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Synthesis temperature-regulated multi-enzyme-mimicking activities of ceria nanozymes

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Ceria (CeO2) nanozymes have drawn much attention in recent years due to their unique physicochemical properties and excellent biocompatibility. It is therefore very important to establish a simple and robust guideline to regulate CeO2 with desired multi-enzyme-mimicking activities ideal for practical bioapplications. In this work, the multi-enzyme-mimicking activities of CeO2 were facilely regulated by a wet-chemical method with different synthesis temperatures. Interestingly, distinct response in multi-enzyme-mimicking activities of CeO2 was observed towards different synthesis temperatures. And the regulation was ascribed to the comprehensive effect of oxygen species, size, and self-restoring abilities of CeO2. This study demonstrates that high-performance CeO2 can be rationally designed by a specific synthesis temperature, and the guideline of radar chart analysis established here can advance the biomedical applications of ceria-based nanozymes.

Introduction

Nanozymes, the nanomaterial-based enzyme mimics, are attractive not only for their stability and eco-efficiency but also for their unique physicochemical properties of nanomaterials.1-10 Particularly, benefiting from rich redox properties and surface chemistry, some nanozymes are endowed with more than one type of enzyme-mimicking activities.11-15 Such multi-enzyme-mimicking activities are demonstrated to act as self-cascade reactors and found to be helpful for eliminating or producing multiple reactive oxygen species (ROS) in different therapies, unlike natural enzymes with sole activity against various ROS.16, 17 Among the developed nanozymes with multi-enzyme-mimicking activities, ceria nanozyme (CeO2), a typical and widely-explored nanozyme, can mimic superoxide dismutase (SOD), catalase (CAT), oxidase (OXD), peroxidase (POD), alkaline phosphatase (ALP), etc.18-24 The diverse range of enzyme-mimicking activities has led ceria nanozyme to various biomedical applications, from in vitro diagnosis (such as glucose, glutathione, and ATP detections) to in vivo therapies (such as ischemic stroke protection, septicemia, and tumour therapeutics).25-35

Despite significant progress has been achieved in ceria nanozyme, few studies focus on regulation accompanied with analysis for multi-enzyme-mimicking activities, so that lacking an effective guideline for further applications. On the one hand, till now, for most CeO2 nanozymes, strategies such as doping, surface modification, and complex formation were proved to regulate single type enzyme-mimicking catalytic property.36-42 On the other hand, different catalytic reaction processes and uncertain regulation mechanisms make it difficult to regulate multi-enzyme-mimicking activities by a universal strategy. For instance, both SOD- and CAT-mimicking activities were helpful for eliminating ROS, but the regulation of Ce3+ fraction was opposite for simultaneously adjusting of SOD- and CAT-mimicking activities.20, 21 Of note, the role of CeO2 nanozymes will be switched by changing the pH of microenvironment, like being a pro-oxidant under acidic condition (for its peroxidase- and oxidase-like activity) while anti-oxidant under neutral or alkaline microenvironment (for its SOD- and CAT-like activity).43 Nevertheless, it is worth noting that pH-dependent regulation of the multi-enzyme-mimicking activities could not provide the most beneficial...
window for practical applications. For example, the retained SOD-mimicking activity under acidic conditions though poor, would still weaken the pro-oxidant effect, and even cause potential side effects. On account of above dilemma, the development of effective strategies and robust guidelines is highly desired to achieve precise and simultaneous control over multi-enzyme-mimicking activities of ceria nanozyme.

In this work, a facile synthetic strategy combining with radar chart analysis has been developed to regulate the multi-enzyme-mimicking activities of CeO$_2$ with precise and simultaneous adjustment for biomedical applications (Fig. 1).

**Fig. 1** Synthesis of ceria nanozymes via temperature regulation to optimize multi-enzyme-mimicking activity for biomedical applications.

**Experimental**

**Preparation of CeO$_2$**

CeO$_2$ was synthesized following our previously published procedure.$^{37}$ First, 504 mg Ce(NO$_3$)$_3$·6H$_2$O was dissolved in 20 mL of ethylene glycol aqueous solution (v/v=1:1) under vigorous stirring, and then the mixture was placed under different temperatures (-30, 0, 30, 60, and 90 °C) for further vigorous stirring. After 5 min, 4 mL of ammonia water (28–30%) was quickly injected into the mixture. Keeping stirring for 3 h, the products were then collected by centrifugation, washed with excess deionized water, and modified with citric acid to adjust pH until about 7.0. Finally, the CeO$_2$ solutions were stored or dried by lyophilization for further applications. Note, the as-prepared CeO$_2$ under different temperatures were denoted as Ceria_-30, Ceria_0, Ceria_30, Ceria_60, and Ceria_90.

**SOD-mimicking activity of CeO$_2$**

According to the protocol of SOD assay kits (Dojindo, Japan), the CeO$_2$ nanozyme (20 µL, 1 mg/mL) was first mixed with 200 µL of a 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H tetrazolium sodium salt working solution in a microplate well, respectively. Then, 20 µL of the enzyme working solution was added into each mixture, gently mixed, and incubated for 30 min at 37 °C. Later, the absorbance at 450 nm was measured by using a microplate reader.

**CAT-mimicking activity of CeO$_2$**

First, dopamine (0.1 mL, 1 mg/mL) and H$_2$O$_2$ (5 µL, 20 mM) were added into 50 mM tris-HCl buffer (pH = 8.5) containing CeO$_2$ nanozyme. Detection solutions were incubated in a low oxygen environment at 37 °C by anaerobic gas generating bag. After 30 min, all samples were measured at 405 nm by using a microplate reader.

**1,1-diphenyl-2-picrylhydrazyl (DPPH)-scavenging activity of CeO$_2$**

The CeO$_2$ nanozyme (0.08 mL, 1 mg/mL) was mixed with DPPH (0.5 mL, 0.05 mg/mL) in methanol solution and 0.42 mL methanol, respectively. After incubation in dark at 37 °C for 24 h, the absorbance of mixture at 517 nm was recorded by using a microplate reader.

**POD-mimicking activity of CeO$_2$**

In a typical POD-mimicking activity measurement, CeO$_2$ nanozymes (0.02 mL, 2 mg/mL), H$_2$O$_2$ (0.1 mL, 1 M), and TMB (100 µL, 20 mM) were sequentially added into 1.78 mL of 200 mM acetate buffer solution (pH = 4.5). After 4 min, the absorbance at 652 nm of the reaction solution was measured by using a UV-vis-spectrometer.

**OXD-mimicking activity of CeO$_2$**

In a typical OXD-mimicking activity measurement, CeO$_2$ nanozymes (0.025 mL, 2 mg/mL), and TMB (0.1 mL, 20 mM) were sequentially added into 1.875 mL of 200 mM acetate buffer solution (pH = 4.5). After 24 h, the reaction solutions were measured at 652 nm by using a UV-vis-spectrometer.
ALP-mimicking activity of CeO$_2$

In a typical ALP-mimicking activity measurement, CeO$_2$ nanozymes (0.1 mL, 2 mg/mL) and p-NPP (0.1 mL, 0.05 mg/mL) were added into 0.8 mL tris buffer solutions (pH = 10.0) in sequence. After incubation at 37 °C for 1 h, the reaction solutions were recorded at 405 nm by using a microplate reader.

Results and discussion

Synthesis and characterization of CeO$_2$

The CeO$_2$ was prepared using a wet-chemical method. To investigate the effect of different synthesis temperatures on the structures and physiochemical properties of CeO$_2$, five different temperatures (-30 °C, 0 °C, 30 °C, 60 °C, and 90 °C) were chosen here to synthesize CeO$_2$ (Fig. 2A). The ethylene glycol/water (1:1) antifreeze solution and ammonia water (28%) with low melting points were utilized to prepare CeO$_2$ under different temperatures, especially for low temperature environment below 0 °C.

Fig. 2 Synthesis scheme (A) and characterizations (B-D) of different CeO$_2$. (B) TEM images. (C) Size distribution histograms of CeO$_2$ measured from TEM images. (D) XRD patterns.

As shown in Fig. 2B, all obtained CeO$_2$ were monodispersed due to their negative zeta potentials (about -30 mV) with a crystal size smaller than 10 nm (Fig. S1 and Table S1, ESI). Their high crystalline was manifested by high resolution transmission electron microscope (TEM) images in the insets (Fig. 2B). A comparison between synthesized-CeO$_2$ under different temperatures showed that the size of CeO$_2$ decreased as the synthesis temperature decreased. Further analysis by counting about 65 particles illustrated that the average size of Ceria$_{-30}$, Ceria$_{0}$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ were 4.2±0.7 nm, 3.1±0.6 nm, 3.1±0.6 nm, 2.6±0.3 nm, and 2.5±0.5 nm, respectively (Fig. 2C). The X-ray diffraction (XRD) patterns of different CeO$_2$ shown in Fig. 2D matched well with the standard cubic fluorite structure of ceria, proving the identical structure of CeO$_2$ synthesized under different temperatures. Notably, the full width at half maxima of CeO$_2$ synthesized at low temperatures was significantly larger than that at high temperatures, which indicated that a smaller size was easy to acquire at low temperatures, matching with the TEM results.

The X-ray photoelectron spectroscopy (XPS) results in Fig. S2 confirmed the presence of both Ce and O elements in all synthesized CeO$_2$. Further XPS analyses for Ce 3d core levels in Fig. S3 provided the oxidation state of Ce on the surface. The results in Fig. S3 and Table S1 showed that both Ce$^{3+}$ and Ce$^{4+}$...
existed in all the obtained CeO$_2$ with Ce$^{4+}$ dominant. And the fraction of Ce$^{3+}$ depicted “Volcanic” type tendency with Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ (Fig. 54). In the collection of O 1s core level spectra for all synthesized CeO$_2$ samples (Fig. S5), the broad signal between 527.5-537.5 eV was obtained and deconvoluted to analyse the surface oxygen (O$_{\alpha}$) and lattice oxygen (O$_{\beta}$) species. And a similar “Volcanic” tendency with Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ was observed in Fig. S6. Moreover, the specific surface areas (S$_{BET}$) of all synthesized CeO$_2$ were also determined through N$_2$ adsorption isotherm, and the S$_{BET}$ of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ were 158.2, 179.8, 192.5, 166.0, and 135.6 m$^2$/g, respectively (Fig. S7). Therefore, all above characterizations indicated that different synthesis temperatures allowed the fine regulating over size, surface potential, Ce$^{3+}$ fractions, O$_{\alpha}$ fractions, and surface area of CeO$_2$. And these factors mentioned above played important roles in most catalytic reactions, which encouraged us to further investigate the multi-enzyme-mimicking activities of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$.

Multi-enzyme-mimicking activities of CeO$_2$

Before investigating the multi-enzyme-mimicking activities of CeO$_2$, the catalytic self-restoring ability of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ was assessed through treating with H$_2$O$_2$. As shown in Fig. S8A, a red-shift phenomenon in UV-visible light transmittance was first observed for Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ with H$_2$O$_2$ injected for 5 min. And the corresponding solution changed from faint pale yellow to orange (Fig. S8B, red box), indicating the change from Ce$^{3+}$ to Ce$^{4+}$. Then after 7 days, the colour of all the solutions returned back (Fig. S8C, blue box), and a blue-shift reflecting the change of Ce$^{4+}$ to Ce$^{3+}$ was also detected in the UV-visible light transmittance. This finding illustrated that Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ possessed the catalytic self-restoring abilities, guaranteeing the basis for enzyme-mimicking catalytic abilities. Motivated by the above results, diverse enzyme-mimicking activities (Fig. S9) of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ were performed and compared under the same condition to study the effect of different synthesis temperatures on the multi-enzyme-mimicking activities of ceria nanozyme. As shown in Figs. 3A and S10, the SOD-mimicking activity of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ was studied with a SOD assay kit. The SOD-mimicking activity of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ was similar, better than that of Ceria$_{60}$ and Ceria$_{90}$. Remarkably, a more than twenty-fold increase in the SOD-mimicking activity was observed by changing the synthesis temperature from 90 °C to -30 °C.

The CAT-mimicking activity of ceria nanozyme was studied by monitoring the absorbance changes at 405 nm of oxidized dopamine in a hypoxic environment, as the O$_2$ produced by decomposing H$_2$O$_2$ could oxidize the dopamine. As shown in Fig. 3B, the CAT-mimicking activity of Ceria$_{-30}$, Ceria$_0$, and Ceria$_{30}$ was similar, better than that of Ceria$_{60}$ and Ceria$_{90}$. Remarkably, a more than twenty-fold increase in the SOD-mimicking activity was observed by changing the synthesis temperature from 90 °C to -30 °C.

The POD- and OXD-mimicking activities of Ceria$_{-30}$, Ceria$_0$, Ceria$_{30}$, Ceria$_{60}$, and Ceria$_{90}$ were monitored by using TMB as the model substrate. The ceria nanozyme catalysed oxidation of TMB, and subsequently generated a blue product with an absorption feature peak at 652 nm (Fig. S12).
As shown in Fig. 3D, the POD-mimicking activity enhanced with synthesis temperature increasing from -30 °C to 60 °C, and then sharply declined at 90 °C. The POD-mimicking activity of Ceria_60 exceeded about 5 times than that of Ceria_90. The other two types including Haloperoxidase (HPO)-mimicking activity and glutathione peroxidase (GPx)-mimicking activity of ceria nanozymes were also systematically evaluated. As shown in Figs. S13-14, negligible HPO- and GPx-mimicking activities were observed. For OXD-mimicking activity, the results shown in Fig. 3E depicted a similar “Volcanic” tendency as that observed in CAT-mimicking and DPPH-scavenging activities.

Besides the redox-type enzyme-mimicking activities mentioned above, ceria nanozyme was also reported to behave as a hydrolase mimic. To systematically study the ALP-mimicking activity of ceria nanozyme, para-nitrophenyl phosphate (p-NPP) was used as the model substrate, and the absorbance at 405 nm of p-nitrophenol was monitored. As shown in Fig. 3F, distinguished from redox-type enzyme-mimicking activities, the ALP-mimicking activity of ceria nanozyme increased with the synthesis temperatures elevated. And the ALP-mimicking activities of Ceria_60 and Ceria_90 were comparable, about six times than that of Ceria_-30.

These above observations unambiguously demonstrated that synthesis temperature could regulate the multi-enzyme-mimicking catalytic activities of ceria nanozymes. We subsequently found that SOD-mimicking, CAT-mimicking, OXD-mimicking, and DPPH-scavenging catalytic activities were well correlated with the ratio of $O_β/O_α$, while for the POD-mimicking and ALP-mimicking catalytic activities, a negative correlation was displayed with the ratio of $O_β/O_α$ (Fig. S6). These results collectively indicated that the oxygen species played a dominant role in the multi-enzyme-mimicking catalytic activities of Ceria_-30, Ceria_0, Ceria_30, Ceria_60, and Ceria_90, consistent with previous reports. To be worthy of mention, there are some rationales underlying the multi-enzyme-mimicking catalytic activities of ceria nanozymes. As for Ceria_90, all the redox-type catalytic activities were low, which can be attributed to the worse catalytic self-restoring ability of Ceria_90 with excessive blue shift shown in Fig. S8A. Likewise, the SOD-mimicking activity of ceria nanozymes was not in a “Volcanic” type, and the higher activity of Ceria_-30 than that of Ceria_0 may come from the smaller size of Ceria_-30. Taken together, all the results indicated that for the modulation of these multi-enzyme-mimicking activities, the key factor was the oxygen species, and other factors such as crystal size also played certain roles. Therefore, several factors including crystal size, oxygen species, and self-restoring abilities affected by different synthesis temperatures would give a comprehensive effect on the multi-enzyme-mimicking activities of ceria nanozymes.

Fig. 4 Radar charts of the multi-enzyme-mimicking activities of Ceria_-30, Ceria_0, Ceria_30, Ceria_60, and Ceria_90.

Despite that the multi-enzyme-mimicking activities of Ceria_-30, Ceria_0, Ceria_30, Ceria_60, and Ceria_90 could be regulated by different synthesis temperature, the different response existed between Ceria_-30, Ceria_0, Ceria_30, Ceria_60, and Ceria_90. To make it easier for elucidating and analysing, a radar chart was drawn based on the results in Fig. 3. As shown in Fig. 4, Ceria_0 has the highest activities in both SOD-mimicking, CAT-mimicking, DPPH-scavenging, and OXD-mimicking. In contrast, the worst activity in SOD-mimicking, CAT-mimicking, DPPH-scavenging, POD-mimicking and OXD-mimicking was found for Ceria_90. According to the previous studies, SOD-mimicking, CAT-mimicking and DPPH-scavenging activities could eliminate the reactive free radicals, thus endowing ceria nanozymes with anti-oxidant ability. While POD-mimicking and OXD-mimicking activities offered the pro-oxidant property of ceria nanozymes. Therefore, combining these findings together, Ceria_0 with high SOD-mimicking, CAT-mimicking, and DPPH-scavenging activities would be chosen as an anti-oxidant, rather than Ceria_-30 or Ceria_30. Moreover, compared with Ceria_-30 and Ceria_30, it
would be better to select Ceria_60 and Ceria_90 as pro-oxidant. Based on the above results, the strategy of synthesis temperature-guided regulation and the guidelines developed here would not only enhance the enzyme-mimicking activities of ceria nanozyme, but also provide a guideline for rational applications of nanozymes in complex biological systems.

Fig. 5 Cytoprotection under different treatments. (A) Photos of hMSCs staining with X-gal (blue or green area). (B) Quantitative statistical results of aging cells from (A) (n=5). * means P<0.05 vs. control group. (C-D) Cell viability for human normal chondrocyte cell line (C28/I2 cell) and human breast cancer cell line (Michigan cancer foundation-7, MCF-7 cell) (n=5). * means P<0.05 vs. H$_2$O$_2$ group. ** means P<0.01 vs. H$_2$O$_2$ group. *** means P<0.001 vs. H$_2$O$_2$ group.

**Anti-aging effect of CeO$_2$**

Since Ceria_0 possessed excellent anti-oxidant property, an anti-aging cytoprotection was studied here to demonstrate the ability of Ceria_0 to relieve cellular oxidative stress in biological systems. Before investigating the potential biological applications, the biocompatibility of ceria nanozymes was first assessed. As showed in Fig. S15, after incubation with human bone marrow mesenchymal stem cells (hMSCs) for 24 h, at concentrations even up to 200 μg/mL, ceria nanozymes showed no cytotoxicity on hMSCs, indicating excellent biocompatibility of ceria nanozymes. Subsequently, considering the accumulation of oxidative stress with the increasing age, the ability of cytoprotection from senescence of Ceria_0 was investigated by co-incubating with cells. After 7 days of cultivation, compared with the control group, the group treated with Ceria_0 nanozyme remained spindle cells with regular shape and distinct profile, which suggested that Ceria_0 nanozyme could provide cytoprotection from aging (Fig. S16). To quantify the anti-aging effect of Ceria_0 nanozymes, we used a senescence β-galactosidase staining kit assay. As showed in Fig. 5A, Ceria_0 nanozyme treated group showed a significant anti-aging effect, with only 178 aging cells per square millimetre (Fig. 5B). While for the control group, the galactosidase staining showed that untreated cells were obviously in aging status with around 234 aging cells per square millimetre. Thus, the significantly decreased number of aging cells evidenced the excellent anti-aging capability of Ceria_0 nanozymes, protecting cells from aging induced oxidative stress. However, when applying Ceria_90 with a worse activity, the anti-aging effect was not so obvious, which was comparable to control group (Fig. 5B). Besides, to further evaluate the anti-aging effect of Ceria_0 nanozymes, another typical aging model induced by D-galactose was also studied and a similar result as the natural aging model was obtained (Fig. S17). Together, the above results verified that Ceria_0 nanozyme selected from the developed guidelines did exhibit excellent anti-oxidant property and protect cells from aging-induced oxidative damage.

**Selective cytoprotection effect of CeO$_2$**

To further evaluate the guiding effect of developed guidelines for biomedical applications, the human normal chondrocyte cell line (C28/I2 cell) which needs to be protected from oxidative stress, and human breast cancer cell line (Michigan cancer
foundation-7, MCF-7 cell) which needs to be killed were chosen here. As shown in Fig. 5C, when being exposed to H\textsubscript{2}O\textsubscript{2}, the C28/I2 cell viability decreased to 40%, in comparison with that of the control group. And the treatment of Ceria\textsubscript{0} would alleviate H\textsubscript{2}O\textsubscript{2}-induced oxidative stress, with the cell viability restored to 70%. While for Ceria\textsubscript{90}, the weaker CAT-mimicking and DPPH-scavenging activities could not protect C28/I2 cell effectively against oxidative stress. The finding here was consistent with the above anti-aging results, confirming the excellent anti-oxidant property of Ceria\textsubscript{0} nanozyme guided by the Radar guidelines.

In contrast, another MCF-7 cell which needs to be killed, Ceria\textsubscript{90} with a pro-antioxidant activity was capable to further reduce the cell viability (Fig. 5D). Notably, even though with OXD- and POD-mimicking activities to act as a pro-antioxidant, Ceria\textsubscript{0} could not kill MCF-7 cell effectively as Ceria\textsubscript{90}. The worse effect may be attributed to the still retained anti-oxidant (such as SOD-mimicking) activity under the acidic pH of MCF-7 cell environment. The results here not only highlighted the importance of simultaneous control and analysis of multi-enzyme-mimicking activities, but also verified the guiding effect of the developed radar-map guidelines for biomedical applications. With this meaningful strategy, a suitable ceria nanozyme could be selected to obtain the most effective window for advancing further biomedical applications.

Conclusions

In summary, we have developed an effective and convenient strategy to modulate the multi-enzyme-mimicking activities of ceria nanozymes by changing synthesis temperatures from -30 to 90 °C. Further characterizations and multi-enzyme-mimicking activities studies allowed us to elucidate oxygen species as the key factor and other synergistic cofactors (such as size and self-restoring ability) in regulating the multi-enzyme-mimicking activities of ceria nanozymes. Moreover, a detailed radar analysis of multi-enzyme-mimicking activities of ceria nanozymes may guide the rational development and selection of a desired nanozyme. Finally, we demonstrated that Ceria\textsubscript{0} with the best anti-oxidant activity guided by the radar analysis, did exhibit significant cytoprotection from aging- and H\textsubscript{2}O\textsubscript{2}-induced oxidative damage. While for killing cancer cells, Ceria\textsubscript{90} rather than Ceria\textsubscript{0} would be a better choice. Thus, this work provides not only a facile strategy to simultaneously modulate multi-enzyme-mimicking activities of nanozymes, but also an effective guideline to advance the development of ceria nanozymes and their further biomedical applications in biological systems.

Author Contributions

X. L. and J. W. performed the experiments and wrote the paper. Q. L., A. L., S. L., Y. Z., Q. W., T. L., X. A., and Z. Z. directed and performed the analysis of experiments. Q. L. and Y. Z. revised the paper. H. W., J. W. and M. Y. contributed to supervision and directed the project.

All authors reviewed the paper. X. L. and J. W. contributed equally to this work.

Conflicts of interest

There are no conflicts to declare.

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