV,[63] which exceeds the energy gap between O_2 and $^1O_2$ (0.98 eV) and is therefore theoretically feasible for cancer PDT. Due to a dense concentration of surface oxygen vacancies, nanoceria may alternate between the oxidation states of Ce(III) and Ce(IV) depending on the pH. As a result, combining CeO_2 NPs and PCPDTBT NPs can significantly amplify anticancer effects in an acidic cancer microenvironment while reducing the side effects on normal tissues.

The different effects of Ce under neutral and acidic conditions determine the underlying mechanism of pH-dependent PDT. The presence of reduced-state Ce(III) and oxidized-state Ce(IV) facilitates the antioxidant action of nanoceria, which can extinguish ROS under neutral circumstances while converting $O_2^{\bullet-}$ to H_2O_2 to generate ROS under acidic conditions.[62] In addition, H_2O_2 can generate more ROS, including •OH, hypochlorite (OCl^-), or hypobromite (OBr^-), using metal-catalyzed Fenton reactions and peroxidase-catalyzed reactions.[64] There have been many reports that high levels of H_2O_2 are more detrimental to cellular equilibrium than high concentrations of $O_2^{\bullet-}$.[65,66] These integrated effects ultimately result in an increase in total ROS generation under pathologically acidic settings and a reduction under physiologically neutral ones. This study introduces a hybrid optical approach to modulate nanotheranostic agents based on organic SPNs and nanoceria and provides alternative design guidelines for PDT.

4. Future Perspective

PDT is a ROS-induced local therapy with excellent efficacy for cancer treatment. The PDT function depends on the effect of light, PSs, and O_2.[67]

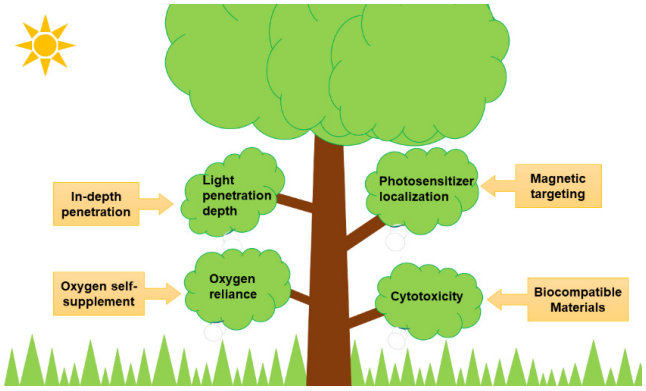

Fig. 10. Schematic diagram of challenges that the conventional PDT processes have encountered at different levels, as well as the advanced strategies to solve these matters.

However, there are still some serious challenges for PDT (Fig. 10), as follows: (i) the development of highly effective and nontoxic or low cytotoxic PSs; (ii) the light penetration depth that severely impairs the application of photodynamic therapy to epidermal cancers (e.g., oral cancer, skin cancer, and bowel lesions[42]); (iii) oxygen dependence compromising the effectiveness of PDT against hypoxic cancers; and (iv) continuing difficulties with the delivery and the clearance of exogenous PSs.

Zhang *et al.* found negligible cytotoxicity for CeO_2 NPs.[22] Furthermore, CeO_2 NPs exhibit different enzyme-like activities in different physiological environments; for example, CeO_2 NPs can scavenge ROS in normal cells but not in cancer cells and can thereby be used for the specific treatment of cancers. One of the current challenges for PDT is the development of biocompatible PSs to minimize potential biotoxicity. From this perspective, the exploitation of cerium-based PSs have exceptional application prospects.

The light penetration depth is a barrier to using PDT for deep-tissue cancer. X-rays are a light source with considerable promise because of the absence of tissue penetration restrictions. Therefore, Albuquerque *et al.* designed and synthesized cerium-based hybrid materials (CeO_x/TiO_2) and used the {110} face of Ce to absorb X-ray radiation to successfully implement deep-tissue PDT.[43]

In addition, poor accumulation of PSs in cancers limits therapeutic efficacy. Cerium-based magnetic hybrid materials could be used to ameliorate this drawback.[68] For example, Wang *et al.* exploited the magnetic property of citrate–Ce complexes to construct a multifunctional nanoplatform ($AuNR@SiO_2/Ce@Dox@polydopamine@aptamer$) for dual-targeted therapy of non-small-cell lung cancer. *In-vitro* anticancer studies indicated that the adhibition of a magnetic field enhanced the anticancer effect of $AuNR@SiO_2/Ce@Dox@$ polydopamine@ aptamer on A549 cells.[69]

The enzymatic properties (superoxide-dismutase-like and catalase-like activities) of CeO_2 and cancer microenvironment characteristics can be utilized to convert high concentrations of ROS (such as $O_2^{\bullet -}$ and H_2O_2) into oxygen,[54] thereby increasing the content of endogenous oxygen and achieving oxygen self-supplementation. Based on the unique physicochemical properties of cerium-based nanoparticles, we have full confidence in the expansion of cancer treatment options from the rational design of PDT strategies. However, most revealed PDT treatments are still in the early stage because of a lack of clinical evidence. The *in-vivo* biological effects of cerium-based nanoparticles should be investigated in the future. Finally, we hope that this review provides a timely overview of cerium-based PDT that opens up a new avenue in the future for the ongoing fight against cancer.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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