

Review

Oxygen-Generating Metal Peroxide Particles for Cancer Therapy, Diagnosis, and Theranostics

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Abstract

Theranostic materials, which combine therapeutic and diagnostic capabilities, represent a promising advancement in cancer treatment by improving both the precision and personalization of therapies. Recently, metal peroxides (MePOs) have attracted significant interest from researchers for their potential use in both cancer diagnosis and therapy. This review provides an overview of recent developments in the application of MePOs for innovative cancer treatment strategies. The unique properties of MePOs, such as oxygen generation, are highlighted for their potential to improve therapeutic outcomes, especially in hypoxic tumor microenvironments. Initially, methods for MePO synthesis are briefly discussed, including hydrolyzation–precipitation, reversed-phase microemulsion, and sonochemical techniques, emphasizing the role of surfactants in regulating the particle size and enhancing bioactivity. Next, we discuss the main therapeutic approaches where MePOs have shown promise. These applications include chemotherapy, photodynamic therapy (PDT), immunotherapy, and radiation therapy. Overall, we focus on integrating MePOs into theranostic platforms to enhance cancer treatment and enable diagnostic imaging for improved clinical outcomes. Finally, we discuss potential future research directions that could lead to clinical translation and the development of advanced medicines.

Keywords: calcium peroxide; metal peroxide; theranostics; cancer; oxygen generating



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1. Introduction

Materials that have both therapeutic and diagnostic imaging modalities are referred to as theranostic, blending the two words together (i.e., therapeutic and diagnostic), a term originally coined by Funkhouser in 2002 [1,2]. However, the origins of the concept can be traced to 1946 in nuclear medicine's use of radio-iodine pharmaceuticals for thyroid cancers [3]. This unique approach allows for the simultaneous delivery of an imaging agent and a therapeutic one, significantly aiding in the therapy of some diseases [4,5]. For example, in the treatment of cancer, it is essential to initially carry out disease staging, which is often performed with the aid of imaging before starting therapy [6,7]. Nevertheless, separate materials are often used for imaging and therapy, which may lead to differences in biodistribution. This means that the imaging and therapeutic agents may not accumulate in the same areas at the same time, reducing treatment effectiveness.

A more effective approach would be to integrate both imaging and therapeutic functions into a single theranostic platform or material. This approach ensures a consistent

biodistribution, thereby improving the precision of the treatment and minimizing side effects [8,9]. Ultimately, using theranostic nanomaterials, it might be possible to obtain real-time feedback and/or the long-term monitoring of cancer progression with the goal of tuning the therapy more quickly and precisely [10,11]. Thus, shifting cancer treatment to include theranostic approaches using nanomaterials could propel more personalized and effective treatments with improved outcomes for a more diverse range of patients [5,12].

One of the more promising aspects of using theranostically based nanomaterials is their potential for minimizing unwanted side effects by being precisely targeted to diseased tissues [12,13]. Larger particles are usually limited in their penetration of tumors and are generally localized to tumor tissue due to a phenomenon known as the enhanced permeability and retention (EPR) effect [14,15]. The EPR effect is a result of the poor lymphatic drainage typical of tumors and the often irregular, enlarged, and leaky vasculature surrounding the tumor tissue, which enables these particles to escape from the bloodstream [15].

Targeted nanomaterials can also benefit from their reduced size by not being easily filtered out by the kidneys, allowing them to remain in the bloodstream longer [16]. Furthermore, altering nanomaterial surface properties and engineering them with targeting ligands and cloaking agents, such as poly (ethylene glycol) (PEG), can significantly improve tumor targeting and reduce undesired systemic toxicity [17,18]. In addition, achieving a higher concentration of nanomaterials in tumor tissue could also improve the contrast in imaging applications [19]. The high surface-to-area ratio relative to the volume of targeted nanomaterials enhances their capacity to simultaneously carry large loads of both therapeutic and imaging agents [12,18].

A variety of theranostic nanomaterials, including gold nanoparticles, carbon dots, graphene, mesoporous silica, and metal peroxides (MePOs), have been investigated for their potential applications in cancer treatment [20]. Among them, the latter has attracted significant interest due to their multifunctional nature [21–23]. One of the main advantages of MePOs is that they can generate oxygen, reactive oxygen species (ROS), and/or hydrogen peroxide [22,23]. These unique features of MePOs could be important for improving therapeutic outcomes and preventing disease progression [22,24,25]. For example, calcium peroxides have been extensively investigated in cancer treatment applications [22,24]. Calcium peroxide (CPO) is particularly attractive since calcium is the most abundant metal element in the human body and can have a better biocompatibility profile versus other peroxides [26,27]. Similarly, CPO can release Ca ions and generate hydrogen peroxide under acidic conditions usually found in the tumor microenvironment (TME) [26,28].

Alternatively, under more neutral pH environments, CPO can release oxygen that could be augmented by another MePO (i.e., manganese peroxide, MnO_2 , MPO) [28–30]. The addition of MPO can significantly improve the release of oxygen from CPO particles [28]. Furthermore, MPO is also unique as it has been used as a contrast agent in magnetic resonance imaging (MRI) [31,32]. Similarly to CPO in the acidic environment, MPO can release Mn(II) ions that have five unpaired electrons, which can increase the likelihood of the presence of Mn(II) paramagnetic centers when in contact with water molecules (i.e., providing the improved MRI contrast) [32,33]. Therefore, the combination of these MePOs can be used in a single platform, providing a theranostic modality for both cancer treatment and imaging. Moreover, when dealing with the nanoparticles of MePOs, the possibility arises for the additional conjugation of drugs and therapeutics on the surface of these materials, thereby extending their applications [34]. Similarly, it is possible to surface modify or add polymer coatings that prevent the premature degradation of the MePO, such as CPO [35,36]. As such, there have been several key aspects in which MePOs have been used in cancer treatment and imaging. In this review, we focus on four main

therapeutic approaches: chemotherapy, photodynamic therapy (PDT), immunotherapy, and radiation therapy.

2. Synthesis of MePO Particles

A variety of techniques have been developed for the synthesis of MePO micro- or nanoparticles (Table 1 and Figure 1), including hydrolyzation–precipitation [37–39], reversed-phase microemulsion [36,40], and sonochemical methods [41,42]. In the majority of cases, water-soluble polymers, such as PEG [29,43], polyvinyl pyrrolidone (PVP) [39,41], and hyaluronic acid (HA) [44], have been employed as surfactants and/or stabilizers to regulate the particle size and improve the dispersibility of the MePO particles [35]. Furthermore, the introduction of these polymers also enhances the stability and bioactivity of the MePO as well as its suitability for biomedical applications [35,45].

Table 1. A comparative summary of metal peroxide particle synthesis methods.

Method	Mechanism	Advantages	Disadvantages
Hydrolyzation–Precipitation	Metal ions form hydroxo–peroxo complexes → nucleation → growth and precipitation.	Simple, low cost, low temperature, scalability, good component homogeneity	Limited control over size/morphology; wide size distribution; possible incomplete precipitation; biocompatibility requires surface functionalization
Reversed-Phase Microemulsion	Nanodroplets act as microreactors—controlled nucleation/growth inside micelles.	Produces narrow size distribution, controlled morphology, versatile shapes (core–shell, nanowires)	Surfactant residues may lead to cytotoxicity and are difficult to remove; complex formulation; scale-up challenging due to emulsion stability
Sonochemical	Acoustic cavitation produces radicals → peroxo complexes → rapid nucleation inside bubbles.	Green (no toxic reagents), quick, mild conditions, yields clean, small (<30 nm), porous particles, easy core–shell formation, moderate scalability	Requires specialized ultrasound equipment; potential agglomeration if not controlled

The hydrolyzation–precipitation method is the most prevalent technique for the synthesis of MePO particles, offering a number of advantages, including simplicity, mild conditions, low costs, and size adjustability [35,46]. The process typically involves the use of metal salts as precursors, which are reacted with hydrogen peroxide in an alkaline solution to form insoluble MePO nanoparticles. By employing this approach, Shen et al. [39] successfully synthesized CaO₂ nanoparticles and nanocrystals. They used ethanol as a solvent to minimize the hydrolysis of CaO₂. The addition of H₂O₂ to an ethanol solution containing CaCl₂ and PVP resulted in the formation of primary nanocrystals with a diameter of 2–15 nm. The resulting CaO₂ nanoparticles exhibited antibacterial activity, as evidenced by the release of H₂O₂ and O₂ upon contact with water. Zhang et al. [38] synthesized BaO₂ using a similar method but incorporated organic ligands in order to control the growth and morphology of the resulting material. The use of coordinating ligands enabled the synthesis of nanosized particles, while modifications of BaO₂ with biodegradable agents such as L-glutamic acid reduced the toxicity of Ba²⁺ and enabled tumor-targeted X-ray therapy applications. In several studies, metal oxides were employed directly in the synthesis process, rather than their corresponding salts. For instance, Heo et al. [37] transformed eggshell waste into calcium oxide (CaO) through calcination at 900 °C, followed by the reaction of the calcined CaO with water, which resulted in the generation of a calcium hydroxide (Ca(OH)₂) solution. Subsequently, a gradual addition of H₂O₂ was employed to synthesize CaO₂ powder. However, the resulting CaO₂ exhibited

an irregular particle size and shape, which may be attributed to the absence of surfactants during the synthesis process.

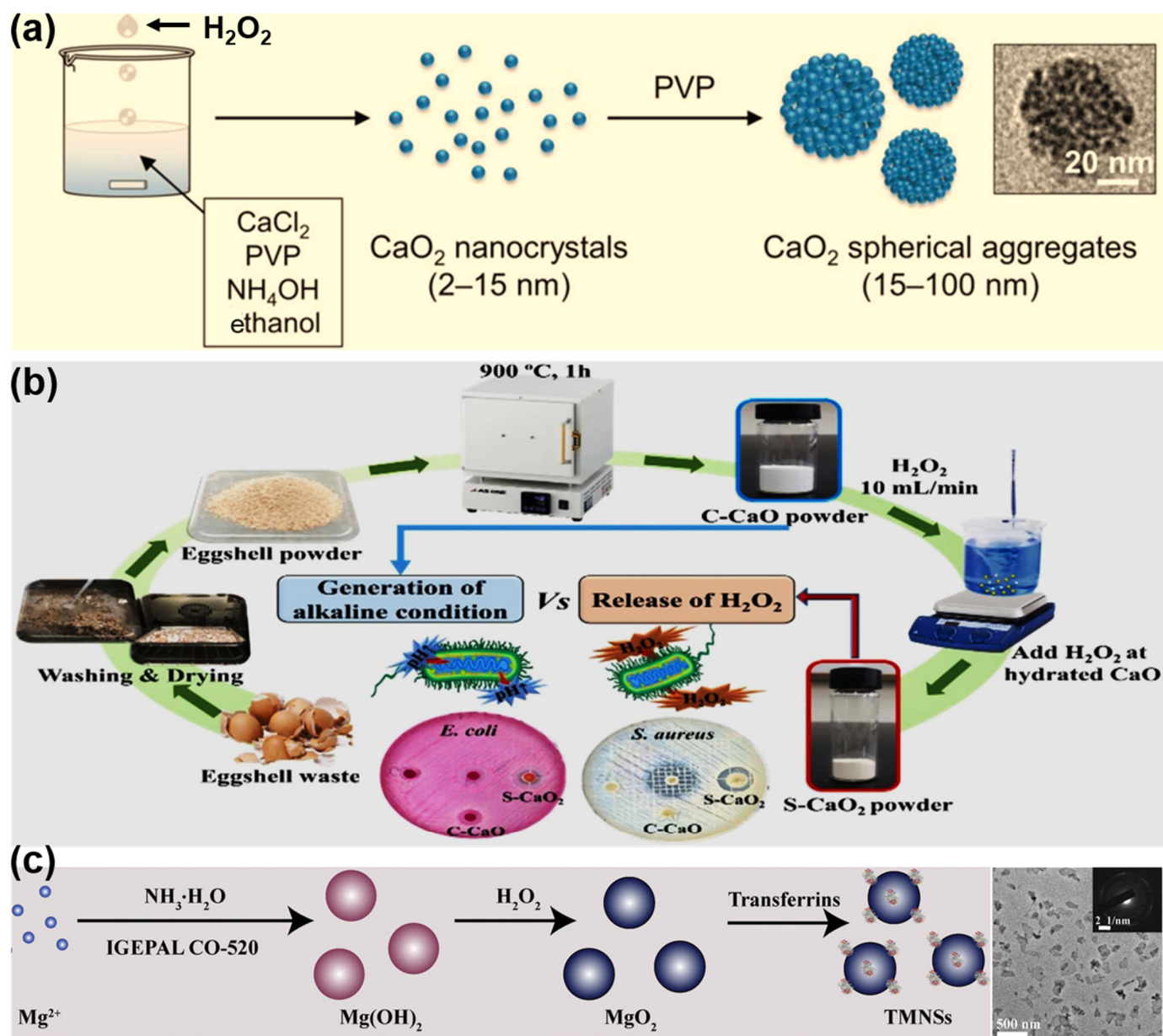


Figure 1. Different methods for the synthesis of MePOs. (a) A schematic illustration of the CaO_2 nanoparticle preparation procedure by the hydrolyzation–precipitation method (adapted with permission from [39], Wiley, 2019). (b) A diagram of the preparation process of CaO_2 nanoparticles using bio-waste eggshells by calcination followed by the hydrolyzation–precipitation method (adapted with permission from [37], Elsevier, 2024). (c) A schematic illustration of the synthesis of MgO_2 nanosheets by the reverse-phase microemulsion method (adapted with permission from [40], Wiley, 2019).

Another promising technique for the preparation of MePO particles is the reversed-phase microemulsion method [35,47]. This method is advantageous for several reasons, including its suitability for the production of small, well-dispersed, and impurity-free particles; its precise control over the nanoparticle size and morphology; and the simplicity of its implementation. The method employs the use of a nanoscale microreactor environment, which is formed by the microemulsion system. As an illustration, Tang et al. [40] synthesized MgO_2 nanosheets through the combination of cyclohexane and CO-520 with a MgCl_2 solution, followed by an ammonium hydroxide injection to facilitate the formation

of $\text{Mg}(\text{OH})_2$. Subsequently, hydrogen peroxide was added to regulate the progression of the reaction, while the addition of ethanol acted to disassemble the microemulsion structure, allowing for the formation of MgO_2 nanosheets (Figure 1c). Furthermore, this method allows for the direct incorporation of chemotherapeutic pharmaceuticals into nanoparticles, thereby enabling the nanoparticle synthesis and drug loading to occur concurrently. For example, He et al. [36] successfully fabricated CaO_2 nanoparticles, simultaneously incorporating the chemotherapeutic drug cisplatin and coating the nanoparticles with a negatively charged phospholipid layer using this method.

Recently, sonochemistry has emerged as a prominent approach for synthesizing nanoparticles, including those of MePOs [48–50]. By employing a high-intensity ultrasound to initiate, enhance, or control chemical reactions, this method has enabled the formation of uniform nanoparticles with unique properties [51]. Pirouzmand et al. [42] employed a sonochemical method to fabricate ZnO_2 nanoparticles. This involved dissolving a zinc salt (ZnSO_4) in an aqueous NaOH solution (pH 8), followed by a H_2O_2 reaction, and finally subjecting the solution to ultrasound sonication. Despite the formation of monodisperse nanoparticles, aggregation was observed. In another study conducted by Alipoor et al. [41], the use of PVP during the ZnO_2 preparation process by the same method resulted in the absence of aggregation. This highlights the crucial role of stabilizers/surfactants during nanoparticle synthesis. Additionally, several novel approaches, including pulsed laser ablation in liquid [52,53], Leidenfrost dynamic chemistry [54], and gas diffusion [30], have also been used to synthesize MO_2 nanoparticles.

3. Application of MePO Particles in Cancer Diagnosis and Therapy

3.1. Chemotherapy

One of the hallmarks of cancer is hypoxia, or low oxygen levels, in the tissue surrounding the tumor [55]. Through the action of several proteins involved or upregulated in hypoxia, the tumor microenvironment (TME) becomes increasingly resistant to chemotherapy, which leads to the efflux of the drugs from the cancer cells they are intended to kill [55,56]. Therefore, increasing the oxygen supply to the TME may inhibit some of these effects and improve chemotherapeutic outcomes [32,57]. In addition, MePOs, such as CPO, might not only increase oxygen but also increase other ROS in the TME that could be proapoptotic in the presence of chemotherapies. For example, Cheng et al. [58] produced magnetic CPO nanoparticles to generate oxygen and enhance the efficacy of the FDA-approved chemotherapeutic agent doxorubicin in the hypoxic microenvironment of triple-negative breast cancer (TNBC). The synthesized nanoparticles reduced the HIF-1 α expression, inhibited autophagy, induced apoptosis, and significantly improved the tumor suppression in TNBC when combined with doxorubicin, both in vitro and in an orthotopic mouse model. Specifically, the HIF-1 α expression decreased 6-fold (i.e., from 2.5 to 0.4) with the introduction of 20 ppm CaO_2 nanoparticles, and the tumor weight decreased by over 90% with the combination treatment (CaO_2 -MNPs + DOX) compared to the treatment with DOX alone.

As mentioned above, chemotherapeutic formulations might benefit from dual MPO and CPO combinations. In such cases, the presence of MPO could improve chemotherapeutic treatments by catalyzing and enhancing the oxygen release from the CPO degradation that initially yields hydrogen peroxide [59,60]. For example, recently, researchers generated MPO on the surface of CPO particles, which significantly enhanced oxygen production [61]. The total dissolved oxygen level in the sample reached 8 mg/L after 3 h, whereas CPO alone generated only 0.5 mg/L of dissolved oxygen within the same time frame. The increased oxygen levels via down-regulating hypoxia-dependent pathways improved the chemotherapeutic agent retention and TME penetration. The water-responsive formulation

provided a controlled doxorubicin release in the lipase-rich TME that degraded the solid lipid monostearin used to coat the CPO/MPO nanocomposite. In addition, in such cases it is possible to perform imaging using MPO as an additional imaging modality. However, CPO could also be used in a catalyst-independent manner. For example, the degradation of CPO in the presence of water leads to the formation of $\text{Ca}(\text{OH})_2$ [62]. This in turn yields an alkaline microenvironment that supports the degradation of H_2O_2 , allowing CPO to directly generate O_2 in a catalyst-free manner [24]. Previous groups have utilized this catalyst-free approach in enhancing hypoxic hepatocellular carcinoma or breast cancer chemotherapy [63].

3.2. Photodynamic Therapy

Photodynamic therapy (PDT) is a minimally invasive treatment modality intended to selectively destroy diseased cells and tissues (usually cancer) by using a combination of a photosensitizer, a light source, and molecular oxygen [64,65]. For example, once the photosensitizer is accumulated in the cancerous tissue, it can be activated using a specific wavelength of light, which in turn can harness that energy and convert the oxygen present in the TME into ROS that destroy the surrounding cancerous cells [65,66]. Although PDT has a low therapy resistance and side effects, the presence of hypoxia in the TME usually presents a challenge for effective PDT treatments, especially in solid tumors [66]. Therefore, to improve oxygenation in the TME, researchers have turned to MePOs as part of the treatment approach. For example, several research groups have turned to CPO and other oxygen-generating peroxides using different coating strategies to tailor the release of oxygen species in the TME to modulate PDT with varying success [24,67]. Some used pH-sensitive polymer coatings, others turned to photosensitive polymer shells, and others, on the other hand, used lipids of liposomes to deliver CPO to the TME in order to improve the PDT efficacy [68,69]. More recently, researchers have used MPO to improve PDT, in which MPO acts as an enzyme that catalyzes the hydrogen peroxide decomposition reaction [70,71]. The TME of solid tumors with increased oxygen can be significant, with markedly improved therapeutic outcomes [70,72]. In addition, MPO can be used as a contrast agent, providing a dual functionality and an opportunity to follow, in real time, the therapeutic effects of PDT [31,73].

However, as in the previous case with chemotherapy, the best outcomes are achieved when combining CPO and MPO into a single platform [29,74,75]. For example, Shi et al. [74] developed a nanosystem comprising a MPO nanosheet coated on CPO nanoparticles. This combination had the unique property of a methylene blue emission suppression that was incorporated on the CPO/MPO platform. In turn, this nanosystem provided switch-controlled (i.e., ON/OFF) fluorescent cell imaging and tumor inhibition capabilities that also provided oxygen for an improved PDT (Figure 2). Specifically, the system exhibited minimal cytotoxicity without laser irradiation. However, when light was irradiated, the tumor cell viability decreased remarkably, dropping to 28% at a concentration of 100 $\mu\text{g}/\text{mL}$ of CPO/MPO nanosheets. In addition to using MPO to control fluorescent imaging, MPO can be directly used in the MRI T1 modality as a contrast agent. Therefore, the combination of MPO and CPO enhances the efficacy of PDT-mediated treatments, while allowing for the detailed imaging of tumors [29]. In addition to CPO and MPO, iridium peroxide (IrOx) has generated significant interest in PDT due to its distinctive optical and chemical properties [76,77]. Ma et al. [76] designed a nanoplatfrom that responds to both acidic conditions and excess glutathione (GSH). This platform is composed of a multi-caged IrOx coated by a metal–polyphenol network (MPN) composed of Fe^{3+} and tannic acid (TA). The research demonstrated that the MPN shell can be degraded under the acidic TME and intracellular excess of GSH. This results in the release of Fe^{3+} and the exposure of

the IrOx core. As a result, the efficient dual-pathway chemodynamic therapy (CDT) is facilitated. The nanoplatform has been shown to effectively mitigate the attenuation of CDT by consuming excess GSH within the tumor. The multi-caged structure of IrOx is advantageous for implementing photothermal therapy (PTT) in coordination with CDT, further enhancing the therapeutic efficacy of tumors. Finally, the team demonstrated the remarkable capabilities of IrOx@MPN in terms of its outstanding computed tomography (CT) and magnetic resonance imaging (MRI) (T1/T2) multimodal imaging. These capabilities are instrumental in facilitating an early diagnosis and timely treatment, which is crucial for effective patient care and management.

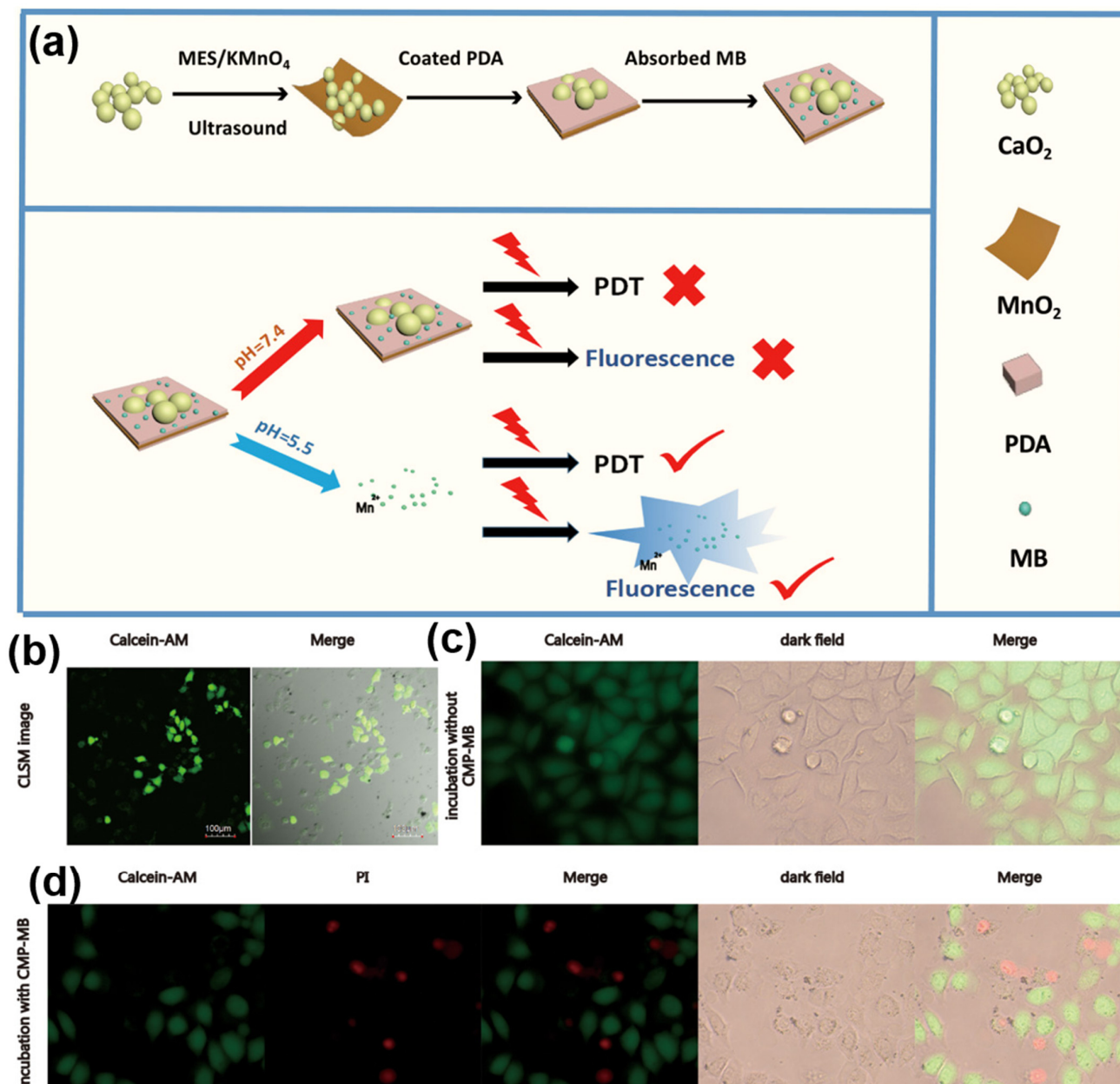


Figure 2. $\text{CaO}_2/\text{MnO}_2@\text{PDA-MB}$ oxygen generation system for photodynamic therapy and tumor cell imaging. (a) Illustration of CPO/MPO nanosheet synthesis and performance for PDT and ON/OFF control tumor cell imaging. (b) LSCM image of HeLa cells incubated with CMP-MB under irradiation; green fluorescence is derived from calcein AM after exposure to irradiation for 5 min. Micrographs of HeLa cells stained with AM (green, live cells) and PI (red, dead cells) and incubated without (c) and with (d) CMP-MB. (Adapted with permission from [74], Wiley, 2018).

3.3. Immunotherapy and Radiation Therapy

A new area of research that has found applications for oxygen-generating particles is immunotherapy [22,78]. The goal of immunotherapy is to improve the body's natural immune response to recognize and attack cancerous cells more effectively, leading to disease regression [79,80]. The hypoxic microenvironment of solid tumors can create a barrier to antitumor immune responses by inducing immunosuppressive conditions that inhibit cytotoxic T lymphocyte activity [22,81]. These effects are primarily driven by hypoxia-inducible factors (HIFs) and A2A adenosine receptors that lead to suppressing the antitumor activity of T cells and natural killer cells via altered cytokine and chemokine secretion [82]. Although the use of hyperoxic breathing has shown success in overcoming the immunosuppression of cancer hypoxia, this approach could significantly benefit from local oxygen generation by micro- and nanoparticles [83].

One example of such an approach is by Colombani et al. [22], where they developed a syringe-injectable oxygen-generating scaffold (i.e., cryogels) by incorporating CPO particles into the polymer walls (Figure 3). To improve the oxygenation of the TME and to mitigate the possible cytotoxicity from hydrogen peroxide, a CPO degradation byproduct, the researchers also conjugated a catalase enzyme into the polymeric scaffolds to improve the CPO conversion. They showed that the incorporated CPO particles were homogeneously distributed within the cryogels, providing a predictable, controlled, and sustained oxygen release under both normoxic and hypoxic conditions with minimal hydrogen peroxide-derived toxicity due to the catalase enzyme presence. This approach was able to reverse the TME hypoxia while simultaneously down-regulating the hypoxia-induced protein expression and increasing proinflammatory cytokines that lead to lower immunosuppression. Ultimately, the researchers demonstrate the preservation of the T cell function and antitumor activity using these oxygen-generating cryogels in what would otherwise be a highly immunosuppressive TME of an advanced-stage murine melanoma model. Nevertheless, the authors emphasized the necessity for more extensive toxicological and long-term safety evaluations before preclinical trials. Furthermore, human immune responses differ significantly from those in murine models, particularly with regard to T cell infiltration levels and the sensitivity to reactive oxygen species. These differences could impact the efficacy of O₂-cryogels when translating these findings into clinical settings with cancer patients.

Similarly, CPO has been used to improve the immune response by inducing enhanced antigen-presenting cell (APC) maturation via ROS generation in draining lymph nodes [84,85]. For example, Su et al. [85] developed a nanovaccine that included CPO particles. These nanovaccines were able to induce ROS generation in endo/lysosomes of APCs found in the draining lymph nodes, at which the nanovaccines were targeted. The stimulation and lipid peroxidation in APCs improved their maturation and enhanced the antigen presentation to T cells, which generated a more robust immune response.

Furthermore, MePOs have demonstrated significant radiosensitization effects, enhancing the efficacy of radiotherapy by generating reactive oxygen species (ROS), alleviating tumor hypoxia, and boosting antitumor immunity [86–88]. Salah et al. [88] demonstrated the anti-cancer effects of titanium peroxide nanoparticles (TiOxNPs) combined with ionizing radiation on radioresistant cancer stem cells (CSCs) in both in vitro and in vivo models. TiOxNPs have shown a synergistic effect with radiation on pancreatic spheres' enriched CSCs by decreasing self-renewal regulatory factors and CSC surface markers. In addition, the combination treatment effectively suppressed the epithelial–mesenchymal transition, migration, and invasion properties in primary and aggressive pancreatic cancer cells. In another study, Nakamaya et al. [87] compared the radiotherapeutic efficacy of TiOxNPs with their polyacrylic acid-modified counterparts (PAA-TiOxNPs). They found that PAA-TiOxNPs generate considerably higher levels of hydroxyl radicals and H₂O₂ upon X-ray irradiation compared to TiO₂ alone. In both in vitro

assays with MIA PaCa-2 pancreatic cancer cells and in vivo xenograft models, PAA-TiOxNPs significantly increased the DNA damage and suppressed the tumor growth when combined with radiation, without an observable systemic toxicity over a 43-day period. These findings indicate that PAA-TiOxNPs are effective radiosensitizers that are safe and enhance the efficacy of radiotherapeutic treatments. They achieve this by increasing the production of ROS over time and improving the response of tumors to treatment.

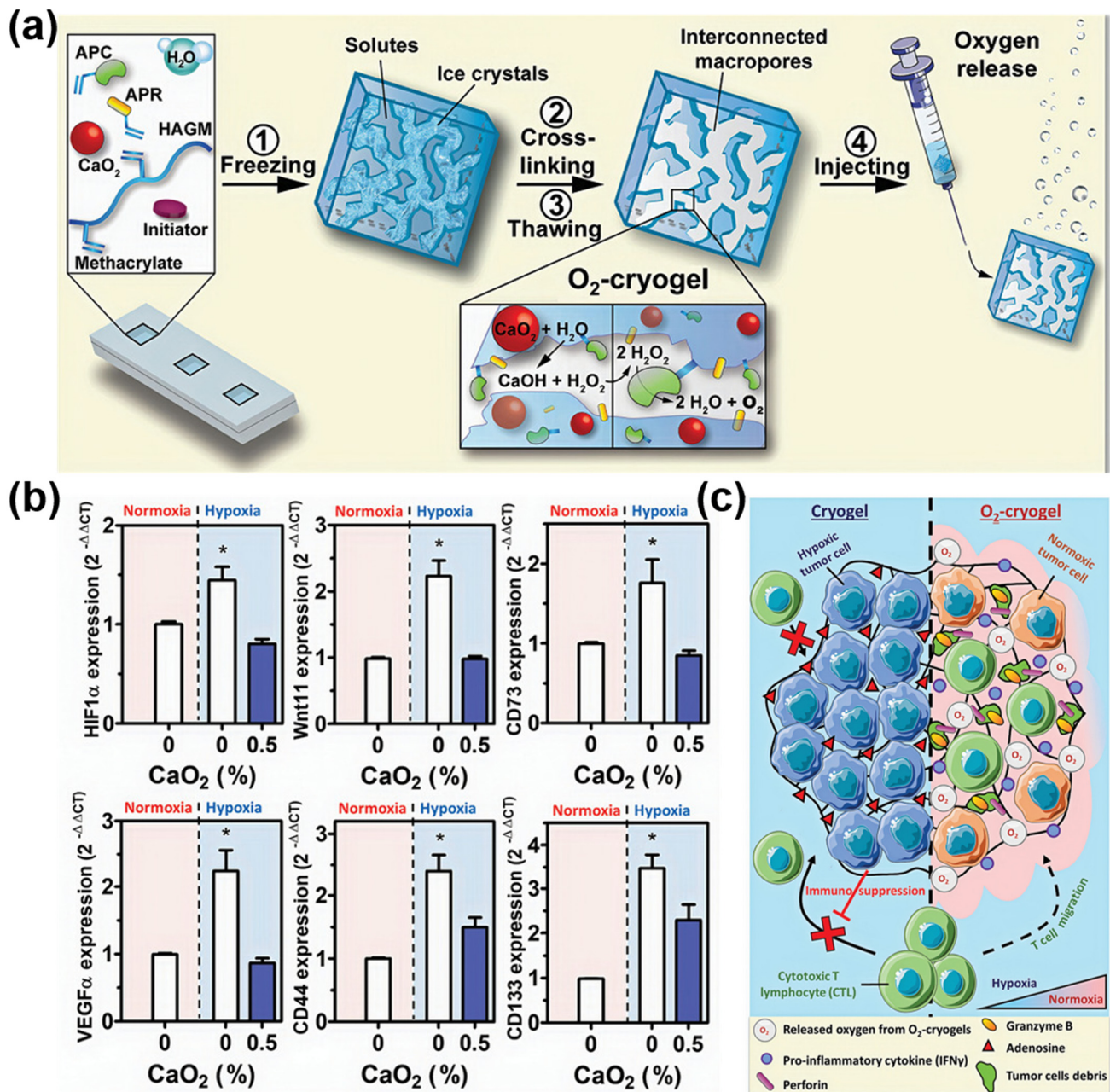


Figure 3. Injectable oxygen-generating scaffold cryogels for immunotherapy. (a) A schematic illustration of the capacity of the cryogels to reverse the immunosuppressive TME and restore the impaired effector T cell function. (b) The expression levels of HIF1α, Wnt11, CD73, VEGFα, CD44, and CD133 in B16-F10 cells after 24 h of incubation in cryogels and O₂-cryogels containing 0.5% CaO₂ under normoxic and hypoxic conditions are presented. * $p < 0.05$. (c) A schematic depicting the mechanism of action of an O₂-cryogel: (i) the induction of local oxygenation in an oxygen-deprived solid tumor, (ii) the reversal of hypoxia-driven immunosuppression, and (iii) the restoration of the tumoricidal function of cytotoxic T cells, which are fatal to tumor cells (adapted with permission from [22], Wiley, 2021).

4. Conclusions and Future Direction

Oxygen-generating particles, and specifically MePOs, present a promising platform for both improving cancer treatment outcomes and also providing the potential for diagnostic imaging. It is clear that MePOs have been applied in several cancer treatment strategies, ranging from chemotherapy and PDT to more recent and developing fields like immunotherapy and radiation therapy. Furthermore, it is clear that MePOs' functions stretch well beyond just oxygen generation and can include other mechanisms through which they derive treatment benefits. However, several challenges still exist.

One of the first challenges that should be addressed, to achieve clinically relevant results and translation, is the engineering of MePO stability. Most of the MePOs are likely to react with water and potentially decompose prematurely, leading to a loss of efficacy [24]. This is especially important for biological processes and responses that require days or weeks to achieve their full potential [24,68]. It might be possible to improve MePO stability and mitigate toxicity by surface modifications or coating by various biomolecules [36,68,89]. For example, multi-anchor phosphonic-PEG, dextran/PEG bilayers, and zwitterionic polymers form protective, hydrophilic shells that stabilize metal peroxide nanoparticles. Biomimetic coatings—such as lipids or cell-membrane-derived vesicles, as well as protein/peptide grafts—enhance biocompatibility, immune evasion, and controlled oxygen release kinetics, thereby reducing toxicity in biomedical environments [90,91]. However, to date, long-term stability while preserving a low toxicity and controlled prolonged oxygen release, which might be particularly beneficial for immunotherapy-based approaches, still remains challenging [22]. Some of the challenges stem from the inorganic nature of MePOs that tend to aggregate and precipitate in aqueous environments. The tendency to agglomerate not only lowers the accessible surface area but also can lead to potential side effects, including toxicity in normal tissues and a proportional decrease in the oxygen release potential. Therefore, biocompatibility in general is another important aspect to take into consideration [92]. As MePOs like CPO decompose, they generate calcium and hydroxyl ions as well as hydrogen peroxide, which in some applications might be beneficial but in other settings might derive unnecessary toxicity for normal tissues. Biomolecular coatings can improve biocompatibility, but close attention needs to be given to the formulation so that the controlled release profile of the oxygen species is preserved [35]. Ultimately, more comprehensive and long-term toxicity studies of MePOs need to be performed, not only in vitro but also in in vivo settings, to ensure the absence of systemic toxicity.

Other challenges that exist are related to the way MePOs are synthesized and developing methods that provide tunable control of the MePO particle synthesis. For example, having the ability to precisely control the size and shape of MePO particles on scales that would support commercial production is still lacking. Having optimized synthetic protocols that provide predictable MePO physicochemical properties would address a major obstacle to the clinical translation of such therapies [35,39]. Finally, biomedical applications of MePO nanoparticles encounter stringent regulatory challenges due to their altered physicochemical properties at the nanoscale. The regulatory standards established by the FDA (Montgomery County, MD, USA) and the EPA (Washington, DC, USA) are applicable to bulk chemicals, rather than to nanoscale forms. This discrepancy results in the following consequences: unclear size thresholds; an inconsistent jurisdiction over nanomaterials; redundant reviews (e.g., under TSCA, FDA, FIFRA); and burdensome, case-by-case data requirements that strain agency resources and slow innovation.

To conclude, MePOs and their properties, including oxygen generation, hold great potential in both the treatment and diagnosis of cancer, which have been applied in several different settings. The promising antitumor effects of MePOs could be further improved

and lead to the clinical translation and development of advanced medicines guided by filling the necessary research gaps and addressing the existing challenges.

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