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REVIEW

The Advances of Ceria Nanoparticles for Biomedical Applications in Orthopaedics

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Abstract: The ongoing biomedical nanotechnology has intrigued increasingly intense interests in cerium oxide nanoparticles, ceria nanoparticles or nano-ceria (CeO_2-NPs). Their remarkable vacancy-oxygen defect (VO) facilitates the redox process and catalytic activity. The verification has illustrated that CeO_2-NPs, a nanozyme based on inorganic nanoparticles, can achieve the anti-inflammatory effect, cancer resistance, and angiogenesis. Also, they can well complement other materials in tissue engineering (TE). Pertinent to the properties of CeO_2-NPs and the pragmatic biosynthesis methods, this review will emphasize the recent application of CeO_2-NPs to orthopedic biomedicine, in particular, the bone tissue engineering (BTE). The presentation, assessment, and outlook of the orthopedic potential and shortcomings of CeO_2-NPs in this review expect to provide reference values for the future research and development of therapeutic agents based on CeO_2-NPs.

Keywords: CeO_2-NPs, green synthesis, ROS, bone tissue engineering, coating, orthopedic implants

Introduction

Cerium is the first element with 4f electron among the 17 rare earth elements or lanthanides. The peculiar 4f orbitals of equal energy endow cerium with characteristic physicochemical properties.[1] Besides, cerium turns out the most abundant of the rare earth elements. Light, electricity, magnetism, and other fields have witnessed inordinately ample scope for the application of cerium.[2–5] At present, efforts have gone into exploring the further application of cerium. CeO_2-NPs are nanocrystalline derived from cerium. Cerium is mostly in the form of ceria with unique face-centered cubic fluorite lattice structure. The common knowledge believes that the fast and convenient oxidation state transition from Ce^{3+} to Ce^{4+} contributes to the high redox activity of CeO_2.[6] During the oxidation state transition, the alternating loss of oxygen and/or other electrons in CeO_2 and CeO_{2-x} (non-stoichiometric compounds) generates oxygen vacancies or defects in the lattice structures[7] seen in Figure 1. The high oxygen storage capacity of the lattice and the high oxygen mobility in the lattice impel a broad application of ceria to biological effect relevant to redox reaction.[8] Evidence suggests that a higher surface to volume ratio of CeO2-NPs makes the surface atomic lattices softer than those in bulk. Nanometer effect is significant to the catalytic activity of CeO_2. Compared with the conventional block structure, nano-CeO_2 can improve catalytic activity by two orders of magnitude.[9] The reduced particle size and increased surface-to-volume ratio lead to the formation of more oxygen vacancies. Loss of even one

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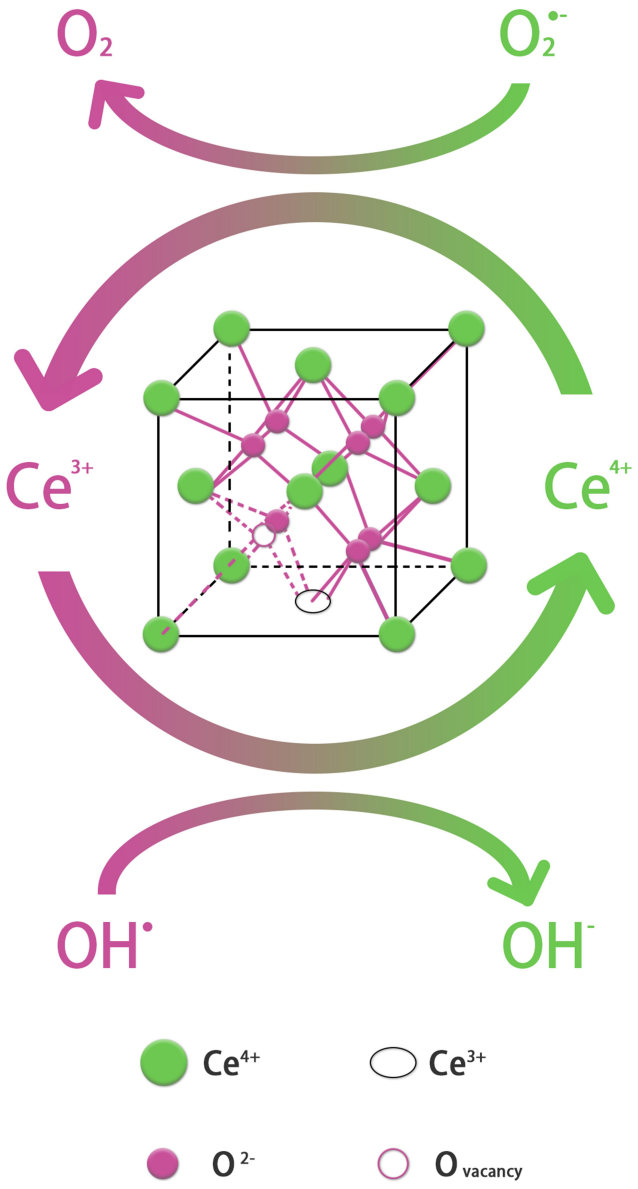

Figure 1 The structural representation of CeO2-NP, and its self-storage stability and self-regeneration capacity exerting antioxidant chemical reaction.

oxygen atom after size reduction will result in a high lattice strain.[10] The stronger the catalytic activity, the higher the effect of CeO_2-NPs in biomedical applications.

The rapid development of nanotechnology has broadened the heuristic path for nanoezyme based on inorganic nanoparticles. The combination of computer simulation and theoretical calculation has solved the possible catalytic mechanism of these nano-enzymes. CeO_2-NPs is a typical nano-enzyme, the Ce^{3+} to Ce^{4+} valence conversion of which is analogous to various redox enzymes' mechanisms and can also catalyze the reversible redox in cells and tissues.[11] The Ce^{4+} and low surface vacancy formation are essential for oxidation, while the Ce^{3+} and electron reshuffling in lattice oxygen vacancy provides the impetus for reduction. The specific catalytic mechanisms of the simulated enzymes are partly precise, such as automatic recovery after redox and substrate binding, but some are still under study.[12,13] The ability to mimic the activity of multiple enzymes provides excellent convenience for biomedical applications that are primarily dependent on redox activity, such as anti-inflammation, anti-bacteria, angiogenesis, and others.

Excellent catalyst performance distinguishes CeO_2-NPs' multipurpose industrial application to photochemistry and electrochemistry, such as solid oxide battery,[14] degradation of organic pollutants,[15] high-performance catalyst,[16] sensors,[17] abrasive particles,[18] coating material,[19] and others. The application of CeO_2-NPs to bioinformatics and computational biology has been receiving increasing attention. CeO_2-NPs have played an essential role in tissue engineering and regenerative medicine, especially for orthopedic medical treatment,[20] for their prospective oxidation resistance, anti-bacterial property, anti-inflammation, cancer resistance, non-toxicity, angiogenesis, drug/gene delivery, and others.[21,22]

CeO_2-NPs' Properties and Synthesis

CeO_2-NPs' Properties

The application of CeO_2-NPs to nano-biomedical technology has been increasingly conventional. The increasing research on their atomic lattice model, lattice parameter, surface oxygen vacancy, and others by electron microscope and microscope provide the experimental basis for their robust catalytic mechanism.[23,24] Huang et al[25] further discovered the highest reactivity on the surface of CeO_2 (100) through transmission electron microscopy and first-principles calculations. After the investigation of the electronic nano-structure of CeO_2 and associated catalytic complexes through density functional theory (DFT), Bruix and Neyman[8] elaborated on the reasons why CeO_2-NPs in specific size represent a higher reactivity and the interaction between nanostructures and metal carriers. Size also affects CeO_2-NPs' enhanced electronic conductivity, pressure-induced phase transformation, size-induced lattice relaxation, and blue shift in ultraviolet absorption spectra.[9,26] The size will limit or enhance the uptake of CEO_2-NPs by cells, and affect the biological parameters such as biological half-life, diffusivity, immunogenicity, and others.[27,28] Besides, size also affects the toxicity of CEO_2-NPs in vivo and internal environment.[29] Except for catalytic performance, for, the recommendation is to read on for more specific material physics and defect chemistry of ceria.[9,30]

In nanomedicine, inorganic enzyme mimic nanomaterials have become the latest research focus. Besides mimicking the structure and function of natural enzymes, enzyme mimic nanomaterials are more stable, more controllable, and more natural to prepare at a lower cost. CeO_2-NPs have become one of the research proprieties because of their multiple enzyme activities,[31,32] such as mimetic activities of superoxide dismutase,[33] catalase,[7] phosphatase,[34,35] peroxidase,[36] oxidase,[37] and others. Although studies have illustrated that the mimic activities of phosphatase and catalase follow different chemical methods and involve different active sites,[38] the more complex mechanisms warrant further study. Surprisingly, superoxide dismutase- and catalase-mimetic activities serve as the two primary methods to eliminate reactive oxygen species (ROS). Proverbially, ROS is the initiator of oxidative stress in many diseases. The adaption of various enzymes' properties to 3D biomaterials in the treatment system achieves CeO_2-NPs' antibacterial, anti-inflammatory, anticancer effect directly or indirectly.[21,39]

CeO_2-NPs' Synthesis

The temperature, reactants' concentration, pH, reaction environments, and stabilizers in the synthesis of CeO2-NPs affect CeO2-NPs' physicochemical and biological properties.[40] A well-designed synthetic method can fine-tune CeO_2-NPs' surface properties. Traditional chemical synthesis and maturing green synthesis are the primary synthetic methods for CeO_2-NPs. General views believe that the green synthesis without the requirement for severe reaction conditions of high temperature and high pressure is more propitious to biological applications for avoiding potential chemical toxicity and maintaining higher biocompatibility.[41] However, chemical synthesis's advantages suggest it shall continue befittingly, for instance, the increasingly maturing ability to control the reaction conditions and reactant properties, achievable mass production, and diminishable chemical toxicity by altering end-capping reagent and other measures.[42] A large number of recent research on synthetic methods for CeO_2-NPs have emerged.[21,43] The review recapitulated some of the recently reported synthetic approaches related to or potential for biomedical applications. The strong recommendation is to read on for synthetic methods and more detailed classifications.

Precipitation Method

Precipitation proves the easiest and most widely used synthetic method CeO_2-NPs. The common precursor is cerium nitrate hexahydrate and the reaction environment is alkaline (seen in Table 1).[44–48] Other precursors and capping agents are still in research and development.

Hydrothermal Method

The hydrothermal method is a common synthetic method for CeO_2-NPs by heating water as the solvent in the autoclave. The synthetic process of the hydrothermal method can complete by the mediation of the surface-active agent. The hydrothermal method can produce multiple forms of CeO_2-NPs. The solvents, stabilizers, and synthesis condition can influence CeO_2-NPs' biomedical-related performances (seen in Table 2).[7,49–52]

Green Synthesis

Green synthesis for CeO_2-NPs has received increasing focus. Except for the elimination of the adverse effects of agents and chemical methods on the synthetic environment,

Table 1 CeO_2-NPs Synthesized by Precipitation Method for Biological Applications

Capping or Stabilizing Agent	Related Organisms	Biomedical-Related Performances	Particle Size (nm)	References
–	Human keratinocyte cell line (HaCaT)	Biocompatibility, light protection, reduce free-radical production of core TiO_2 nanoparticles	4.8	[44]
Citrate acid ethylenediaminetetraacetic acid (EDTA)	Neuro-2a murine neuroblastoma cells (N2A cell).	Product stability, non-toxic to cells, highly monodispersed 13 nm crystallites with a pH at the potential of zero point charge (pH_{zpc}) of 2.2	13	[45]
DNA	–	Excellent and adjustable optical properties	6	[46]
Urea	*Escherichia coli (E. coli)*	Photothermal sterilization and deep tissue imaging potential	181 (composite nanosphere)	[47]
Xanthan gum	*Rattus norvegicus*	Dose-dependent, paramagnetic	22	[48]

Table 2 CeO_2-NPs Synthesized by Hydrothermal Method for Biological Applications

Capping or Stabilizing Agent	Related Organisms	Biomedical-Related Performances	Particle Size (nm)	References
–	Gram-positive bacteria S. aureus and B. subtilis, Gram-negative bacteria *E. coli and P. aeruginosa*	Better antibacterial and antioxidant activity, and more suitable for biological application than precipitation method under uniform conditions;	10	[49]
E. globulus leaf extract	Human cell lines A549 and HCT-116	Excellent photocatalysis, anticancer activity;	8–20	[50]
β-Cyclodextrin (β-CDs)	Imiquimod (IMQ)-induced Psoriasis mouse model	β-CDs on the surface endowed the NPs with drug-loading function via host-guest interactions;	80	[7]
Justicia Adhatoda leaves extract	HeLa (human cervical cancer cells)	Good antibacterial and anticancer activity;	28	[51]
–	Human lung cancer epithelial (A549) cells	Cerium oxide-reduced graphene oxide (CeO_2-RGO) reducing cytotoxicity, CeO_2 nanoparticles (NPs) alone significantly increasing glutathione (GSH) levels in A549 cells	–	[52]

green synthesis is not harsh on the reaction conditions, which is popular with the biological application, especially when the biocompatibility is enhanced. Nutrients, fungi, plants, bacteria, and biopolymers are the known material able to mediate the synthesis of CeO_2-NPs (Seen in Table 3).[27,43,53–59] For instance, primary and secondary metabolites in plant extracts can serve as capping or stabilizing agents.[60] Most natural CeO_2-NPs represent antioxidant, antibacterial, photocatalytic activity.[61–64] When the reactants for synthesis combine with biocompatibility materials or other materials beneficial to biological applications will achieve better synthesizing effect,[65–67] such as biological sensing property and others.

Alternate Methods of Synthesis

The synthetic methods determine the configuration, physical and chemical properties, surface groups, zeta potential, and others, thus determining the application behavior and therapeutic effect of CeO_2-NPs. Recently, the solvothermal method, a microwave-mediated end-capping of alcohols such as ethylene glycol, could synthesize CeO_2-NPs co-doped with Co^{2+} and La^{3+}, which presented a certain weak magnetism, different shapes, and controllable sizes.[68,69] The study on the application of magnetic nanoparticles to the drug delivery system started early.[70] Alzheimer's disease model has witnessed the application of magnetic CeO_2-NPs constitution to the magnetic separation of amyloid-beta (A-beta) peptides; Moreover, the magnetic CeO_2-NPs constitution could enhance the magnetic resonance imaging (MRI) in the treatment for cerebral hemorrhage.[71,72] This review believes that CeO_2-NPs co-doped with Co^{2+} and La^{3+} has potential in the future magnetic drug delivery field.

Spray coating has also recently been applied to the synthetic CeO_2-NPs in cellular biology. Vassie et al[73] first investigated the effect of particle size on uptake and intracellular transport of CeO_2-NPs (d = 7 and 94 nm) synthesized by flame spray pyrolysis in human cancer cells. The findings demonstrated that larger CeO_2-NPs presented a more robust clearance of intracellular ROS than the smaller ones, and the longer the therapy went, the more clearance of intracellular ROS. Simultaneously, folic acid-functionalized CeO_2-NPs showed a greater regulation on ROS than the control group of CeO_2-NPs in colon cancer cells.[74] However, CeO_2-NPs induced ROS in ovarian carcinoma cells, probably because of the increasing uptake of CeO_2-NPs by ovarian carcinoma cells. The experimental results imply a prospect in the application of CeO_2-NPs to anticarcinogen delivery.

The synthesis of CeO_2-NPs via the sol-gel process is one of the classic popular methods. The microemulsion of reverse micelles acts as one of the generic assistive technologies in the

Table 3 CeO_2-NPs Synthesized by Green Synthesis for Biological Applications

Capping or Stabilizing Agent	Related Organisms	Biomedical-Related Performances	Particle Size (nm)	References
Garlic extract	Gram-positive and gram-negative bacterial strains fungal strains	Ag@CeO_2 composite shows excellent photocatalytic and sonocatalytic activity, a superior synergetic effect, excellent recyclability, improved antimicrobial activity.	10–20	[53]
Glucose, fructose, lactose	CCL30 (squamous cell carcinoma) cells	Concentration changes shape, and smaller CNP presents passive cellular uptake function.	3–5	[27]
An aqueous extract of *Ziziphus jujube* fruit	Colon (HT-29) cancer cell	Excellent UV protection and sunscreen physical absorption properties.	18–25	[54]
Thermal decomposition of cerium alginate biopolymer gel	–	Surface charge and surface functional groups which can act as a binding template, Drug release and potential applications to biological scaffolds.	5	[55]
Aqueous extract of *Salvadora persica*	HT-29	Rapid production process, high yield, non-toxic products.	10–15	[56]
Linum usitatissimum L. (*Lu*) seeds Extract	Labeled with technetium (^{99m}Tc) for in vivo bio-distribution study in Wistar rat	Smaller particles are produced at a lower calcination temperature, which significantly reduces the reactive oxygen species produced by cell metabolism, in vivo stability, and nontoxicity.	3–5	[57]
Fresh egg white (EW)	Human periodontal fibroblasts cells	Controllable size, nontoxicity even at high doses.	25	[58]
Pectin	Human erythrocyte	Broad-spectrum of antibacterial activity, antioxidant potential, and no cytotoxicity.	5–40	[59]

sol-gel process, which is easy to control the superficial area, form, and other properties of nanoparticles. Torres-Romero et al synthesized Titania-Ceria composite at different sizes through titanium butoxide and cerium nitrate hexahydrate as the precursors.[75] Three years later, Torres-Romero et al[76] indicated that the Titania-Ceria composite presented excellent biocompatibility and delivery efficiency in the drug delivery systems (DDSs) with daunorubicin (DNR) against cancer. Another exciting piece of research demonstrated that CeO_2-NPs synthesized by the sol-gel process reduced brain edema, microglia/macrophage recruitment around the hemorrhagic lesion, and inflammatory protein expression after the intravenous injection into mouse models of cerebral hemorrhage.[77]

Reverse-Phase has been applied in the first study in which liposomes acted as the carrier for cerium oxide nanoparticles.[78] Such a system has the advantages of liposome targeting, protection from protein scavenging, static stability, as well as CeO_2-NPs catalytic activity, and potent antioxidant capacity. Besides, the system presented excellent biocompatibility, tolerance, and uptake efficiency in fibroblasts. Except for the above methods, oxidation, ball grinding, thermal decomposition, acoustic chemistry, and others are outside the scope of this review for their little value in the biological application.

Orthopedic Biomedical Applications

Bone defects caused by congenital deformity, natural disasters, traffic accidents, and others are common orthopedic disease in clinical medicine. Traditional treatment methods, including autograft and allograft, have presented limitations.[79] The development of new bone graft substitutes has been a hot research topic. Bone tissue engineering (BTE) provides a new solution to the above limitations.[80] The selection of BTE materials is significant because the required properties are numerous and complex. The acknowledged properties do cover osteoconductivity, biocompatibility, degradability, mechanical properties, pore structure, and processability.[81]

Moreover, traditional treatment methods require regulatory capacity on the shape, imaging, infection, healing,

immune response, and others.[82] At present, the composite materials used for traditional treatment primarily include medical metal, bioceramics, and biopolymer materials.[83] CeO_2-NPs have begun to look for a favorable position in these materials. Further exploration has gone into CeO_2-NPs' potential in stem cells, scaffold materials, and growth factors, namely the three significant elements of BTE. The potentials cover CeO_2-NPs' capacity, properties to enhance or resist other material. Synchronously, as a component of the nano-drug delivery system, CeO_2-NPs will act as a pro-oxidant or antioxidant according to different environments in the complex extracellular environment of cancer cells, to induce apoptosis of cancer cells by relying on oxidative stress.[84,85] CeO_2-NPs have also involved in the treatment of osteosarcoma. Hence, this review designs to summarize the primary data of CeO_2-NPs in orthopedics.

Osteosarcoma

Anticancer therapy has not witnessed a broad application of CeO_2-NPs. Interestingly enough, CeO_2-NPs can exhibit antioxidant activity or oxidizing agents from different pH levels of subcellular localization.[86] For example, in Colorectal Carcinoma Cells, CeO_2-NPs can induce DNA fragmentation by increasing the production of ROS, resulting in cellular apoptosis through the p53-dependent mitochondrial signaling pathway.[84] Yazici et al[87,88] discovered positive effects to varying degrees on osteosarcoma when they studied the cytotoxicity of 0.1 M and 0.01 M dextran-coated CeO_2-NPs based on dose and time dependence. After that, the results found that at pH 6.0, CeO_2-NPs were the most damaging to bone cancer cells and the least damaging to healthy bone cells.[89] Besides ROS and other mechanisms related to redox reactions, activated Cytotoxic CD8+ T cells (CTLs) treated by CeO_2-NPs released more effector molecules and cytokines, including interleukin-2 (IL-2) and tumor necrosis factor-α (TNF-α), granzyme B and perforin, which could lead to better immunotherapy for cancer.[90] The above research attested CeO_2-NPs a type of promising nanoparticles for bone cancer treatment. Surface functionalization of CeO_2-NPs and tumor microenvironment will affect the activity of antioxidants or pro-oxidant. Cell type or cell microenvironment may also pose different effects on cytotoxicity. However, the specific influencing mechanism needs further exploration.

Recombination with Hydroxyapatite (HA)

Hydroxyapatite (HA), the natural form of calcium apatite, is the primary mineral component of bones and teeth. HA can bind to tissue at the interface by chemical bonds to release ions and participate in metabolism.[91] What is more remarkable, the new bone will regenerate along the surface of the direct bone-to-implant contact where HA serves as the implant.[92] HA has found a broad application in the clinical and experimental field for biocompatibility, non-toxicity, and osteoconductivity. However, HA's mechanical modulus and fracture toughness are not ideal.[93] The two primary recombinations between CeO_2 and HA are HA-based scaffolds, and surface coatings for other bone implants, namely the composite coating of CeO_2 and HA.

Pandey et al have made a further study on hydroxyapatite reinforced with ceria and silver (HA-CeO_2-Ag). After obtaining hydroxyapatite with 5 wt% CeO_2 NPs and 2.5 wt% Ag NPs (HA-5C-2.5Ag) by spark plasma sintering (SPS), they first tried to make up the low mechanical and tribological properties of HA alone by HA-CeO_2-Ag.[94] Fretting and scratch tests testified the protective tribofilm and oxide protection in CeO_2/Ag reinforced hydroxyapatite. HA-CeO_2-Ag restricted the tribological damage effectively over multi-length scales. They further improved the tests on the bactericidal activity, inoxidizability, and bioactivity of HA-CeO_2-Ag.[95] The results showed that the count of human osteoblasts (hFOBs) in the experimental group increased by 6.7 times compared to the control group. The filopodial extensions (60–150 μm) and matrix-like deposition reflected the cell-substrate intimacy. The analysis believed that increased protein hydrophobicity might enhance the absorptivity of HA-CeO_2-Ag to cells. They also believed that HA-CeO_2-Ag could act as not only the independent porous scaffolds, surgically for internal fixation, to be a reliable substrate with effective load-bearing capacity in orthopedic applications, but also a type of antimicrobial bioactive coatings on the femur stem (during implant manufacturing) for total hip arthroplasty.

Li et al[96–98] prepared CeO_2-HA composite coatings by plasma spraying technique and conducted considerable research to testify the coatings' application. Because of the antioxygenic property of CeO_2, the increase of CeO_2 content in the coatings can improve the cell viability and reduce the cell apoptosis, but decrease the chemical stability slightly. The up-regulation of Wnt/β-catenin signal transduction can better protect BMSC from H_2O_2-induced damage in

osteoblasts differentiation. Besides, CeO_2-HA composite coatings can protect H_2O_2-induced BMSC from generating osteoclasts, which is in reflection by the increased OPG/RANKL ratio. The above research results provide a theoretical basis for the material in osteoporosis bone regeneration.[96] In the study on the inflammatory response, the results found that the increase of CeO_2 content in HA coatings enhanced the osteogenic activity of BMSC through the Smad-dependent-BMP signaling pathway.[97] The addition of CeO_2 also endowed HA coatings with anti-inflammatory effect. HA-30Ce, by inducing a drift towards an M2 phenotype, presented an ideal effect on macrophage polarization. Such results suggested that the composite coatings had osteogenic and anti-inflammatory properties. Except for the above experiments, a group result found that a higher Ce^{4+} concentration up-regulated the expression of anti-inflammatory cytokines (IL-10 and IL-1RA) and osteoinductive molecules (BMP2 and TGF-1) by macrophages, implying that the regulation of cerium valence might be a valuable strategy for improving osteogenic properties and reducing inflammatory responses.[99]

Another application is that the CeO_2 and HA composites attach to other materials with specific mechanical stability, such as AZ91 Mg alloy.[100] Researchers developed manganese (Mn), and strontium (Sr) substituted hydroxyapatite (Mn, Sr-HAP) coatings on the CeO_2 coated AZ91 Mg alloy, which enhanced the corrosion resistance of the whole material to facilitate the clinical application of AZ91 Mg alloy. Sanyal et al[101] prepared ceria-stabilized zirconia (CSZ) in fluorohydroxyapatite (FHA) by the sol-gel method. As a hard material, CSZ has received verification on toughness and osteoconduction. Besides, the composite of HA-CNT-CeO_2 -Ag, namely plasma-sprayed HA-coated Ti-6A1-4V,[102] is 2.3 times, 1.6 times, and 3.1 times enhanced Vickers hardness, estimated modulus, and fracture toughness, respectively, than HA alone. Meanwhile, the composite of HA-CNT-CeO_2-Ag also presented cell adhesion, bactericidal activity, and others. Similar effects were also in a composite of cerium-doped glass-reinforced hydroxyapatite (GR-HA).[103]

Ceria Doped in Mesoporous Bioactive Glasses

Mesoporous bioactive glasses (MBG) based on SiO_2-CaO-P_2O_5 composition were prepared in 2004 by combining the sol-gel method and supramolecular chemistry method.[104] Subsequently, Shruti et al[105] synthesized mesoporous bioactive glass scaffolds (MBG_Scs), based on 80% SiO_2-15% CaO-5% P_2O_5 (in molar ratio) mesoporous sol-gel glasses substituted with Ce_2O_3, Ga_2O_3, and ZnO. This composite contains super-pores suitable for vascularized interconnections for nutrient supply and normal cell growth, seen in Figure 2.

Direct addition of ceria into HA will generate cerium phosphate, which affects the biocompatibility to some extent.[106] Therefore, Nicolini et al[107] dopped CeO_2-NPs with Ce^{3+} and Ce^{4+} at different molar ratios into MBGs with 80%SiO_2–15%CaO-5% P_2O_5. These MBGs with a high superficial area would form HA after being immersed in simulated body fluid (SBF). The test illustrated that Ce-MGB could reduce catalase and superoxide dismutase mimic (SOD). The best catalase activity appeared in 45S5 bio-glass containing cerium, and the highest cerium content could achieve 5.3%. Both infrared spectroscopy and X-ray diffraction analysis verified the existence of HA in some type of Ce-MGB. The above tests, including bioactivity tests, indicated the feasibility of MBG with inoxidizability and synthetase mimic activity. Atkinson et al[108] synthesized Ce-MBGs by evaporation-induced self-assembly (EISA) and conducted the above tests. They verified the biocompatibility by mouse fibroblasts. The antibacterial and biological activities of 50% SiO_2-(45-x) % CaO-5% P_2O_5 MBG with molar content of 1, 5% CeO_2-NPs have also been verified.[109,110] Recently, 45S5 bio-glass with ceria has been developed with a polyhedral shape and large size, and the cellular uptake capacity, survivability, and proliferate ability have been demonstrated.[111] CeO_2-NPs doped in MBG with MgO could decrease the degradation rate and enhance chemical durability. Meanwhile, the tests verified that the "sol-gel" synthesis technique promoted hydroxyapatite growth rate over the conventional "melt quenching" route.[106]

The above experiments are the preliminary evidences for the application of CeO_2-NPs doped in MBG to bone regeneration materials. Future research may focus on MBG based on 3D bioactive scaffolds and in vivo experiments. Recently, Lu et al[112] constructed CeO_2-NPs modified Ce-BG scaffolds using hollow Ce-BG microspheres with chitosan (CTS) via a freeze-drying procedure. The CeO_2-NPs in the scaffolds could rapidly promote the proliferation and osteogenic differentiation of hBMSC, which was verified by the up-regulation of osteogenic markers of osteocalcin (OCN), alkaline phosphatase (ALP), type I collagen (COL-1), and others. The enhancement of Ce-MBG scaffolds' osteoinduction primarily relates to

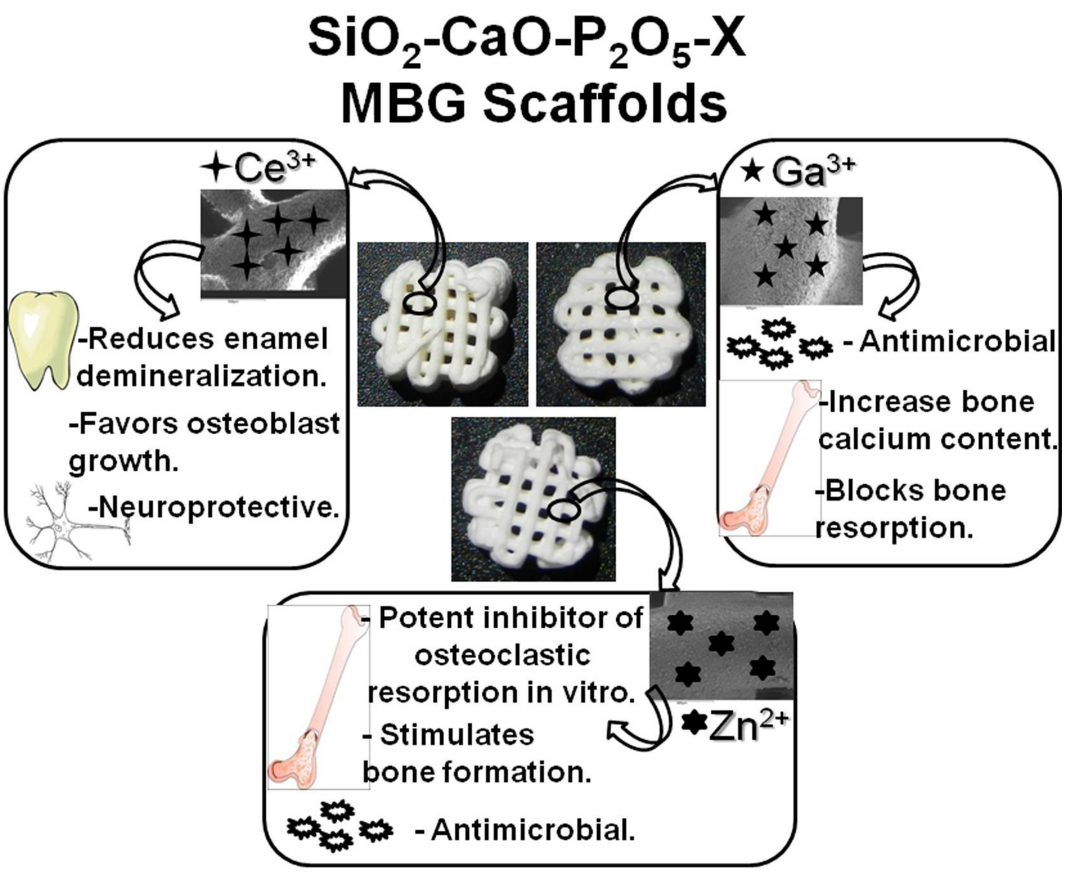

Figure 2 Schematic representation of possible biological properties possessed by Ce^{3+}, Ga^{3+}, and Zn^{2+}-substituted MBG_Scs prepared by rapid prototyping: 3-D printing.
Notes: Reprinted from *Acta Biomaterialia*, 9(1), Shruti S, Salinas AJ, Lusvardi G, Malavasi G, Menabue L, Vallet-Regi M. Mesoporous bioactive scaffolds prepared with cerium-, gallium- and zinc-containing glasses. 4836–4844, Copyright 2013, with permission from Elsevier.[105]

activated ERK pathways and can be prevented by the addition of selective ERK1/2 inhibitors (SCH772984). In vivo experiments on rat skull defect models showed that Ce-MBG scaffolds could promote collagen deposition, osteoblastic formation, and bone regeneration compared with sole MBG scaffolds.

Stabilized Zirconium Oxide Coating

Metal-free dental zirconia implants have attracted much attention. Due to the excellent mechanical properties, stable physical and chemical properties, and excellent biocompatibility, metal-free dental zirconia implants can avoid the grey appearance of gums and potential hypersensitivity of titanium implants.[113] The durability of traditional materials raises questions. Yttria stabilized zirconia (3Y-TZP) is aging or low-temperature degradation (LTD), which basically involves a phase transformation that leads to microcracking, resulting in catastrophic failures;[114] High-purity alumina (Al_2O_3) is weak in toughness. Base material of novel zirconia is emerging to overcome the significant shortcomings of 3Y-TZP.[115]

At present, the mainstream uses tetragroconic zirconia polycrystal (CE-TZP) with stable cerium dioxide as the second phase to improve the toughness of alumina composites and finally forms the composite of CE-TZP/Al_2O_3. The macroscopic and microscopic mechanisms for increased toughness have been demonstrated.[116] Scientists have previously attested that CE- CE-TZP/Al_2O_3 could promote HA formation and osteoblast proliferation and differentiation.[117] The research compared the biomechanical and histological behaviors of Ce-TZP/Al_2O_3 and 3Y-TZP in rats.[118] Ce-TZP/Al_2O_3 showed stronger shear strength but slightly lower average surface roughness. No significant difference appeared in the new bone thickness around the implant in the bone marrow region and bone-implant contact (BIC). Osteoclasts were not observed at any time in the experiment of CE-TZP/Al_2O_3, but in 3Y-TZP group, which indicated the better biocompatibility of Ce-TZP/Al_2O_3. The surface roughness could be treated with hydrofluoric acid, and the nanometer morphology could significantly enhance bone formation and bone integration in vivo.[119] In addition

to rats, the study in dogs also proved CE-TZP/Al_2O_3 an excellent dental implant, including excellent bone resorption and soft tissue attachment.[120,121]

Based on CE-TZP/Al_2O_3 to continue to solve hydrothermal aging, Altmann et al developed a new type of stable zirconia-alumina-aluminate composite ceramics (ZA_8Sr_8-Ce_{11}). The result found the most conspicuous long-term attachment of primary osteoblasts, and mineralized deposition of extracellular matrix (ECM). ZA_8Sr_8-Ce_{11} with microporous morphology is one of the best materials for clinical application.[122] The 3D-printed Ce-TZP/Al_2O_3 showed compression strength similar to that of leather bone, almost 200 MPa. Besides, the viability and differentiation ability of cultured cells are also powerful. In general, such composites present excellent aesthetic properties, chemical stability, and negligible corrosion and abrasion, as well as excellent mechanical and biological properties.

Cerium Oxide Coating for Titanium-Based Implants

Titanium and its alloys have found a broad application in orthopedic and dental implants.[123] The three critical factors for long-term clinical success of implants are antimicrobial, anti-inflammatory, and stability of osseointegration, which have been addressed in many ways.[124,125] CeO_2-NPs would undoubtedly be a suitable potential material. Li et al[126] developed a novel Ti surface modified with different shapes of CeO_2-NPs (nanorod, nanocube, and nano-octahedron). They also tested the antimicrobial and anti-inflammatory responses of the composite of different CeO_2-NPs deposited into Ti. The results showed that the three types of CeO_2-modified Ti showed the same strong antibacterial properties. Nano-octahedron CeO_2 modified Ti had the best anti-inflammatory effect (Figure 3). Zhao et al[127] deposited TiO_2 coating doped with different percentages of CeO_2 on the cp-TI substrate through APS. The results demonstrated that the dose dependence of CeO_2 determined the corrosion resistance, cellular compatibility, and antibacterial properties. Less than 20% of doping would not affect the crystal structure.

As with the recombination with HA, the effect of CeO_2-NPs as a coating for titanium-based implants on the cerium valence state was also investigated. The results showed significantly up-regulated expression of osteogenic genes and proteins at a high Ce^{4+} concentration, and high expression of the polarization of macrophages to the M2 phenotype. The increase in M2 percentage could increase the production of anti-inflammatory cytokines.[128] Also, the high Ce^{4+} presented a higher catalase activity, but a lower peroxidase activity. Results of protein adsorption and conformation indicated that the exposed cell-binding sites of fibronectin and subsequent cell morphology were associated with the Ce valence state.[80] Overall, regulation on cerium

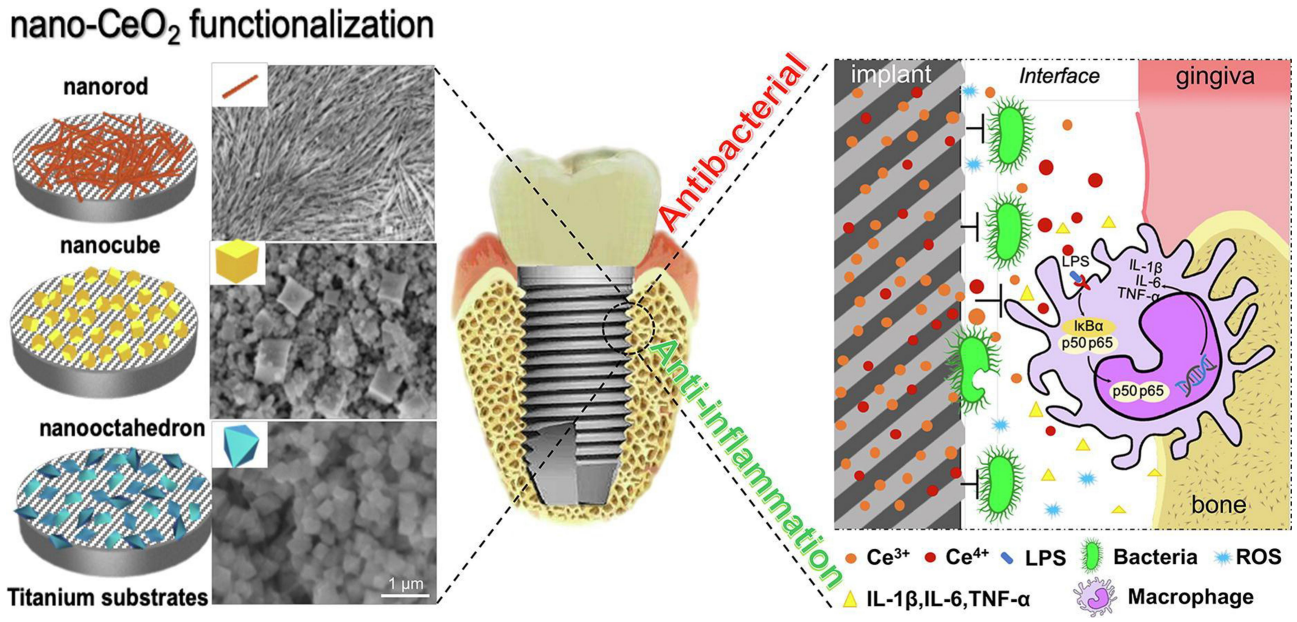

Figure 3 Schematic illustration of implant surface modified by CeO_2-NPs (rod- CeO_2, cube-CeO_2, octa-CeO_2) for antibacterial and anti-inflammatory properties.
Notes: Reprinted from *Acta Biomaterialia*, 94, Li X, Qi M, Sun X, et al, Surface treatments on titanium implants via nanostructured ceria for antibacterial and anti-inflammatory capabilities. 627–643. Copyright 2019, with permission from Elsevier.[126]

valence may be a good strategy for designing orthopedic/dental implant coatings with beneficial immune responses.

Other Applications

To further understand the biomaterial potential of CeO_2, Ball et al[129] fabricated porous ceria via direct foaming. The tests of cytotoxicity, inflammatory response, and reactive oxygen species found CeO_2 similar to commercially available bioglass. Another study found that cultured HMSCs increased osteogenic differentiation and collagen production when CeO_2-NPs were doped to 3D nanocomposite scaffolds.[130] Evidence suggested that ceria promoted the migration of bone marrow stromal cells and osteogenic differentiation through the Smad1/5/8 signaling pathway.[131] An essential finding illustrated that CeO_2-NPs could induce stem cells' growth in PLGA scaffolds. The formed PLGA/nano-CeO_2-NPs scaffolds could regulate roughness, thus improving cells' sensitivity to host surface characteristics.[132]

Insufficient angiogenesis hinders the clinical application of bone tissue engineering materials. The current mainstream solution is that bone tissue materials carry endogenous angiogenic factors to promote the proliferation, migration,

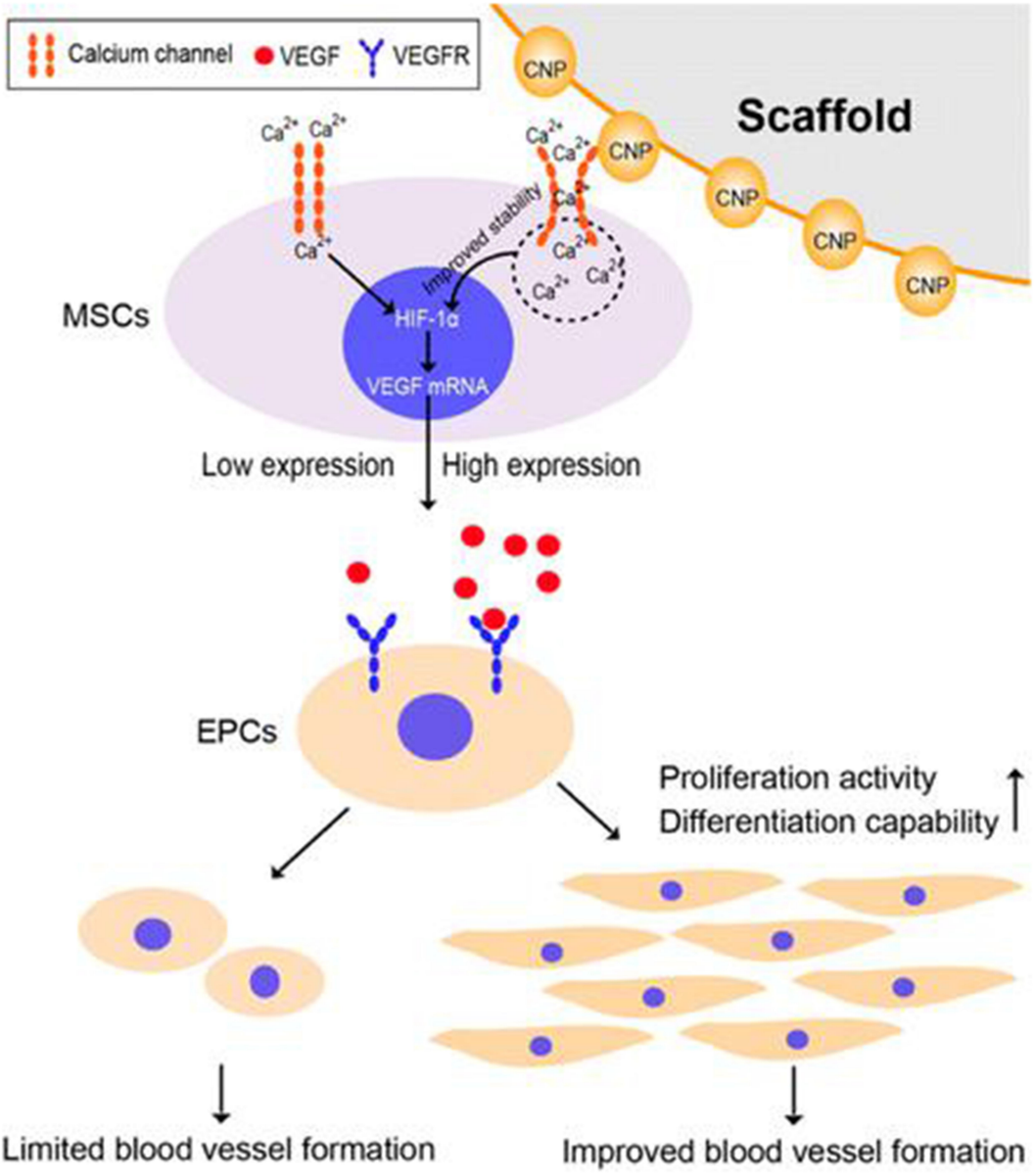

Figure 4 Scheme illustrates the mechanism of CNPs enhancing the blood vessel formation of EPCs.
Notes: Reprinted with permission from Xiang J, Li J, He J, et al Cerium Oxide Nanoparticle Modified Scaffold Interface Enhances Vascularization of Bone Grafts by Activating Calcium Channel of Mesenchymal Stem Cells. *ACS Applied Materials & Interfaces*. 2016;8(7):4489–4499. Copyright © 2016 American Chemical Society.[137]

differentiation, and angiogenesis of endothelial cells (EC) and/or endothelial progenitor cells (EPC).[133,134] Nethi et al[135] demonstrated the angiogenic property of functional nanoconjugates of organosilane functionalized CeO_2-NPs (nanospheres), and suggested that the expression of p38 MAPK/HIF-1α may be a reasonable signal transduction mechanism for its angiogenic property. In another research, CNPs accelerated the process of endochondral ossification by promoting sufficient hypertrophic differentiation of BMSCs via activation of the DHX15–p38 MAPK signaling pathway, which could better overcome the lack of vascularization and relevant hypoxia at the initial stage of implantation.[136] CeO_2-NPs can also activate calcium channels in mesenchymal stem cells and ultimately lead to EPC proliferation, migration, and differentiation through chain reaction[137] (seen in Figure 4).

Challenges

The research on CeO_2-NPs as a nanozyme based on inorganic nanoparticles is just unfolding. At present, the activity and specificity of nano-enzyme are still lower than that of a natural enzyme, and the influence of pH value is crucial.[31,32] Significantly, in vivo biocompatibility is assessed by protein corona, and the presence of hard and soft protein corona will affect the bioactive interface, including usability, stability, and ecotoxicity. Haptens formed by adsorptive proteins also caused abnormalities in immune homeostasis.[138] Antioxidant and pro-oxidant conversion is a double-edged sword, which needs total control on the external environmental conditions to ensure that the conversion can achieve the desired effect rather than the opposite effect. For instance, the pro-angiogenic and anti-angiogenic characteristics of CeO_2-NPs are affected by the microenvironmental parameters, including pH, production of reactive oxygen species, and intracellular oxygen concentration.[134] The same conversion issues that have led to conflicting toxicological reports pose challenges for future regulatory and environmental risk assessments for CeO_2-NPs applications.[29] Besides, Ce^{3+} enhances the expression and activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (Nox1) in bone metabolism, which increases ROS levels, thus activating the RANKL-dependent osteoclast differentiation pathway and generating osteoclasts, which may cause abnormal bone resorption.[139] The latest study showed that the genotoxicity of CeO_2-NPs was a function of concentration and particle diameter in vitro.[140] While in vivo experiments showed that short-term exposure of rats to uncoated CeO_2-NPs could induce pulmonary inflammation and non-dose-dependent DNA damage,[141] which increased the difficulty in modification and synthesis. In conclusion, the establishment of long-term clinical safety and ecological environmental safety assessment still needs a long process of research.

Discussion

CeO_2-NPs has found a broad potential in the biomedical field. This review discussed the latest developments of CeO_2-NPs' orthopedic biomedical applications. The green synthetic method using biocompatible stabilizers grows in importance in the production of CeO_2-NPs and its orthopedic biomedical applications. The surface chemistry, particle diameter, physical and chemical properties of CeO_2-NPs need reasonable control. CeO_2-NPs doped in the substitutes of metallic elements, like hot materials of graphene, PLGA, and others, are making progress in the application to bone implant materials. Besides, in terms of imaging, such as reducing the harmful effects of Gd, enhancing the contrast of MRI is very attractive;[28] Regarding drug carrier, CeO_2-NPs are applied as carrier encapsulated in liposome or pegylated to combine with other materials; magnetic nanoconjugate delivery system with core-shell structure is in research.[27,142] In clinical application, the ability of CeO_2-NPs to promote angiogenesis and development turns out critical. Despite the challenges mentioned above, it is expected that in the future, CeO_2-NPs will overcome the limitations to work well in 3D tissue-engineered materials and flourish in interdisciplinary nanomedicine.

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Disclosure

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