Progress of Nanomaterials in Photodynamic Therapy Against Tumor

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Photodynamic therapy (PDT) is an advanced therapeutic strategy with light-triggered, minimally invasive, high spatiotemporal selective and low systemic toxicity properties, which has been widely used in the clinical treatment of many solid tumors in recent years. Any strategies that improve the three elements of PDT (light, oxygen, and photosensitizers) can improve the efficacy of PDT. However, traditional PDT is confronted some challenges of poor solubility of photosensitizers and tumor suppressive microenvironment. To overcome the related obstacles of PDT, various strategies have been investigated in terms of improving photosensitizers (PSs) delivery, penetration of excitation light sources, and hypoxic tumor microenvironment. In addition, compared with a single treatment mode, the synergistic treatment of multiple treatment modalities such as photothermal therapy, chemotherapy, and radiation therapy can improve the efficacy of PDT. This review summarizes recent advances in nanomaterials, including metal nanoparticles, liposomes, hydrogels and polymers, to enhance the efficiency of PDT against malignant tumor.

Keywords: photodynamic therapy, tumor microenvironment, nanomaterials, tumor-targeting, photosensitizers

1 INTRODUCTION

PDT mainly relies on PSs to generate \(^{1}\text{O}_2\) from \(\text{O}_2\) under the induction of specific wavelengths of light, causing oxidative damage to tumor cells and killing them, and even triggering immunogenic cell death (ICD). However, the insufficient supply of key factors such as PSs, light, and \(\text{O}_2\) in tumor tissue greatly reduces the therapeutic effect of PDT (Lee et al., 2022). Nanoparticles (NPs) as drug carriers have received extensive attention in the field of tumor therapy. They can achieve high-efficiency delivery of PSs to tumor tissues through physicochemically optimized passive targeting, ligand-modified active targeting, and stimulus-responsive release (Zhao et al., 2021). Attempts have been made to overcome the unfavorable tumor microenvironment through photocatalytic oxygen production, Fenton reaction, and combination with other chemical drugs (Wan et al., 2021). In this review, we first describe the composition and tumor-promoting mechanisms of the tumor microenvironment, and then introduce metal NPs, nanoliposomes, mesoporous silica NPs, dendrimers, hydrogels, polymer micelles and these creative methods to solve the problems faced by tumor PDT. In particular, in this review, we focus on recent advances in diverse metal NPs including metal-organic frameworks (MOF), which provide a promising approach for the design of integrative therapeutics in clinical treatments.
2 TUMOR MICROENVIRONMENT

TME refers to the non-cancerous cells and components presented in the tumor, including blood vessels, extracellular matrix (ECM), fibroblasts, the surrounding immune cells, molecules produced and released by them (Figure 1) (Chang et al., 2021). Hypoxic and acidic microenvironment, caused by tumor vascular tissue distribution disorder and structural abnormality, is the most important supporting component in TME and immunosuppressive microenvironment and has offered a favorable niche for tumor growth, proliferation and invasion (Yuan X. et al., 2022). The immune cells, including granulocytes, lymphocytes, and macrophages, are involved in various immune responses and activities orchestrated by the tumor to promote tumor survival. Among them, the macrophages abundantly infiltrating TME are called tumor-associated macrophages (tumor-associated macrophages, TAMs), which are the most prominent immune cell type in the TME. According to the difference of phenotype and function, activated macrophages can be divided into M1 and M2, and their polarization direction is regulated by microenvironment (Wang et al., 2021a). For example, tissue microenvironment, external factors and inflammatory response factors can activate macrophages in different forms (Cenowicz et al., 2021). The macrophages that promote tumor growth are M2 phenotype and have the function of repairing injury and inhibiting inflammatory response in normal tissues. The macrophages that inhibit tumor growth are M1 phenotype, which can induce inflammatory response and activate immune response to kill tumor cells (Chen J. et al., 2021). In the process of tumorigenesis, TAMs can often stimulate angiogenesis, promote tumor cell migration and invasion, and mediate tumor immune escape (De Lerma et al., 2021). In the site of tumor metastasis, TAMs promote tumor cell exosmosis, survival and follow-up activity. At the same time, TAMs affect the clinical therapeutic effect of tumors by enhancing the genetic instability of tumor cells, nourishing tumor stem cells, and promoting infiltration and metastasis, and they are the key driving force for tumor growth. The degree of macrophage infiltration in tumor tissues is related to the poor prognosis of patients, and the number of TAMs is negatively related to the survival time of patients (Munir et al., 2021). In addition, an increase in neutrophils in blood also accounts for a sign of poor prognosis for cancer. Imitating the naming method used to define macrophages (M1-like and M2-like/TAM), tumor-associated neutrophils (TANs) can obtain at least two different phenotypes: N1 neutrophils, endowed with anti-tumor activities, and N2 neutrophils endowed with immunosuppressive and pro-angiogenic properties to support tumor progression (Li et al., 2020). The tumor-promoting activity of TAN can cover a variety of mechanisms (Taucher et al., 2021). TAN can’t only promote tumor angiogenesis by secreting matrix metalloprotease-9 (MMP-9) and vascular endothelial growth factor (VEGF) from the extracellular matrix (ECM), but also inhibit CD8T cells and produce immunosuppressive environment by secreting arginase 1 (Xiao et al., 2021).

Cancer cells harbor a different metabolic profile with respect to healthy cells (Chou and Yang, 2021). Cancer cells can maintain a high rate of glycolysis even in the presence of O2, consume large amounts of glucose and significant areas in tumors exhibit lactic acidosis. This phenomenon known as “aerobic glycolysis” or the “Warburg effect” (Yuan et al., 2021). The tumor-promoting mechanisms of TME include: 1) HIF-1α nuclear transport pathway: Hypoxia inducible factor-1 (HIF-1) is a key transcriptional activator responsible for regulating target genes that contribute to survival and growth of cells in hypoxia condition (You et al., 2021). It consists of two subunits (HIF-1β and HIF-1α) and HIF-1α is sensitive to hypoxia. Under hypoxic conditions, HIF-1 becomes a stable and transcriptionally active dimer and then induces transcriptional and post-transcriptional regulation of target genes. In addition, overexpression of HIF-1α also promotes the transcription and activation of angiogenic factors, such as angiogenin, platelet- derived growth factors, plasminogen activator inhibitors and VEGF (Sun et al., 2022). 2) STAT3 phosphorylation pathway: Acidic TME inhibits T cell activation and cytotoxicity by inducing STAT3 phosphorylation (Liang et al., 2021). 3) mTOR signaling pathway: The persistent stress of hypoxic TME leads to excessive activation of mTOR signaling in NK cells, mitochondrial fission, and impaired metabolism, ultimately leading to NK cell depletion and reduced anti-tumor ability (Liang et al., 2021). 4) VEGF pathway and nuclear transcription factor (NF-κB) pathway: Enriching cytokines such as VEGF and eosinophil chemokine (Eotaxin) in tumor tissue, inducing macrophage polarization into M2 type. M2 TAMs further produce factors such as CC motif chemokine 2 (CCL2), CC motif chemokine 5 (CCL5) or macrophage colony stimulating factor 1 (CSF-1) to participate in immunosuppression (Huang et al., 2021). 5) Promote the production of factors such as hyaluronic acid (HA) and VEGF, thereby maintaining tumor growth and migration (Niu et al., 2021).
3 PHOTODYNAMIC THERAPY

Taking advantage of the fact that PSs can’t generate ROS in the dark environment, and is not toxic to cells and tissues. By finely controlling the illumination area, the PDT process can be confined within the tumor tissue, achieving highly selective killing of tumor cells and reducing the side effects of normal cell death (Lee et al., 2020). According to the different types and production methods of ROS, PDT can be divided into two mechanisms, type I and type II (Algorri et al., 2021). Type I reactions can directly react with biomolecules to produce radicals by transferring protons or electrons. In Type II reactions, the excited PS transfers energy to oxygen molecules to produce singlet oxygen ($^1$O$_2$). Both oxygen-containing free radicals and $^1$O$_2$ have extremely high reactivity, which can damage a variety of biomolecules and kill tumor cells. Type II PDT requires PSs to generate ROS. However, PSs are often excited by visible light, which limits the efficacy of PDT for deep tumors. Furthermore, due to the short intracellular half-life of ROS ($\approx$10–320 ns), the light penetration depth and the distribution of PSs in tumor tissue limit the efficacy of PDT (Lee et al., 2022). Nanomaterials provide a powerful tool to overcome many drawbacks of PSs in cancer PDT, such as hydrophobicity, short blood circulation time after intravenous injection, which lead to insufficient accumulation, retention and internalization in tumor tissues (Silva et al., 2021). Furthermore, some multifunctional nanomaterials can increase the levels of O$_2$ and ROS in tissues by mediating photocatalytic oxygen production and Fenton reaction. In addition, upconverting NPs can enhance light delivery in tumor tissues by converting more penetrating NIR to visible light or preparing them as persistent luminescent NPs (Liu B. et al., 2021). In addition to enhancing PSs in tumor tissues through physicochemically optimized passive targeting, ligand-modified active targeting, and stimulus-responsive release. Nanomaterials can also be combined with chemotherapy, gene therapy, immunotherapy, photothermal therapy, hyperthermia/ magnetothermal therapy, radiotherapy, sonodynamic therapy to overcome the limitations of PDT (Yang G. et al., 2021; Zhang P. et al., 2022). This study focuses on the commonly used PSs nanomodiﬁcation techniques and the application of different types of novel nanomaterials for cancer treatment and diagnosis, such as nanoparticles, liposomes, hydrogels, polymers, etc.

4 STRATEGIES FOR NANOPARTICLE-BASED PHOTOCONTROLLED DELIVERY

4.1 Metal Nanoparticles

Among the NPs, metal NPs have the advantages of high biocompatibility and stability, adjustable size, good optical properties, easy surface functionalization, and a long activity period (Desai et al., 2021). They can be used as PSs, delivery carriers and up-conversion tools to improve the delivery of chemotherapy, radionuclides and antibody drugs to tumor cells.

4.1.1 Metal Based Nanoparticles

4.1.1.1 Au Based Nanoparticles

Au NPs have surface plasmon resonance (SPR), chemical inertness and excellent biocompatibility, which are mainly used as passivation agents, drug delivery agents, imaging agents, and photothermal agents, which have different characteristic shapes, such as particles, rod-shaped, cluster-shaped, shell-shaped, spike-shaped and star, etc., (Younis et al., 2021). In PDT, gold nanoparticles can be used alone or as part of a multifunctional nanomaterial hybrid system for PSs delivery.

DNA is considered to be one of the best components for building nanomaterials due to its excellent sequence specificity and programmable supramolecular self-assembly. Among them, functional modification of nanomaterials can significantly improve the cellular stability of DNA nanomaterials. Based on this, Yu et al. utilized doxorubicin (Dox), antisense DNA (target Survivin mRNA) that could inhibit Survivin expression, photosensitizer (ZnPc), and Au NPs with excellent plasmonic properties, to develop a multifunctional nanotherapeutic platform with both diagnostic and therapeutic functions, termed Apt-DNA-Au nanomachines, for in situ imaging and targeted PDT/PTT/CDT synergistic therapy of breast cancer (Figure 2) Yu et al. (2021). Moreover, the tightly packed DNA sequences on the surface of nanomaterials were used as highly specific aptamers, which not only resisted the enzymatic hydrolysis of DNA sequences, but also improved the tumor targeting of PDT (Lv et al., 2021). Su et al. took persistent luminescent nanoparticles (PLNPs) as the core, and formed a novel nanoprobe TCPP-gDNA-Au/PLNP for persistent luminescence imaging-guided photodynamic therapy by coupling DNA sequences containing AS1411 aptamers through AuNPs Su et al. (2021). PLNPs could emit long-term fluorescence under near-infrared light irradiation. The AS1411 aptamer could specifically recognize the overexpressed nucleolin in cancer cells and improve the tumor targeting of the photosensitizer TCPP. Furthermore, increasing the types of DNA modified on the surface of NPs can improve the accuracy of PDT tumor identification. Cai et al. designed and synthesized a nano-therapeutic platform for fully automatic diagnosis and treatment of Au/Pd nanomachines with the main marker miRNA-21 and two auxiliary markers miRNA-224 and TK-1 mRNA as the targeted detection unit (Au/Pd ONP-DNA nanomachine) Cai X. et al. (2021). Using ONPs as a carrier, when all specified targets were detected [logic system input was (1, 1, 1), output was (1, 1)], the 808 nm laser could be programmed to automatically irradiate the tumor and perform PDT and PTT. However, the stability of the Au-S bond is poor, and the DNA is non-specifically detached from the surface of AuNPs, resulting in false positive signals and severe side effects. Zhang et al. used a simple and highly stable amide bond (-CO-NH-) instead of the Au-S bond and combined the DNA probe on Au@graphene (AuG) to prepare Label-rcDNA-AuG Zhang J. et al. (2021). Label-rcDNA-AuG could improve the anti-interference ability of nanoprobe against nucleases, GSH and other biological agents. By accurately monitoring the level of intracellular miR-21, Label-rcDNA-AuG could identify positive
cancer cells even in a mixture of cancer cells and normal cells, improving the precision of PDT treatment and reducing damage to normal cells.

Besides DNA modification, surface modification of biotin (Bt) is also an effective way to improve the tumor targeting of NPs (Li J. et al., 2021). The targeting of Bt-modified Au-NPs (BT@Au-NPs) to C6 glioma cells was more than 2 times that of Au-NPs (He F. et al., 2021). Modification of arginine (R)-glycine (G)-aspartic acid (D) (RGD) on the surface of NPs, which could bind to integrin $\alpha_v\beta_3$ integrin with high affinity, could not only improve the anticancer ability of NPs, but also reduced tumor migration rate. The HB-AuNRs@cRGD prepared by Liu et al. had a tumor inhibition rate of up to 77.04% in the ECA109 esophageal cancer model, and significantly reduced the migration and invasion of cancer cells in ECA109 cells Liu D. et al. (2021).

Besides improving the PDT efficiency of Au-NPs in combination with other nanomaterials, oxygen production can also be optimized by changing the physical structure of Au-NPs. By adjusting the ratio of silicon core radius and gold shell thickness, Sajid et al. enhanced the field strength of Au nanoshells with 40/20 core radius/shell thickness by 35 times and increased $^{1}\text{O}_2$ yield by 320% compared to before optimization (Farooq and de Araujo, 2021). Furthermore, the introduction of ionic complexes assembled by heterometallic colloids (Mo$_6$-Au$_2$) can affect the cytotoxicity, cellular internalization and PDT activity of NPs by regulating the order of their supramolecular stacking (Kirakci et al., 2021). For example, through the 1:1 binding of $[\text{Mo}_6\text{I}_8(\text{L'})_6]^{2-}$ ($\text{L'} = 1$, CH$_3$COO-) with $[\text{Au}_2\text{L}_2]^{2+}$ (L was the ligand of cyclic double amines and phosphine), Faizullin et al. synthesized a heterometallic colloids composed of positively and negatively charged metal-organic complexes Faizullin et al. (2021). Among them, the cellular internalization of Mo$_6$-Au$_2$ ($\text{L'} = \text{CH}_3\text{COO}$-) assembled with poly-DL-lysine (PL) exhibited a three-fold enhancement when $\text{L'} = \text{CH}_3\text{COO}$- and could accumulates in the cytoplasm by fast endo-lysosomal escape. In addition, the
photodynamic effect of [Mo6I8 (L′)6]2− clusters was much higher at L′ = CH3COO− than at L′ = I−. In recent years, bimetallic NPs are also improving the therapeutic efficiency of PSs due to the inherent properties of the introduced metal elements and the interaction between two metal atoms (Park et al., 2021). He et al. synthesized Au4Bi4-SR NPs by introducing Bi into captopril-coated Au NPs (Au-SR NPs) by utilizing the X-ray CT signal enhancement effect of Bi He G. et al. (2021). Au4Bi4-SR NPs not only exhibited higher ROS yield than Au-SR NPs, but also enabled CT imaging-guided and light-mediated PDT for synergistic tumor therapy. In addition, Jia et al. further modified Au-Bi bimetallic nanoparticles with IR808 fuel and prepared Au-BiGSH@IR808 to obtain higher NIR photon capture ability, which effectively solved the problem of low absorption rate of Au-Bi nanoparticles in the near-infrared region Jia et al. (2021). Noble metal Pt nanozymes have catalase-like activity (Cao et al., 2021). Truncated octahedral Au (ToH Au) can enhance LSPR by increasing the spatial separation and realizing the simultaneous participation of holes and electrons in the reaction due to the special structure of twin planes and stacking faults (Yoon et al., 2017). Accordingly, Bu and his team designed and synthesized a comprehensive phototherapy nanomodulator (ToH Au@Pt-PEG-C6/HA) based on the enhanced LSPR effect Bu et al. (2021). Pt was deposited on ToH Au to form a spatially separated structure, which enabled the reactive molecules to freely enter the hot holes and electron fluxes, and had strong photothermal and photodynamic properties. The antitumor effect of NPs is also closely related to their size. For example, large NPs (>100 nm), despite their enhanced permeability and penetration (EPR) effect, cannot fully infiltrate into tumor tissue due to dense extracellular matrix and elevated interstitial fluid pressure (Zmerli et al., 2021). In contrast, small NPs (<20 nm) exhibited better tumor penetration but were easily cleared by the blood circulation. Therefore, it is particularly important to design a TME-responsive size-tunable NPs. To this end, Liu et al. designed and prepared Au-MB-PEG NPs by exploiting the efficient polymerization ability of AuNPs and the excellent performance of TME ROS-triggered HOCI-responsive platform Liu H. et al. (2021). Small-sized Au-MB-PEG NPs responded to highly expressed HOCI in the tumor region through a HOCI-sensitive molecule (FDOCI-24). After reaching the tumor tissue, Au-MB-PEG NPs were cleaved by HOCI to release Au NPs that rapidly aggregated into larger aggregates in the tumor through electrostatic interactions, and simultaneously released methylene blue as a photosensitizer for photodynamic therapy (PDT). The aggregated AuNPs red-shifted the light absorption to the NIR region, resulting in enhanced photoacoustic imaging (PAI) and PTT under laser irradiation.

4.1.1.2 Ag Based Nanoparticles
Ag NPs have higher 1O2 yield than Au NPs and Pt NPs due to stronger SPR (Younis et al., 2021). Inspired by the ability of ICD to transform tumors from cold to hot by inducing tumor cells to release tumor antigens and damage-associated molecular patterns (DAMPs) and then enhance T cell proliferation and infiltration (Xu et al., 2022). Jin et al. developed a corn-like Au/Ag nanorod (Au/Ag NR) that could induce ICD in tumor cells under NIR-II (1064 nm) light irradiation (Figure 3) Jin F. et al. (2021). They covered the Ag shell on Au NRs, and by changing the amount of Ag+, the SPR band in the vertical region with higher 1O2 yield was red-shifted to the NIR-II window. In addition, Au/Ag NRs could maintain the immune memory effect for up to 40 days in animal experiments by enhancing the therapeutic effect of immune checkpoint blocking (ICB). Wang and his team further used DNA probe technology to prepare the DNA-functionalized nanoprobe Au-AgNP-Ag-HM loaded with the photosensitizer hematoporphyrin monomethyl ether (HMME) Wang et al. (2021b). Au-AgNP-Ag-HM not only had the ROS production mediated by the LSPR signal change of Au-Ag-HM and photosensitizer HMME, but also had fluorescent probe technology mediated by caspase-3 specific recognition sequence (DEVD), which effectively integrate the functions of pro-apoptosis and detection, and can be used for the treatment and efficacy evaluation of tumor cells.

4.1.1.3 Cu Based Nanoparticles
Cu-based Fenton reagents have superior ROS yields to Fe-based systems (Zhu F. et al., 2021). In addition, Cu-doped layered double hydroxide (Cu-LDH) nanosheets can not only further enhance the yield of ROS, but also take advantage of the small size and positive charge to actively infiltrate cancer cells for deep tumor therapy (Wu et al., 2021). But positively charged NPs have a shorter residence time in the blood circulation than negatively charged NPs (Smith et al., 2019). To this end, Wu and his team used negatively charged liposomes to encapsulate Cu-LDH (Cu-LDH@Lips) and embedded HMME into the bilayer of CuLDH@Lips, forming a dual size/charge switchable reactive oxygen species generator (Cu-LDH/HMME@Lips) (Figure 4) Wu et al. (2021). Liposomes could prolong the residence time in the circulatory system by reducing the clearance of Cu-LDH/HMME@Lips by immune cells, and HMME could disintegrate Cu-LDH/HMME@Lips in response to ultrasound to release positively charged Cu-LDH, which could penetrate deep into tumor cells and then caused oxidative stress damage to tumor cells through Fenton-like reaction. Similarly, Wang et al. prepared ICG/CAC-LDH nanosheets by intercalating indocyanine green (ICG) into a hydrophobic bilayer of Ce-doped Cu-Al layered double hydroxide (CAC-LDH) Wang X. et al. (2021). ICG/CAC-LDH could not only induce the depletion of intracellular GSH, but also decompose to generate Cu2+ and Ce3+ to stimulate the Fenton-like reaction to generate OH.

4.1.1.4 Ruthenium Based Nanoparticles
Ru complexes are commonly used as PDT PSs due to their high water solubility, photostability, and high ROS yield (Smithen et al., 2020). However, it has the disadvantages of dark toxicity, DNA mutation and being excited only by short-wave visible light, which limit its clinical application (Chen M. et al., 2021). To this end, He et al. synthesized a new red light-responsive Ru complex PSs (Ru-I) without two-photon activation, by using large conjugated indolepyridine benzopyrans as ligands He Y. et al. (2021). Positively charged Ru-I could effectively target cancer cell
lysosomes and activate PSs under 660 nm red light to induce apoptosis. In addition, Karges et al. proposed to wrap Ru (II) polypyridine complexes with amphiphilic polymer DSPE-PEG2000-folate to prepare nanoparticles without dark toxicity, which could target cancer cells overexpressing the folate receptor Karges et al. (2021). It exhibited significant phototoxicity under irradiation at 480 or 595 nm and induced tumor cell apoptosis through the caspase3/7 pathway. Furthermore, this complex not only shown the highest 1- and 2-photon absorption to date, but also exhibited properties of inhibiting multidrug-resistant tumors.
in a rat model. In addition to the introduction of folate groups, bio-orthogonal labels such as copper-catalyzed azide-alkyne cycloaddition (CuAAC) are also effective methods to improve tumor cell recognition (Kappenberg et al., 2022). Lin et al. prepared the first bio-orthogonal two-photon PSs based on Ru (II) complexes by bio-orthogonally labeling Ru-alkynyl-2 Li. C.-C. et al. (2021). In addition to generating ROS to exert cytotoxic effects, it could also exert anti-tumor effects by specifically binding to cancer cell membranes and inducing membrane damage.

4.1.1.5 Iridium Based Nanoparticles
In recent years, new photoredox catalyst systems based on Ir compounds have been widely used in catalysis and PDT, and can also be used to prepare new PSs (Raza et al., 2021). Liu and his team prepared two Ir (III) complex dimers that could self-assemble into NPs in aqueous media, named Ir1 and Ir2 Liu J. et al. (2021). Ir1 and Ir2 not only enhance cancer cell uptake through positive charges on the surface, but also exhibit type I and type II PDT activity in the 350–500 nm (UV-Vis spectrum) range, even in hypoxic microenvironments. Ir NPs might be promising alternatives to traditional organic PSs. Ir (III) complexes show great potential in the construction of oxygen-sensitive sensing probes due to their unique oxygen quenching pathway (Yasukagawa et al., 2021). Xiao et al. designed and synthesized a red light-excited Ir (III) complex encapsulated in the hydrophobic pocket of Cyanine7-modified β-cyclodextrin (β-CD) Xiao and Yu (2021). Ir (III) complexes achieved different degrees of oxygen quenching according to the change of oxygen concentration in the environment. β-CD could not only be used to improve the water solubility of Ir (III) complexes, but also be used to carry Cyanine7 to establish a proportional oxygen fluorescent probe. The results of in vitro and in vivo experiments showed that the prepared probe had remarkable oxygen sensitivity and could be used for quantitative determination of the oxygen level in the hypoxic microenvironment of solid tumors. Mitochondria are not only the decisive regulators of cellular metabolic function and apoptosis, but also the organelles with the highest intracellular oxygen concentration (Tabish and Narayan, 2021). Therefore, the preparation of PSs that target the mitochondria of cancer cells will be the key to maximize the therapeutic potential of PDT. Recently, Redrado et al. prepared four novel mitochondria-selective trackable PSs, which are called bifunctional Ir (III) complexes of the type [Ir (CN)2(NN-R)]+, where NC is either phenylpyridine (PPY) or benzoquinoline (BZQ), NN is 2,20-dipyridylamine (Dpa), and R either anthracene (1 and 3) or acridine (2 and 4) (Redrado et al., 2021). Only complex 4 ([Ir (Bzq2) (dpa-acr)]+) clearly shown a dual emission mode. The organic luminescent chromophore (acridine) could display the cellular localization of the complexes under irradiation at 407–450 nm. Ir (III) had more than 110-fold higher photosensitivity values under 521–547 nm irradiation than under dark conditions, and promoted apoptotic cell death and a possible apoptotic pathway by generating ROS. Although two-photon near-infrared photoactivation can partially overcome the lack of absorption or weak absorption of Ir (III) complexes in the red to near-infrared region, the requirements of ultrafast femtosecond laser source and small irradiation area limits its application in solid tumor therapy. To this end, Liu and his team designed and synthesized bifunctional micelles (Micelle-Ir) for synergistic PDT and PTT therapy in vivo (Figure 5) Liu N. et al. (2021). They were prepared by micellization of a neutral Ir (III) complex (BODIPY-Ir) containing a distyryl boron-dipyrrrole methane group (BODIPY-Ir). BODIPY enabled BODIPY-Ir to acquire the ability to absorb in the far-red/near-infrared region, and micellization enabled BODIPY-Ir to acquire the ability to synergize PDT and PTT therapy, not only destroying primary 4T1-Luc tumors, but also preventing lung metastases.

4.1.2 Metal Oxide-Based Nanoparticles
Metal oxide nanomaterials have found promising biomedical applications for fluorescent labeling due to the advantages of high photostability, large extinction coefficient, high emission quantum yield and easy surface modification (Younis et al., 2021). In view of the fact that nano-heterostructures can promote photo-induced electron-hole separation and the generation of ROS, 2D nano-heterostructure-based PSs can provide a major advancement in PDT. Qiu et al. designed and synthesized a bismuthene/bismuth oxide (Bi/BiOx)-based lateral nano-heterostructure synthesized by a regioselective oxidation process Qiu et al. (2021). Upon irradiation at 660 nm, the heterostructure could effectively generates \(^{1}\text{O}_2\) under normal oxygen conditions but produces cytotoxicity OH and H\(_2\) under hypoxic conditions, which synergistically improves the intensity of PDT. In addition, this Bi/biox nano-heterostructure had biocompatibility and biodegradability, with the surface molecular engineering used here, it improved the penetrability of tumor tissue and increased the cellular uptake, and then produced an excellent oxygen-independent tumor ablation effect. Iridium dioxide (IrO\(_2\)) with semiconductor behavior has high catalytic activity for oxygen release reaction (OER) in a wide pH range, and also has excellent photocatalytic efficiency (Arias-Egido et al., 2021). For this, Yuan et al. synthesized IrO\(_2\)-Gox@HA NPs that could target TME by combining glucose oxidase (GOx) and IrO\(_2\) NPs on hyaluronic acid (HA) Yuan Y. et al. (2022). First, Gox converted the high levels of glucose in tumors to \(\text{H}_2\text{O}_2\), and then IrO\(_2\) NPs converted \(\text{H}_2\text{O}_2\) to \(\text{O}_2\), thereby enhancing type II PDT, which could effectively alleviate hypoxia in tumor tissues.

Relevant literature points out that the larger the specific surface area of the sheet-like structure, the higher the zeta potential, and the greater the drug-carrying capacity of nanomaterials (Duo et al., 2021). Dai et al. synthesized a radiosensitizer based on 4-layer O-Ti\(_2\)O\(_3\) nanosheets by using two-dimensional titanium peroxide nanomaterials with mesoporous structure to support DOX Dai Y. et al. (2021). O-Ti\(_2\)O\(_3\) could quickly load the drug within 5 min while other nanomaterials need 24 h and release the drug continuously in an acidic microenvironment. In addition, under the action of high-energy X-rays, titanium dioxide could absorb radiation energy to synthesize ROS and kill tumor cells.
O-Ti$_7$O$_{13}$ could reduce the X-ray dose and irradiation frequency, and reduce damage to normal tissues while ensuring the therapeutic effect. Mn$^{3+}$-rich oxides (MnO$\times$) can be decomposed into catalytically competent Mn$^{3+}$ and Mn$^{2+}$ in TME, accelerating the conversion of endogenous O$_2$ into highly toxic 1O$_2$ and OH. Meanwhile, the released Mn$^{2+}$ can be used as a magnetic resonance imaging agent with higher spatial resolution. Studies have shown that Zinc gallogermanate (ZGGO) persistent luminescent NPs can be loaded with therapeutic drugs to achieve long-term imaging tracking of drugs and significant tumor treatment effects. To improve the poor resolution of ZGGO, Ding et al. used MnO$\times$ to coat chromium-doped ZGGO NPs (Mn-ZGGO) Ding D. et al. (2021). Mn-ZGGO could not only generate 1O$_2$ and OH without light, but also serve as a diagnostic tool for MR, US, and sustained luminescence to guide precise cancer therapy. Similarly, Li and his team used MnO$_2$ and IrO$_2$ to prepare nanozymes (MnO$_2$/IrO$_2$-PVP, MIP NPs) to combine photothermal effect, catalytic effect and magnetic resonance imaging function Li R. et al. (2021). IrO$_2$ enabled the photothermal conversion efficiency of MIP NPs to reach 27.57%. Polyvinylpyrrolidione (PVP) enabled the Ce6 loading efficiency of MIP NPs to be as high as 76.07 $\pm$ 0.52%, and could shed PVP from the surface of MIP NPs in an acidic microenvironment, realizing the local enrichment of MIP NPs at tumor. Besides MnO$_2$, CeO$_2$ also has similar functions to catalase (CAT) and superoxide dismutase (Yang Y.-L. et al., 2021). Zeng et al. prepared a dual-targeted tumor drug delivery system (ICG@PEI–PBA–HA/CeO$_2$) by using ICG, inorganic nanozyme (HA/CeO$_2$) and pH-sensitive cationic polymer carrier phenylborononic acid-modified polyethyleneimine-4-carboxyphenylboronate (PEI-PBA) Zeng et al. (2021). After ICG@PEI–PBA–HA/CeO$_2$ targeted cancer cells with HA, the CeO$_2$ released from the pH cleavage reaction of phenylboronic acid catalyzed H$_2$O$_2$ to generate O$_2$ through the cerium valence cycle of Ce$^{3+}$/Ce$^{4+}$. The regenerable CAT-like nanozyme activity of CeO$_2$ increased the bioavailability of ICG and promoted tumor cell apoptosis by improving the tumor hypoxic microenvironment.

The efficacy of PDT/PTT combination therapy was better than that of PDT or PTT monotherapy. Traditional PDT/PTT synergistic therapy requires two light sources to excite the PSs of PDT and the thermosensitive agent of PTT respectively, which increases the difficulty of nanoparticle preparation. Guo and his team used B-TiO$_2$ with oxygen vacancies and narrow band gaps to prepare a nanothermosensitive system (B-TiO$_2$@SiO$_2$-HA) with full-spectrum response to light stimulation Guo et al. (2021). Under NIR-II laser irradiation, B-TiO$_2$@SiO$_2$-HA...
could not only provide PDT/PTT synergistic therapy for tumors, but also perform high-resolution photoacoustic imaging (PAI) to achieve precise nanothermothermal effects. Similarly, Gao and his team used SnO$_{2-x}$ with oxygen vacancies to prepare a multifunctional nano-thermosensitive material (SnO$_{2-x}$@SiO$_2$-HA) with a target-specific synergistic PDT/PTT with full spectrum response Gao et al. (2021a). In addition to exerting precise PDT/PTT synergistic antitumor therapeutic effect through PAI, SnO$_{2-x}$@SiO$_2$-HA also had antibacterial effect, which effectively promotes the healing of skin wounds. But most metal or carbon NPs are toxic to normal cells or tissues. Sengupta et al. used the biosafety and magnetic properties of magnetite (Fe$_3$O$_4$) nanoparticles to synthesize a new PS E-NP with anti-inflammatory and immunoprotective effects Sengupta et al. (2022). E-NP could not only upregulate the expression of cyclin kinase inhibitory protein p21, but also inhibit cancer cell cycle arrest in sub-G0/G1 phase. It also acted as an anti-inflammatory by reducing macrophage myeloperoxidase (MPO) and nitric oxide (NO) release, thereby minimizing collateral damage to healthy cells.

4.1.3 Upconversion Nanoparticles
UCNPs have nonlinear anti-Stokes properties and can emit high-energy photons under low-energy NIR light excitation through lanthanide ion doping. UCNPs also have the advantages of low toxicity, narrow emission bandwidth, large decay time, resistance to photobleaching, and no autofluorescence background (Liu et al., 2022). The emission wavelength of UCNPs can be controllably adjusted from ultraviolet light to near-infrared light to match PSs with different absorption wavelengths, which provides a new method to solve the problem of PDT light penetration depth (Zhang L. et al., 2021). The photosystem-I/photosystem-II (PS-I/PS-II) PDT system can only be excited by red light to generate O$_2$, so that it can quickly supply its own O$_2$ consumption in $^{1}$O$_2$ production, showing a spatiotemporal synchronous system of O$_2$ self-supply and ROS production. However, the tissue penetration ability of red light is unsatisfactory, so it is unsuitable for the removal of deep tissue tumors (Fakurnejad et al., 2019). Recently, Cheng et al. used the ability of UCNPs can emit red light to activate PS-I and PS-II under NIR light, decorated thylakoid membrane of

![FIGURE 6](image)

**FIGURE 6** | Schematic illustration of the PDT effect of UCTM NPs on hypoxic TME. (A) The fabrication process of UCTM NPs. The corresponding electron transfer of UCTM NPs under NIR laser irradiation and the mechanism for realizing spatiotemporally synchronized O$_2$ self-supply and ROS production. (B) The therapeutic process of oxygen supply and ROS generation by UCTM NPs under NIR laser irradiation. Reproduced with permission from (Cheng Y. et al., 2021).
chloroplasts on UCNPs to form UCTM NPs, and developed a new photosynthesis-based PDT strategy for realizing spatiotemporally synchronous O₂ self-supply and ROS production (Figure 6) Cheng X. et al. (2021). Both in vitro and in vivo assessments prove that UCTM NPs can effectively relieve hypoxia, induce cell apoptosis, and eliminate tumors with NIR light irradiation. A large amount of APT produced during the ICD process can be hydrolyzed by the extracellular enzyme CD73 into ADO (immunosuppressant), which prevents the cytotoxic T-cell immune response (Workenhe et al., 2021). To this end, Jin and his team prepared cancer-cell-biomimetic UCNPs (CM@UCNP-Rb/PTD) by exploiting the properties of anti-CD73 antibody to block the adenosine pathway Jin F. et al. (2021). CM@UCNP-Rb/PTD utilized the cancer cell membrane (CM) to target cancer cells and avoid macrophage uptake. After reaching the tumor tissue, UCNPs converted NIR into visible light to generate ROS, and released DOX to achieve a Chemo-PDT synergistic combination therapy. CD73-blocked CM@UCNP-Rb/PTD enhanced spontaneous antitumor immunity through the combined effect of chemotherapeutic drugs, PDT-triggered ICD and CD73 blockade. In immunotherapy, ligands that block PD-L1 can also directly prevent PD-1/PD-L1 immune blockade (Lee et al., 2021). Liu and his team modified UCNPs with MIPs formed by Pd-L1 peptide phase transfer imprinting, and prepared MC540/MNPs@MIPs/UCNP composite imprinted particles Lin M. et al. (2021). MC540/MNPs@MIPs/UCNP utilized MIPs to target tumor cells, which improved the binding rate to tumor cells and achieved targeted PDT. The nucleus is the control center of cellular biological activities, and targeting PDT to the nucleus can lead to severe DNA damage and inactivation of nuclear enzymes (Teng et al., 2021). Based on this, Chen and his team proposed a PDT strategy of “one treatment, multiple irradiation” Chen X. et al. (2021). They modified hollow mesoporous silica nanoparticles with amine group with acidification effect and loaded RB and UCNPs to synthesize UCNP/ RB@mSiO₂-NH based on the lysosome-nucleus pathway. After UCNP/ RB@mSiO₂-NH entered the lysosome, it entered the nucleus through the nuclear pore by generating ROS and destroying the lysosome under the first 980 nm (3 min) NIR irradiation. Subsequently, efficient nuclear-targeted PDT was achieved under a second 980 nm NIR irradiation. Dual PSs PDT is also one of the effective strategies to improve ROS yield. Pham and his team utilized SiO₂-coated core-shell UCNPs to support two PSs (Rb and Ce6) to form UCNP/RB, Ce6 Pham et al. (2021). UCNP/RB, Ce6 produced a large amount of ¹O₂ under 1550 nm NIR-IIb irradiation, which had higher PDT efficiency than single PS. However, the application of UCNPs in the biomedical field still faces challenges due to the low quantum yield and superheating effect of the 980 nm light source, and the low drug loading capacity (Lee et al., 2020).

4.1.4 Carbon-Based Nanoparticles

However, g-C₃N₄Ns have poor PDT efficacy due to wide band gap and low utilization of visible light (He F. et al., 2021). Graphitic carbon nitride nanosheets (g-C₃N₄Ns) are a recently reported promising carbon-based nanomaterial with the advantages of high biocompatibility, high photoluminescence quantum yield and surface modifiability. However, g-C₃N₄Ns have poor PDT efficacy due to wide band gap and low utilization of visible light (Younis et al., 2021). It has been proposed that the PDT efficiency of g-C₃N₄Ns can be enhanced by doping metal ions or UCNPs. Although Ru (II) polypyridine complexes have high ¹O₂ generation and stability, the hypoxic microenvironment limits their PDT efficacy (Karges et al., 2020). Therefore, Wei’s group synthesized a novel oxygen self-sufficient PS (Ru-g-C₃N₄) by grafting [Ru (Bpy)₂]²⁺ onto g-C₃N₄ nanosheets through Ru-N bonds Wei et al. (2021). The incorporation of [Ru (Bpy)₂]²⁺ enabled Ru-g-C₃N₄ to obtain high loading capacity, narrow bandgap and high stability, thereby greatly improving the PDT efficiency. In addition, Ru-g-C₃N₄ not only had catalase-like activity in hypoxic environment, but also could effectively react with H₂O₂ to generate free radicals, causing oxidative stress damage to tumor cells. Molybdenum carbide (MoxC) has an electronic structure similar to that of noble metals, among which, Mo₂C nanospheres can simultaneously induce PTT and PDT under illumination in the entire near-infrared radiation region due to their metallic properties and interband/ intraband transitions, exhibiting highly efficient redox capacity (Zhang et al., 2019). Based on this, Hou and his team prepared a novel nanocomposite, Mo₂C-N-Carbon-3@PEG, by combining Mo₂C nanospheres with N-carbon. N-carbon could improve the photogenerated charge separation of Mo₂C-N-Carbon-3@PEG, which doubles its photocatalytic performance Hou et al. (2022). However, the doping of metal ions and integration with other nanomaterials increases the risk of biological toxicity and side effects on the one hand, and increases the complexity of the PSs multistep synthetic protocols on the other hand. Based on this, Liu’s group had designed and synthesized a nitrogen-rich graphitic carbon nitride nanomaterial, 3-amino-1,2,4-triazole (3-AT) derived g-C₃N₄Ns Liu X. et al. (2021). The photocatalytic activity of g-C₃N₄Ns was 9.5 times higher than that of g-C₃N₄Ns. Compared with g-C₃N₄, the nitrogen-rich triazole group could achieve low-energy transition by reducing the band gap of g-C₃N₄Ns conjugation, thereby improving the utilization efficiency of visible light.

4.1.5 Sulfur-Based Nanoparticles

Metal sulfides are often used as photothermal agents for photothermal therapy, among which NiS₂, CuS and Co₃S₄ nanoparticles can be used to synthesize semiconductor PSs, which is an effective way to combine PTT/CDT/PDT (Shukla et al., 2021). Co₃S₄ NPs will be degraded in the acidic microenvironment and trigger a Fenton-like reaction to generate hydroxyl radicals (·OH), which exerts the efficacy of CDT. Based on this, Jiang and his group prepared a nanocomposite Co₃S₄-ICG, which could responsive release PSs in an acidic microenvironment and realize the synergistic antitumor effect of CDT/PTT/PDT under NIR by loading indocyanine green (ICG) into hollow Co₃S₄ Jiang Y. et al. (2021). The combination of Fenton-like reaction and PDT enhanced ROS production and antitumor effect. Similarly, Feng and his team designed and prepared a nanocomposite Fe₃S₄@SRF@BSA with bovine serum albumin
Ni$_3$S$_2$. It not only had catalase/peroxidase-like activity to generate 1O$_2$ to relieve hypoxic internal environment, but also had a targeted recognition effect on cancer cells with high CD44 expression, thus further promoting the oxygenation level in the tumor and maintain a tumor inhibition rate of more than 100%.

Although black phosphorus quantum dots (BPQDs) have larger surface area and higher 1O$_2$ quantum yield than BP (up to 0.91 in oxygen-saturated solution), the instability and poor biocompatibility, with cyanobacteria, have been rapidly developed and used in cancer therapy and other diseases related to oxygen tension (Dahiya et al., 2021; Qamar et al., 2021). Qi and his team hybridized cyanobacterial cells with 2D BP nanosheets to form a microbe-based nanoplatfrom, Cyan@BPNSs Qi et al. (2021). In vivo experiments, Cyan@BPNSs could effectively increase the oxygenation level in the tumor and maintain a tumor inhibition rate of more than 100%.

4.1.6 Phosphorus-Based Nanoparticles

Black phosphorus (BP) is a kind of post-graphene two-dimensional (2D) nanomaterials with special structural in-plane anisotropy, which have better optical and electrical properties than carbon-based metal NPSs and sulfur-based metal NPSs (Younis et al., 2021). In recent years, microorganisms with photosynthetic properties and biocompatibility, such as cyanobacteria, have been rapidly developed and used in cancer therapy and other diseases related to oxygen tension (Dahiya et al., 2021; Qamar et al., 2021). Qi and his team hybridized cyanobacterial cells with 2D BP nanosheets to form a microbe-based nanoplatfrom, Cyan@BPNSs Qi et al. (2021). In vivo experiments, Cyan@BPNSs could effectively increase the oxygenation level in the tumor and maintain a tumor inhibition rate of more than 100%.

besides BP, red phosphorus (RP) can also generate reactive oxygen species under visible light irradiation (Zhang P. et al., 2021). Among them, Z-type RP/BP nanosheets prepared by exploiting the high separation efficiency of electron-hole pairs not only have photocatalytic activity, but also ROS can be generated with higher efficiency (Liu et al., 2019). To this end, Kang and his team prepared M-RP/BP@ZnFe$_2$O$_4$ NSs hybrid nanomaterials with higher stability and tumor targeting by loading Z-type RP/BP nanosheets with ZnFe$_2$O$_4$ and tumor cell membranes Kang et al. (2022). Among them, ZnFe$_2$O$_4$ could not only increase the productivity of ROS by catalyzing the Fenton reaction, but also induced apoptosis of MB-231 cells through oxidative stress.

4.1.7 Metal-Organic Frameworks

MOFs are a new class of molecular crystal materials, composed of metal ions or clusters bridged by organic connectors. MOFs can integrate NPs and/or biomolecules into a single framework hierarchically through taking advantage of their synthetic tunability and structural regularity, and can be used as highly active sites for multifunctional therapy (Gao et al., 2021b). Focusing on the key factors of O$_2$ production, Ren et al. designed and assembled a novel two-stage intelligent oxygen generation nanoplatfrom based on metal organic framework core modified by Pt and CaO$_2$ NPs (UIO@Ca-Pt) Ren et al. (2021). It was based on the porphyrin metal-organic framework (UIO), and at the same time loaded by CaO$_2$ NPs with polydopamine (PDA), and then used Pt to further improve biocompatibility and efficiency. In TME, CaO$_2$ could react with water to increase the content of H$_2$O$_2$. These H$_2$O$_2$ were further decomposed into O$_2$ by Pt NPs, thereby promoting the TCPP in the nanometer parent nucleus to convert the surrounding O$_2$ into 1O$_2$ under laser irradiation. On the other hand, as the most toxic ROS, OH has stronger oxidizing property and better therapeutic properties than 1O$_2$ (Manivasagan et al., 2022). Recently, the strategy to induce in situ generation of OH has been proposed by introducing Fenton-based agents into tumor cells to induce over-expressed H$_2$O$_2$ in tumor cells. Chen et al.’s research focused on designing nanocarriers for the transport of Fenton catalysts or metal ions such as iron ions. They synthesized MIL-101(Fe)/TCPP using nanoscale iron-based metal-organic framework MIL-101(Fe) loaded with 5,10,15,20-tetrakis (4-carboxyphenyl) porphyrin (TCPP) PS Chen et al. (2021d). MIL-101(Fe) catalyzed the conversion of H$_2$O$_2$ to OH through Fenton reaction under acidic TME, and served as a nanocarrier to deliver TCPP PS to generate photocatalized 1O$_2$ for tumor-specific therapy without serious side effects, showing antitumor great potential for applications.

Iron-based MOFs have the advantages of high drug loading capacity, adjustable degradability and flexible structure. Porphyrin-based MOFs can be used as PSs for high-efficiency PDT with high stability (Ren et al., 2021). Hypoxic TME and endogenous antioxidant defense (AOD) (such as high expression of glutathione and GSH) can weaken the therapeutic effect of PDT. Therefore, breaking cellular redox balance through ROS enrichment and AOD inactivation may lead to effective tumor suppression with high clinical significance (Zhao et al., 2020).
combining iron with porphyrin-based MOFs, the maximum anti-tumor efficacy can be exerted by intelligently responding to exogenous and endogenous stimuli. Inspired by all this, Yu et al. first prepared a metal organic framework nanosystem (NMOF) based on coordination between Fe (III) and TCPP by a one-pot method (Fe-TCPP NMOF). Then, after capping the surface of silk fibroin (SF) to form NMOF@SF NPs, this nanoplatform can load a hypoxia-activated precursor tirapazamine (TPZ) to form NMOF@SF/TPZ (NST) Yu et al. (2022). Utilizing Fe (III) in Fe-TCPP, NST could effectively react with tumors to generate glutathione disulfide (GSSG) and Fe (II), for the ineffectiveness of AOD system. On the other hand, Fenton-like activity of Fe (II) and TCPP-mediated PDT promoted the accumulation of OH and ROS, and aggravated the intracellular oxidative stress under light laser irradiation. The redox metabolism disorder caused by the ineffective AOD and the enrichment of ROS might cause irreversible tumor cell damage. In addition, the deoxygenation of PDT led to an increase in hypoxia and then activated TPZ to transform into cytotoxic hypoxic-sensitive drug. Under ultraviolet light, although Zr-MOF@PPa/AF@PEG produced O2 under light stimulation with PPa, thereby improving the hypoxic challenge and improve anti-tumor effect Wang Y. et al. (2021). Nano-carrier system Zr-MOF@PPa/AF@PEG based on the consideration that PDT oxygen consumption could activate chemotherapy (CT) drugs to solve the hypoxic challenge and improve anti-tumor effect. Similarly, Wang et al. also prepared nano-carrier system Zr-MOF@PPa/AF@PEG by adjusting the percentage of PPa, leading to the 1O2 yield (40%) was lower than that of PPa (60%), it solved the problem of self-agglomeration caused by hydrophobicity of PPa, thereby improving the PDT effect. In addition, Zr-MOF@PPa/AF@PEG produced O2 under light stimulation with temporal-spatial selectivity. Therefore, Zr-MOF@PPa/AF@PEG took advantage of the PDT-induced hypoxia to activate HIF-1 inhibitor AF to enhance the anti-tumor effect and achieve the synergistic PDT-chemotherapy (PDT-CT) therapeutic effects. In addition, tuning the PDT efficiency by adjusting the thickness of the MOF shell is also a good approach. The Au@MOF core-shell hybrids prepared by Cai et al. could tune the thickness of the MOF shell by controlling the interlayer coordination reaction Cai Z. et al. (2021). As the MOF shell thickness increased, the percentage of TCPP and the efficiency of PDT also increased. The use of solar energy to drive the photocatalytic reaction has always been considered an ideal way to obtain O2 (Liu et al., 2021). Compared with the previous oxygen-generating substances, water-splitting materials have the unique advantage of the O2 self-supply and generation of ROS, because there is abundant water in the organism. At present, ultraviolet (UV) light, visible light (Nguyen et al., 2021) and a limited region of the first near-infrared (NIR-I) (650–950 nm) light (Huang L. et al., 2020) can activate water-splitting materials to achieve light-driven endogenous water oxidation (photocatalytic water-splitting reaction) to obtain O2 and ROS, but water splitting materials with NIR-II light triggered molecular O2 generators have not been reported for tumor therapeutics, even though NIR-II can provide deeper tissue penetration. For this, Liu et al. synthesized a new type of plasmonic Ag-AgCl@Au core-shell nanomushrooms (NMs) by selectively photodepositing plasmonic Au at the bulge sites of the Ag-AgCl nanocubes (NCS) (Figure 7) Liu B. et al. (2021). Under NIR-II light irradiation, the plasma effect of the Au nanostructure could overcome hypoxia to oxidize endogenous H2O to produce O2, thereby alleviating the hypoxic microenvironment. Almost at the same time, O2 could react with the electrons on the AgCl nuclear conduction band to generate superoxide anion radicals (O2−) for photodynamic therapy. In addition, the combination index value of PDT for Ag-AgCl@Au NMs was 0.92, indicating that Ag-AgCl@Au NMs with excellent PDT properties toward further and promoting the PDT effect in deep O2-deprived tumor tissues. It is also a research hotspot in recent years to use the functionalization of NMOFs with stimuli-responsive gating units to develop signal-controlled drug delivery systems for biomedical applications. One important subcategory of gated drug-loaded NMOF includes stimulus-responsive nucleic acid locked drug-loaded NMOF, gaining from the remarkable versatility of nucleic acid sequences to generate recognition elements and structural elements (Zhao et al., 2020). For this, Zhang et al. designed and synthesized the UIO-66 metal-organic framework nanoparticles (NMOF) modified with aptamer-functionalized DNA tetrahedra functionalized by ATP-aptamer or VEGF-aptamer could be loaded with the DOX, which responded to ATP or VEGF to release the drug Zhang S. et al. (2021). They utilized VEGF-responsive tetrahedral-gated NMOFs to load the photosensitizer Zn (II) protoporphyrin IX (Zn (II)-PPIX) to synthesize Zn (II)-PPIX/G-quadruplex VEGF aptamer-tetrahedral nanostructures. VEGF triggered the release of Zn (II)-PPIX from the complex. Association of the released Zn (II)-PPIX with the G-quadruplex structure yielded a highly fluorescent supramolecular Zn (II)-PPIX/G-quadruplex VEGF aptamer-tetrahedral structure, enabling efficient PDT treatment of malignant cells.

4.2 Nanoliposomes
Nanoliposomes are single-lamellar or multilamellar nano-systems formed spontaneously when phospholipids are dispersed in aqueous medium. Except biocompatibility and biodegradability, liposomes have high structural flexibility, which can combine a variety of hydrophilic and hydrophobic drugs to improve their solubility and pharmacokinetics (Cheng X. et al., 2021). In addition, liposome nanotechnology can also co-package a variety of PSs and/or drugs, provide sufficient binding sites for conjugation with a variety of functional ligands. Several mechanisms have demonstrated that high concentrations of soluble NKG2DLs derived from tumor cells may inhibit tumor immunity and NK cell-mediated target cell lysis by downregulating the expression of NKG2DL, thereby contributing to tumor immune escape (Curio et al., 2021). Based on this, Wang’s group had designed and synthesized a Chlorin-based photoactivable Galectin-3-inhibitor...
FIGURE 7 | Synthesis of Ag–AgCl@Au NMs and schematic diagram of PDT/PTT synergistic therapy under NIR-II irradiation. (A) Schematic diagram of the synthesis of Ag–AgCl@Au NMs. Schematic diagram and electron energy level diagram of O$_2$ reacting with electrons in AgCl nuclear conduction band to generate superoxide anion radical (O$_2^-$). (B) Schematic diagram of PDT/PTT synergistic therapy under in vivo NIR-II light irradiation of Ag–AgCl@Au NMs. Under NIR-II light irradiation, the plasmonic effect of Au nanostructures generates O$_2$ through photocatalysis and enhances the yield of O$_2^-$.

FIGURE 8 | Structure of prostacyclin and its sensitizing effect in tumor cells. After PGIL is taken up by cancer cells, 1O$_2$ generated by Ce6 triggered by NIR causes the liposomes in the outer layer to rupture, releasing Ce6 and LCP. Ce6 mediates PDT, while LCP enhances PDT-induced apoptosis, inhibits cell metastasis, and activates NK cell-mediated immune clearance by inhibiting galectin-3. Abbreviations: Gal-3, galectin-3 protein. Reproduced with permission from (Wang et al., 2019).
nanoliposome (PGIL), which could combine photosensitizer chlorin e6 (Ce6) and low molecular citrus pectin (LCP) (Figure 8) Wang et al. (2019). The intracellular release of LCP inhibits the activity of galecin-3, which increases the affinity of major histocompatibility complex (MHC) proteins on tumor cell membrane for NKG2D on NK cell membranand, and then increases the tumor cell apoptosis, inhibits the invade ability, and enhances the recognition ability of NK cells to tumor cells in melanoma cells after PDT. In addition, pharmacological inhibition of MMPs reduce the level of released NKG2DLs, which could increase the tumor cell surface expression of NKG2DLs, reverse their immunosurveillance escape properties, and make them easier to be cleared by immune cells (mainly NK cells) (Tampa et al., 2021). Based on this, Liu’s group had designed and synthesized a PS-MMP inhibitor nanoliposome (i.e., Ce6-SB3CT@Liposome [Lip-SC]), which combines the PS, Ce6, and a matrix metalloproteinase (MMP) inhibitor (i.e., SB3CT) Liu H. et al. (2021). Nanoliposomes have significant anti-tumor proliferation and metastasis efficacy after laser irradiation in A375 cells. The relatively fast internalization of Lip-SC could accumulate in the tumor area under 660 nm light irradiation, induce apoptosis in cancer cells, which could trigger an immune response. In addition, it could also induce the expression of NK group 2 member D ligand (NKG2D), while activate NKG2D, thus, NK cells could better recognize and kill tumor cells. The subsequent release of SB-3CT could further activate NK cell effectively and strengthen the immune system though inhibiting the shedding of soluble NKG2D ligands. As a result, Lip-SC caused induce apoptosis in cancer cells regardless of the presence or absence of irradiation. In the process of PDT agents inducing tumor cell necrosis and apoptosis, local inflammation occur and a variety of tumor cell antigens are exposed, thereby inducing local immune responses. Therefore, by supplementing immunomodulators to enhance immune activity, the anti-tumor effect of PDT can be increased. Dual-ligand-modified NPs increased the number of total liposomes bound to cancer cells through dual-ligand modification, and had higher tumor enrichment capacity and PDT efficiency than single-ligand-modified NPs. For example, Li and his team prepared Fru-Bio-Lip by co-modifying liposomes with fructose (targeting fructose transporter) and biotin (targeting multivitamin transporter) ligands Li J. et al. (2021). Besides targeted aptamer modification, the combination with near-infrared light-activated photon thermodynamic therapy (PTDT), PTT and other phototherapy methods is also an effective strategy to improve the tumor killing effect of PDT. Dai et al. synthesized thiadiazoloquinoline semiconductor polymer (PTT), 2, 2’-azobis [2-(2-imidazolin-2-yl) propane] dihydrochloride (AIPH) (PTDT prodrug) and γ-aminoacetic acid (GA, heat shock protein inhibitor) were incorporated into thermosensitive liposomes, which were then modified with targeting aptamers to form Lip(PTQ/GA/AIPH) Dai Z. et al. (2021). Under NIR-II laser irradiation, Lip (PTQ/GA/ AIPH) could achieve precise diagnosis and effective suppression of deep triple-negative breast cancer. However, the clinical application of nanoliposomes in PDT still faces challenges due to poor stability in vivo and low drug loading (Cheng Y. et al., 2021).

4.3 Mesoporous Silica Nanoparticles

Among various nanomaterials, mesoporous silica nanoparticles (MSNs) have become an important nano-delivery system for PDT and multiple combination therapy due to their unique physical and chemical advantages, such as high loading capacity, controllable pore size and morphology, versatile surface chemistry, satisfying biocompatibility and biodegradability, which can ensure stable and efficient loading of PSs, targeted delivery of PSs, and regulation of drug release and cellular uptake behavior (Wang Z. et al., 2021). Hypoxia is a typical feature of tumor TME, which seriously affects the efficacy of PDT. The development of nano-enzymes with the ability to produce oxygen is a promising strategy to overcome the oxygen-dependent of PDT. In this regard, Chen’s group had designed and synthesized a dual-nanozymes based cascade reactor HMSN@Au@MnO2-Fluorescein Derivative (HAMF), which was composed of hollow mesoporous silica nanoparticles (HMSN), high-efficiency photosensitizer 4-DCF-MPYM (4-FM), ultrasmall Au-NPs and MnO2 Chen et al. (2021e), 4-Fm was a thermally activated delayed fluorescence (TADF) fluorescein derivative with high fluorescence quantum yield, photostability, two-photon excitation and low biological toxicity. Au NPs exhibited glucose oxidase (GOx)-mimic ability that could catalyze glucose into gluconic acid and H2O2 simultaneously, the consumption of glucose could cut off the energy supply of tumor cells (Zhang Y. et al., 2021). With the response to the hypoxic microenvironment, MnO2 could catalyze H2O2 into O2 and accelerate the oxidation of glucose by Au NPs to generate additional H2O2, which was used as a substrate for the catalytic reaction of MnO2, which can be used in light irradiation, thereby constantly producing O2 for enhanced PDT upon light irradiation. HAMF could alleviate tumor hypoxia and achieve an effective tumor inhibition in vitro and in vivo studies. Yin’s team had also designed and synthesized a kind of H2O2-responsive and oxygen-producing nanozyme by loading a large number of gold nanoclusters (AuNCs) into MSNs to form nanoassembly, and wrapped MnO2 nanosheets in the form of a switch shielding shell (denoted as AuNCs@mSiO2@MnO2) Yin et al. (2021). In a neutral physiological environment, stable MnO2 shells could switch off PDT by eliminating the generation of O2. However, in an acidic TME, the MnO2 shell reacted with H2O2, and simultaneously sufficient O2 generation guaranteed a 74% high O2 yield, which showing strong PDT performance. In addition, multifunctional NPs loading with chemotherapeutic drugs and PSs are also a promising method for effective tumor combination therapy. Zhang’s group had designed and synthesized a novel pH-sensitive and bubble-generating mesoporous silica-based drug delivery system (denoted as M (A) D@PI-PEG-RGD) (Figure 9) Zhang Z. et al. (2021). DOX and NH4HCO3 were loaded into MSNs pores, MSNs was coated with polyethylene glycol (PEG) and RGD. RGD is a ligand for the recognition site of integrins and displays great adhesion capacity between extracellular matrix cells and cells, which can improve the
accuracy of M (A)D@PI-PEG-RGD. Under NIR irradiation, M (A)D@PI-PEG-RGD could generate ROS and induce the temperature rise performed by ICG. In addition, acidic environment and high temperature would also decompose NH₄HCO₃, thereby accelerating the release of DOX. In summary, the multifunctional pH-sensitive and bubble-producing M (A)D@PI-PEG-RGD combines chemotherapy, PTT and PDT to improve the therapeutic effect of tumors.

4.4 Dendrimers

Dendrimers are synthetic high molecular polymers with tree-like and highly branched structure. They are composed of the small initial core, the internal cavity formed by multiple branches, and the peripheral functional groups. Due to their special structure, dendrimers have the advantages of easy surface modification with PSs along with other functional moieties and structural configuration with other components or nanoformulations via the hyperbranched units for enhanced tumor accumulation and penetration (Ouyang et al., 2021). The combination of molecular targeted therapy of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) and photodynamic therapy PDT can combat non-small cell lung cancer (NSCLC) with effective synergistic results (Qiao et al., 2021). However, the hypoxic TME not only affects the efficacy of PDT, but also induces EGFR-TKIs resistance. In this regard, Zhu and researchers had designed a nanocomplex APFHG by loading gefitinib (Gef) and PS hematoporphyrin (Hp) into an aptamer modified fluorinated dendrimer (APF) Zhu L. et al. (2021). Due to the targeting effect of EGFR-TKIs and the good oxygen-carrying capacity of APF, APFHG could specifically recognize EGFR-positive NSCLC cells and release Gef and Hp in response to the hypoxic acidic microenvironment. Under laser irradiation, APFHG could significantly increase the production of intracellular ROS, effectively improve the tumor hypoxia microenvironment, and overcome hypoxia-related drug resistance. In other work, X-ray-induced photodynamic therapy (XPDT) is overwhelmingly superior in treating deep-seat cancers (Chuang et al., 2020). However, low energy transfer efficiency of the therapeutic nanoplatofrom and hypoxic environment presented in the tumor tissue limits the therapeutic effect of XPDT. In order to improve the therapeutic effect of XPDT in deep-seat cancers, it is necessary to develop a delicate architecture to support the organization of nanoscintillator and multiple agents to improve the effectiveness of XPDT (Ahmad et al., 2019). In this regard, Zhao and researchers developed a dual-core-satellite architecture nanosmart system (CCT-DPRS) that the polyamidoamine (PAMAM) dendrimer would be used as an intermediate framework with nanoscintillator, PSs, and sunitinib (SU) (Figure 10) Jiang Z. et al., 2021). It had high XPDT and antiangiogenic capabilities by systematic optimizing the scintillation efficiency and nanoplatofrom structure. After exposure to ultralow dose radiation, the codoped CaF₂NPs converted the trapped energy into green emission, which enable further excitation of Rb to produce 1O₂ to kill malignant tumor cells. At the same time, the antiangiogenic drug SU effectively blocked tumor vascularization aggravated by XPDT-mediated hypoxia, rendering a pronounced synergy effect. However, PAMAM dendrimer and indocyanine green (ICG) have inevitable interaction with proteins and cells, which induces biological toxicity and reduces therapeutic

![DIAGRAM](image-url)
efficacy in vivo (Mindt et al., 2018). To overcome these shortcomings, Cui and researchers had designed a new drug delivery system G5MEK7C (n)-ICG with a “stealth” layer Cui et al. (2021). The surface of G5MEK7C (n)-ICG was modified with p(EK) peptide, which was double-layer super hydrophilic zwitterionic material. When the pH was lower than 6.5, the surface of G5MEK7C (n)-ICG showed a positive charge, which made it more likely to interact with the cell membrane in the tumor tissue. Therefore, under laser irradiation in vitro and in vivo, due to the good targeting effect of G5MEK7C(70)-ICG, G5MEK7C(70)-ICG was more effective in killing tumors than free ICG, while the damage to the liver was less than free ICG. The combination of chemotherapy and other therapeutic modalities can overcome chemoresistance through different mechanisms of action to achieve the purpose of enhancing anti-tumor efficacy. Furthermore, adding chemicals during mitosis to block cell division may be a promising approach to promote nuclear uptake of PSs. Recently, based on dendrimers and phenylboronic acid-sialic acid interactions, Zhong and researchers modified phenylboronic acid (PBA) into the surface of dendrimers, which can selectively recognize the sialic acids, meanwhile, conjugated lipoic acid modified Ps onto the core of dendrimer Zhong D. et al. (2021). In this work, a novel tumor targeting and penetrating, GSH/ROS heterogeneity responsive and PTX-loaded dendrimeric nanoparticles (P-NPs) was developed for mutually synergetic chemo-photodynamic therapy of PTX-resistant tumors. Lentinan was coated on the periphery of dendrimers through boronate bonds, which could avoid non-specific binding of P-NPs with normal cells during blood circulation. P-NPs penetrated into tumor tissues and actively entered into the cells through the PBA-SA interactions, showing enhanced cellular uptake and tumor penetration. Subsequently, P-NPs released PTX in response to high concentrations of glutathione and H2O2 in tumor cells, arresting the cells in the G2/M phase and exerting anti-tumor effects. At the same time, the time of nuclear membrane disintegration increased caused the enhanced intranuclear photosensitizer accumulation, thereby increasing the efficiency of PDT by increasing nuclear DNA damage.

4.5 Hydrogels

Hydrogel is a type of nano-delivery carrier system formed by a hydrophilic polymer material with a three-dimensional network structure through chemical cross-linking or physical cross-linking. Hydrogels are biocompatible and have similar physical
properties like living tissues. Some drugs are easily dispersed in the hydrogel matrix (Hu et al., 2022). Therefore, hydrogels have been widely used for the delivery of hydrophilic drugs. Among them, local injection of hydrogels has received special attention in tumor treatment and prevention of tumor recurrence, because this injection method can achieve desired drug accumulation in
TABLE 1 | Summary of the advantages and disadvantages of Metal NPs.

| Metal NPs              | Advantages                                                                 | Disadvantages                                                                 |
|------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Au based NPs           | • Utilization for PTT, PAI                                                  | • Limited stability under aqueous conditions                                  |
|                        | • Controllable size and structure and easy surface modification             |                                                                               |
|                        | • Optical quenching ability                                                 |                                                                               |
|                        | • Chemical inertness and excellent biocompatibility                         |                                                                               |
| Ag based NPs           | • Tuning optoelectronic properties according to size and shape              | • Ag NPs with diameters less than 200 nm are prone to aggregation              |
|                        | • High ¹O₂ yield                                                            |                                                                               |
| Cu based NPs           | • High photothermal conversion efficiency                                   | • Potential toxicity                                                          |
|                        | • Low price                                                                 |                                                                               |
|                        | • Simple synthesis                                                          |                                                                               |
|                        | • Controllable morphology and size                                          |                                                                               |
|                        | • Microwaves-induced PDT                                                    |                                                                               |
| Ru based NPs           | • Low-lying excitation energy states and high ROS yield                     | • Dark toxicity                                                               |
|                        | • Good photophysical and photochemical properties                           | • DNA mutation                                                                |
|                        | • Controllable photophysical properties                                     | • Being excited only by short-wave visible light                              |
|                        | • Low photobleaching rates                                                  |                                                                               |
|                        | • High water solubility                                                     |                                                                               |
| Ir based NPs           | • Unique oxygen quenching pathway                                           | • Most Ir complexes are water-insoluble                                       |
|                        | • Excellent electrocatalytic performance                                    |                                                                               |
|                        | • Long triplet state lifetime and good photophysical properties             |                                                                               |
|                        | • Significant tumor targeting ability                                        |                                                                               |
| Metal oxide-based NPs  | • Utilization for PDT, PTT                                                  | • Limited stability under aqueous conditions                                  |
|                        | • Clinical used MRI contrast agent                                          | • Toxicity accumulation of NPs                                               |
|                        | • Magnetic hyperthermia and PAI                                             | • Physical damage from magnetic guidance                                      |
|                        | • Easy surface modification                                                 |                                                                               |
|                        | • High photostability                                                       |                                                                               |
|                        | • Large extinction coefficient                                               |                                                                               |
|                        | • High emission quantum yield                                               |                                                                               |
| UCNPs                  | • Utilization for PTT, PTT, bioimaging, diagnosis, and therapy              | • Limited biodegradability                                                    |
|                        | • Narrow emission bandwidth, large decay time, resistance to photobleaching, and no autoluminescence background | • Low drug loading capacity                                                   |
|                        | • Unique optical property and utilization for luminescence imaging           | • Low quantum yield and superheating effects under 980 nm light source       |
|                        | • Ability to absorb light in the NIR region                                 | • Induce inflammatory reactions and cytotoxicity                              |
| Carbon-Based NPs       | • Strong optical absorbance and utilization for PTT, PAI                    | • Limited biodegradability                                                    |
|                        | • Unique electrical property                                                | • Low utilization of visible light                                           |
|                        | • Easy surface modification                                                 | • Expensive and complex synthetic method                                       |
|                        | • High surface-to-volume ratio                                              |                                                                               |
|                        | • Thermal stability                                                         |                                                                               |
|                        | • High photoluminescence quantum yield                                      |                                                                               |
| Sulfur-based NPs       | • Utilization for PTT, CDT, PDT                                             | • The degradation products have potential toxicity                            |
|                        | • Good biocompatibility                                                     | • Killing efficiency on hypoxic tumor cells is limited                        |
|                        | • High photothermal conversion efficiency                                   |                                                                               |
|                        | • Cheap and simple manufacturing method                                      |                                                                               |
|                        | • Biodegradability and rapid metabolism                                     |                                                                               |
| Phosphorus-based NPs   | • Optical and electrical properties better than carbon-based metal NPs and sulfur-based metal NPs | • Weak absorption in the biowindow and low photo catalytic activity in a TEM |
|                        | • For making photosensitizers                                               | • The inherent instability of BP NSs and BP QDs in water-air environments     |
| MOFs                   | • Facile diffusion of ROSs through their porous structures                  | • Complex design, lengthy preparation steps and high operating costs          |
|                        | • High specific surface area                                                | • Early clearance by body immune system                                       |
|                        | • Controllable size, shape and function of the pore                        | • Off-target accumulation                                                     |
|                        | • Effectively enhance the ROS generation effect                              | • Untimely drug release ability                                               |
|                        | • High PSs loadings                                                         |                                                                               |

Tumors. Compared with oxygen-generating nanomaterials, prodrugs that can be activated by external light show the unique advantages of highly consistent responsiveness and high temporal and spatial selectivity (Rapp and DeForest, 2021). Recently, Liu’s group constructed a kind of original oxygen-generating hydrogel (OPeH) with photoactivated enzyme activity by loading the oxygen-generating MnO₂ nanoparticles conjugated with protoporphyrin IXpt (PPIX), and the proenzyme nanoparticles (PeN) crosslinked by a ¹O₂ cleavable linker into alginate hydrogels (Figure 11) Liu J. et al. (2021). Under NIR laser irradiation, MnO₂ NPs converted H₂O₂ into O₂, which further promoted the production of ¹O₂ from PpIX and improved the efficiency of ¹O₂ generation. In addition, after PEN was cross-linked with the ¹O₂ cleavable linker, it
induced cell death and suppressed metastasis by inhibiting the extracellular trap (NET) of neutrophils. In animal experiments, it was found that OPeH integrates PDT and NIR light-activated enzymes to achieve the combined therapeutic effect of inhibiting tumor growth and lung metastasis. In addition, phototherapy against deep tumors may greatly limited by the lack of light flux and the chemotherapy drugs against tumor cells may limited by insufficient resident time. Therefore, Zhong’s group developed a dual drug carrying system DOX-CA4P@Gel, which achieved the best curative effect, efficacy and safety through local sequential delivery of drugs Zhong Y. et al. (2021). With dextran oxide, chitosan, porphyrin and hollow mesoporous silica (HMSN), DOX-CA4P@Gel was constructed, in which combretastatin A4 phosphate (CA4P) and DOX were both loaded. In weakly acidic condition, the degradation rate of the hydrogels increased significantly. CA4P was released rapidly at the early stage and relatively stable after 48 h, while DOX released slowly at first and then quickly released after 48 h, showing an obvious sequential release behavior. The porphyrin in hydrogel could trigger the formation of ROS, DOX could kill cancer cells at different stages of proliferation, while CA4P could inhibit the establishment of blood vessels around the tumor and increase the sensitivity of cancer cells to DOX.

### 4.6 Polymers

Due to the designability and diversity of composition, structure and function, polymers have become one of the preferred carrier materials for nanomedicine. Conjugated polymers can control tissue penetration by adjusting the conjugation length. Among them, the integration of multichromophoric conjugated polymer base NPs into PSs enhanced ROS generation by improving PSs solubility, permeability, and targeting (Jiang and McNeill, 2017). According to the characteristics of carbon-based fluorescent nanomaterials such as carbon dots (CDs) and carbon-based polymer dots (CPDs) with good biocompatibility and high fluorescence yield, Sajjad et al. conjugated green-emitting CPDs to PPa to enhance the photocatalytic performance of PSs through covalent and π-π interactions Sajjad et al. (2022). Semiconducting polymer NPs (PSBTBT NPs) can’t only load PSs, but also act as photothermal agents for PDT/PTT synergistic therapy. Inspired by “biomarker-triggered image”-guided therapy, Bao et al. loaded the fluorescence quenchers Rhodamine B (Rhod B) and C6 on PSBTBT NPs to prepare a smart “Sensing and Healing” nanoplatform for PTT/PDT combination therapy (PSBTBT-C6@Rhod NPs) Bao et al. (2021). Similarly, IR780 iodide can generate heat and oxygen for PDT/PTT synergistic therapy. In addition, it has strong fluorescence intensity and inherent specificity for various tumor cells, which is suitable for near-infrared imaging of tumor cells. In view of this, Potara et al. used temperature-sensitive block copolymer Pluronic F127 to wrap IR780 iodide, and coupled folic acid (FA) to Plu-IR780 micelles through chitosan to design a thermostresponsive and thermal reversible size distribution and spectral properties of a novel FA-targeted near-infrared phototherapy NPs (Plu-IR780-chit-FA) Potara et al. (2021). Plu-IR780-chit-FA not only retained the PTT, PDT and NIR imaging properties of IR780 iodide, but also adjusted the size of the nanocapsules to the smallest (30 nm) at physiological temperature to ensue cellular uptake, while also had maximum absorption and fluorescence emission intensity.

Polymeric micelles, which constructed by amphiphilic polymers, have been regarded as ideal carriers for nanomedicine due to their good biocompatibility, degradability, easy modification of the structure, and special “core-shell” structure (Tian and Mao, 2012). Using

| Type          | Advantages                                                                 | Disadvantages                                      |
|---------------|----------------------------------------------------------------------------|----------------------------------------------------|
| Nanoliposomes | • Biocompatibility and biodegradability                                   | • Low drug loading capacity                        |
|               | • High structural flexibility                                              | • Limited stability in vivo                         |
|               | • Targeted delivery and triggered release                                 | • Uncontrolled drug leakage                        |
|               | • Easy and diverse surface modification                                    | • The inevitable self-quenching effect of water-insoluble PSs |
| MSNs          | • Large specific surface area and huge specific pore volume               | • The larger the specific surface area, the greater the cytotoxicity |
|               | • Easy and diverse internal and external surface modification             |                                                    |
|               | • High loading efficiency                                                 |                                                    |
| Dendrimers    | • Controllable molecular size                                             | • High molecular weight, high-density surface positive charge increases the toxicity of dendrimers |
|               | • Large number of terminal functional groups                              | • Low mechanical strength                          |
| Hydrogels     | • Good biocompatibility                                                    | • Poor repeatability of material properties         |
| Polymers      | • The designability and diversity of composition, structure and function   | • Limited storage stability                         |
|               | • Diverse surface modification                                             | • Potential toxicity                               |
|               | • High loading efficiency and sustained release                            | • Limited loading capacity for hydrophilic drugs    |
|               | • Good circulation stability                                               | • Complex synthesis process                        |
|               | • Improve PSs solubility, permeability, and targeting                      |                                                    |
| Obstacles to overcome | NP type | Name | Strategy | Year |
|-----------------------|---------|------|----------|------|
| PSs delivery | DNA-modified NPs | Apt-DNA-Au nanomachines (Yu et al., 2021) | Tumor-associated TK1 miRNA-responsive PSs release and survivin targeting by antisense DNA | 2021 |
| DNA-modified NPs | TOPP-gDNA-Au/PLNP (Su et al., 2021) | Nucleolin targeting by AS1411 aptamer | 2021 |
| DNA-modified NPs | Au/Pd ONP-DNA nanomachine (Cai et al., 2021a) | Using the primary marker miRNA-21 and two auxiliary markers miRNA-224 and TK-1 mRNA to improve the accuracy of tumor identification | 2021 |
| DNA-modified NPs | Label +DNA-AuG (Zhang et al., 2021b) | Recognition of cancer cells by miR-21 | 2021 |
| Biotin-modified NPs | BT@Au-NPs (He et al., 2021b) | Movement to cellular sites and efficient binding sites in tumor cell lines by biotin | 2021 |
| AuNRs-grafted RGD | HB-AuNRs@RGD (Liu et al., 2021f) | Binding of RGD to integrin avb3 in tumor cells and tumor neovascular endothelial cells | 2021 |
| Au nanoshells | 40/20 core radius/shell thickness | Optimization of nanoshells structure (silica core radius and gold shell thickness) to increase the singlet oxygen production | 2021 |
| Heterometallic colloids | Ir(III) complexes (Xiao et al., 2021) | Different degrees of oxygen quenching | 2021 |
| | Ru(II) complex-based bioorthogonal two-photon PSs | ovarian cancer cell lines by dual-ligand functionalization | 2021 |
| | Graphitic carbon nitride | g-C3N5NSs (Liu et al., 2021h) | Due to the addition of nitrogen-rich triazole groups, the visible light utilization and photocatalytic activity of g-C3N4NSs are higher than those of g-C3N4NSs | 2021 |
| | nanoheterostructures | Ni0.5S0.5Cu0.5S@HA (Sang et al., 2021) | Production of ROS and O2 by Ni0.5S0.5Cu0.5S@HA | 2021 |

### Light delivery

| NP type | Name | Strategy | Year |
|---------|------|----------|------|
| Bimetallic NPs | AuBIGSH@IR808 (Jia et al., 2021) | Modified by IR808 fuel for higher NIR photon capture capability | 2021 |
| Ultra-thin two-dimensional nanosheets | 4-layer O-TiO2 nanosheets (Cai et al., 2021a) | X-ray irradiation-induced ROS generation by OTiO2 nanosheets and chemotherapy mediated by DOX | 2021 |
| Ti-based targeting agent | B-TiO2@SiO2-HA (Guo et al., 2021) | Simultaneous generation of ROS and hyperthermia under NIR-II laser irradiation and full spectral response to light stimulation obtained by B-TiO2 | 2021 |
| Semiconductor metal oxide | SnO2@SiO2-HA (Gao et al, 2021a) | SnO2@SiO2-mediated full-spectrum response target-specific synergistic PDT/PTT | 2021 |
| Block copolymer | Pm-(IR808-chit-FA) (Potara et al., 2021) | PTT/PDT synergistic therapy under NIR via IR808 | 2021 |
| UCNPs | UCNP/RB, Ce6 (Pham et al., 2021) | Dual PSs have higher PDT efficiency than single PS | 2021 |
| New PSs | Ru complex | Ru-I (He et al., 2021c) | Red-Light-Responsive Ru Complex PSs for lysosome localization PDT | 2021 |
| | Amphiphilic polymer | DSPE-PEG2000-Folic encapsulated Ru (II) polypryidine complex (Karges et al., 2021) | Enhanced tumor cell selectivity by DSPE-PEG2000-Folic | 2021 |
| | Ru (II) complex | Ru (II) complex-based bioorthogonal two-photon PSs (Lin et al., 2021a) | Anti-tumor effects by specifically binding to cancer cell membranes and inducing cell membrane damage | 2021 |
| | Ir compounds | Ir (III) complexes (Xiao et al., 2021) | Different degrees of oxygen quenching via Ir (III) complexes | 2021 |
| | Bifunctional Ir (III) complexes | 4 @(Bzq) (dpap-arc) (Pedrado et al., 2021) | Targeted mitochondrial and cellular imaging via organic chromophores and Ir (III) complexes | 2021 |
| | Superparamagnetic Fe3O4 NPs | E-NP (Sengupta et al., 2022) | E-NP show immunoprotective and anti-inflammatory effects by inhibiting MPO and down-regulating NO | 2022 |
| | Ru (II) polypryidine complexes | Ru-g-C3N4 (Sengupta et al., 2022) | Oxygen self-sufficient PSs generated by grafting metal complexes onto g-C3N4 | 2021 |
| | Graphitic carbon nitride | g-C3N4NSs (Liu et al., 2021h) | Due to the addition of nitrogen-rich triazole groups, the visible light utilization and photocatalytic activity of g-C3N4NSs are higher than those of g-C3N4NSs | 2021 |
| | nanoheterostructures | Ni0.5S0.5Cu0.5S@HA (Sang et al., 2021) | Production of ROS and O2 by Ni0.5S0.5Cu0.5S@HA | 2021 |

(Continued on following page)
Summary of recently developed NPs to overcome the obstacles of current photodynamic therapy in tumor.

| Obstacles to overcome          | NP type                                      | Name                                                                 | Strategy                                                                 | Year |
|--------------------------------|----------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------------------------------|------|
| BPQDs                          | BPQDs@PEI + RGD-PEG + DMMA (Liu et al., 2021) | Enrichment of tumor targets through pH-responsive charge switching    |                                                                          | 2021 |
| 2D black phosphorus nanosheets | CyanW@BNPs (Li et al., 2021)                 | Continuous oxygen supply through cyanobacterial photosynthesis       |                                                                          | 2021 |
| Red/black phosphorus composite nanosheet | M-RP/BP@ZnFe2O4 (Kang et al., 2022) | ZnFe2O4 enhances the productivity of ROS through the Fenton reaction and can also induce apoptosis in MB-231 cells through oxidative stress |                                                                          | 2022 |
| Carbon-based polymer dots      | PPa-CDP (Sajjad et al., 2022)                | PPa enhances the photocatalytic performance of photosensitizers via covalent and π-π interactions |                                                                          | 2021 |
| Unfavorable TME                 | Hyaluronic acid-Bimetallic NPs               | ToHAu@Pt-PEG-Ce6/HA (Bu et al., 2021)                                 | Oxygen enrichment in tumor and PDT by Pt                                 | 2021 |
|                                | Synergistic therapy layered double hydroxides | ICG@PEI-PBA-HA/CeO2 (Zeng et al., 2021)                               | Increases heat and ROS production by altering the amount of Ag+, triggering ICd in tumor cells | 2021 |
|                                | Nanozyme                                    | IrO2-Gox@HA NPs (Yuan et al., 2022a)                                 | Enhancement of type II PDT by GOx and IrO2 NPs                          | 2022 |
|                                | ZGGO durable luminescent NPs                | Mn-ZGGO (Ding et al., 2021b)                                         | Oxygen-independent PDT using MnO2 shell                                  | 2021 |
|                                | Nanozyme                                    | ICG@PEI-PBA-HA/CeO2 (Zeng et al., 2021)                               | CeO2 catalyzes H2O2 to O2 through Ce3+/Ce4+ cerium valence cycling       | 2021 |
|                                | UCNPs                                       | UCTM NPs (Cheng et al., 2021a)                                        | Oxygen-enriching role of thylakoid membranes of chloroplasts in tumors and photodynamic therapy | 2021 |
|                                | UCNPs                                       | CMiUCNP-Rb/PDT (Jin et al., 2021a)                                    | PEG-TK-DX releases DX in response to ROS and prevention of tumor metastasis by CD73 antibody | 2021 |
|                                | MIPs modify UCNPs                           | M504/MNPs@mMIPs@UCNP (Lin et al., 2021b)                              | Using MIPs to target tumor cells and prevent PD-1/PD-L1 immune blockade  | 2021 |
|                                | Molybdenum Carbonate                        | Mo2C@Carbon-3@PEG (Hou et al., 2022)                                  | Photocatalytic Oxygen Generation by Mo2C                                  | 2022 |
| Engineered bacteria            | EB                                           | EB (Ding et al., 2021a)                                               | Targeting anoxic TME and catalyzing H2O2 to produce O2 using engineered Escherchia coli | 2021 |
| Metal-organic frameworks       | UIO@Ca-Pt (Peng et al., 2021)                | Increase intracellular oxygen content by endogenous oxygen through CaO2 and Pt |                                                                          | 2021 |
| Nanoscale iron-based metal organic frameworks | MIL-101(Fe)@TCPP (Chen et al., 2021b) | Fenton reaction increases intracellular oxygen levels                   |                                                                          | 2021 |
| Metal Organic Framework        | NMOF@SF/TPZ (NST) (Yu et al., 2022)         | Disturbed redox metabolism in tumor cells caused by GSH depletion and Fenton reaction oxygen enrichment |                                                                          | 2021 |
| Metal-organic frameworks       | Ag-AgCl@Au NMs (Xu et al., 2021a)           | Au nanorods produces O2 via a photocatalytic reaction                  |                                                                          | 2021 |
| Nanoliposomes                  | Ce6-SB3CT@Liposome (Li et al., 2021a)       | The released SB-3CT can effectively activate NK cells and enhance the immune system by inhibiting the shedding of soluble NK2G2D ligands |                                                                          | 2021 |
| Double nanozyme modified       | HMSN@Au@mMnO2-Fluorescein Derivative (HAMF) (Chen et al., 2021d) | Enhancement of intracellular oxygen level by catalytic reaction of MnO2 and Au NPs |                                                                          | 2021 |
| HMSN                           | HMSN@Au@mMnO2-Fluorescein Derivative (HAMF) (Chen et al., 2021d) | Enhancement of intracellular oxygen level by catalytic reaction of MnO2 and Au NPs |                                                                          | 2021 |
| Double nanozyme modified       | AuNCis@mSiO2@MnO2 (Yin et al., 2021)        | Acid-TME-responsive dual nanozyme-catalyzed reaction to enhance intracellular oxygen level via MnO2 nanosheets |                                                                          | 2021 |
| Polyamidoamine Dendrimers      | CCT-DPRS (Mindt et al., 2018)               | CaF2NPs convert low-dose X-radiation to Wei-green light to excite Rb to generate ROS, while releasing SU to inhibit tumor angiogenesis |                                                                          | 2021 |
| Hydrogels                      | OPeH (Liu et al., 2021b)                    | MnO2 NPs convert H2O2 to O2, which further promotes the generation of O2 from PpIX and improves the generation efficiency of 1O2 |                                                                          | 2021 |
| Fluorinated polymer micelles   | (PFFA)-Ce6 (Tseng et al., 2021)             | Using perfluorocarbons to increase intracellular oxygen levels         |                                                                          | 2021 |
| Amphiphilic polymer micelles   | MPEG-S-S-PCL-Por (MSLP) (Xia et al., 2021)  | Amplifies oxidative stress in tumor cells by depleting GSH and producing ROS |                                                                          | 2021 |
| Synergistic therapy            | layered double hydroxides                   | ICG/CAC-LDH (Wang et al., 2021a)                                      | Induces intracellular GSH depletion through redox reactions, and can also be decomposed to generate Cu2+ and Ce3+, which stimulates Fenton-like reactions to generate OH | 2021 |
| Bimetallic NPs                 | Au3Bi-SR NPs (He et al., 2021a)             | The photothermal effect of NPs is enhanced by the introduction of Bi |                                                                          | 2021 |
| Bifunctional micelles          | Micelle-Ir (Li et al., 2021c)               | Promotion of singlet oxygen generation and photothermal effect via BODIPY-Ir |                                                                          | 2021 |
| Nanozyme                       | MIP/Ce6 (Li et al., 2021a)                  | PTT by IrO2 and TME-responsive PDT by MnO2 |                                                                          | 2021 |
perfluorocarbons (PFCs) as oxygen carriers to directly deliver oxygen to tumors and relieve tumor hypoxia and enhance the PDT effect. Recently, Tseng et al. developed a folate-conjugated fluorinated polymeric micelle (PFFA)-Ce6 micellar system, which exhibited a higher ROS production, good long-term stability, higher oxygen carrying capacity and improved PDT efficacy in inhibiting tumor growth as compared to those of non-PFC system Tseng et al. (2021). The fluorinated segment in PFFA-Ce6 could not only maintain the oxygen carrying capacity of polymer micelle without the problem of PFC molecule leakage, but also acted as a reservoir to accommodate the hydrophobic Ce6 to enhance its solubility. The folic moiety in PFFA-Ce6 could not only maintain the oxygen carrying capacity, but also acted as a reservoir to accommodate the hydrophobic Ce6 to enhance its solubility. The folic targeting ligand for cancer cells.

In the in vitro cell study, due to the selective internalization of PFFA-Ce6, the cell growth inhibition of HeLa cells after irradiation was higher. Cancer cells are accustomed to oxidative stress caused by PDT through overexpressing glutathione (GSH) and other antioxidants. Therefore, preferentially amplifying the oxidative stress of tumor cells by consuming GSH or producing ROS is a reasonable treatment strategy to enhance the efficacy of PDT. To this end, Xia et al. designed a GSH-scavenging and ROS-generating polymeric micelle mPEG-S-S-PCL-Por (MSLP), which was composed of methoxy polyethylene glycol (MEPEG)-SS-poly (ε-caprolactone)-protoporphyrin (POR) amphiphilic polymer and the anticancer drug DOX, for amplifying oxidative stress and enhanced anticancer therapy of PDT Xia et al. (2021). MSLP combined with doxorubicin (DOX), for amplifying oxidative stress and enhanced anticancer therapy of PDT Xia et al. (2021). 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5 THE APPLICATIONS AND THE PHOTOSENSITIZERS FOR CLINICAL TUMOR TREATMENT

PDT has been used to treat a variety of cancers, including lung, head and neck, brain, pancreas, peritoneal cavity, breast, prostate, skin, and liver cancer (Kubrak et al., 2022). The first-generation PS are hematoporphyrin derivative. They have long plasma half-life and lack of sensitivity. For example, Photofrin® has been licensed for use in the oesophagus, lung, stomach, cervix and bladder. Since the absorption spectrum of Photofrin sodium peaks at 405 nm, its depth of action is limited to 0.5 cm (Ramsay et al., 2021).

The second-generation PSs are single compound synthesized, derived from porphyrin, bacteriochlorophyll, phthalocyanine, chlorin, benzoporphyrin, curcumin, methylene blue derivatives, etc. Compared with the first-generation PSs, the second-generation PSs have longer absorption spectrum (visible-near-infrared region), higher \( {1^O}_2 \) yields, and better tumor targeting. For example, 5-aminolevulinic acid (5-ALA) has been successfully used in the treatment of basal cell carcinoma, actinic keratosis and oral premalignant disorder, Meso-tetra-4-hydroxyphenyl chlorin (mTHPC-Foscan®) has been commonly used for advanced head and neck cancers (Zhang S. et al., 2022). Other second-generation PSs that have received clinical approval or are in clinical trials include Temoporfin (Foscan®), Motexafin lutetium, Palladium bacteriochlorophorbide, Purlytin®, Verteporfin (Visudyne®), and Talaporfin (Laserphyrin®) (Baskaran et al., 2018).

The third-generation PS are characterized by combining the second-generation PSs with targeting entities or moieties, such as antibodies, amino acids, polypeptides, or by encapsulation into highly biocompatible nanocarriers to improve the ability of PS improve accumulation of PSs at the targeted tumor sites (Baskaran et al., 2018). Now, third-generation PSs that can significantly improve cancer targeting efficiency through chemical modification, nano-delivery systems, or antibody conjugation are widely studied for preclinical studies, and if satisfactory results are obtained, then more third-generation PSs will be promoted to enter the clinical research stage (Mfouo-Tynga et al., 2021).

6 CONCLUSION AND PERSPECTIVE

In summary, we have introduced the advantages and disadvantages (Tables 1, 2) and recent studies (Table 3) based on Metal NPs, Nanoliposomes, MSNs, Dendrimers, Hydrogels, Polymers, which overcome the obstacles of PDT in tumor tissues, such as poor biocompatibility and low delivery efficiency of PSs, compromising poor light transmittance of deep tissues, and hypoxia, reactive oxygen species scavenging and immunosuppression in tumor TME (Lee et al., 2022). Insufficient supply of pivotal factors including PSs, light, and \( O_2 \) highly reduces the therapeutic efficacy of PDT. Therefore, the primary source of photodynamic therapy should be optimized by setting parameters such as input dose, intratumoral drug level, light source, and tissue oxygen conditions. Based on recent progress in the combination of nano- and biotechnology, various kinds of NPs have been developed for PDT, and they showed promising potential to overcome these obstacles. PSs are an indispensable key ingredient in photodynamic therapy. In most cases, PSs are aggregated inside the nanoparticles, and \( O_2 \) has the disadvantages of short half-life (<40 ns) and short intracellular distance (<20 nm), resulting in \( O_2 \) needing time and space to diffuse out from NPs to attack cells of biomolecules and further impairs the efficiency of PDT (Deng et al., 2021). Therefore, it is very necessary to release free PSs from nanoparticles before irradiating cancer cells or tumor tissue with light. In addition to the optimization of the physical structure and chemical composition of passive targeting of PSs and the modification of active targeting ligands for efficient, safe, and better tissue penetration, improving drug delivery and combination therapy are also effective strategies. In recent years, stimuliresponsive nanomaterials have received increasing attention because they can react to both endogenous stimuli (low pH, enzymes, redox agents, hypoxia) and exogenous stimuli (light, temperature, magnetic field, ultrasonic) and other stimuli to change its physicochemical properties and release PSs (Chang et al., 2021). However, the release of PSs from endogenous stimuli-responsive nanocarriers is slow due to weak stimulation intensity. In contrast, exogenous stimuli are easily modulated remotely in intensity and timing to release drugs on demand in diseased tissues or cells. However, the poor penetration of drugs into deep tumor tissue and the poor penetration of excitation light source into deep tumor tissue are important issues that need to be solved for NPs delivery systems. The use of UCNPs, XPDT, and fluorescence imaging techniques provides clues for efficient light delivery to deep tissues. Among them, the potential toxicity of heavy metals is a serious limitation, and their potential toxicity needs to be carefully considered, and favorable distribution, degradation and excretion should be achieved (Medici et al., 2021). Attempts to overcome hypoxia caused by hypoxia in tumor tissues include artificial oxygen production, Fenton reaction, and the combined application of chemical drugs related to hypoxia. In addition to promising results, combined with the latest methods to normalize tumor blood vessels and reduce hypoxia itself, it is also expected to become an effective method for PDT to treat tumors. Although many of these ideas are at the level of cell experiments and animal experiments, these studies have made significant progress over traditional PDT research. Therefore, we hope that the results of these trials can maximize the clinical efficacy of PDT in the future. In addition, future research and development of new nanomaterials should focus on targeted therapy and personal medicine. In order to improve the specificity and safety of drugs, targeted delivery and on-demand controlled/triggerable release are still the focus of drug delivery platform development.

AUTHOR CONTRIBUTIONS

The manuscript was written through the contributions of all authors. LC, JH, and SL conceived this work. LC and JH mainly wrote the manuscript. All authors have given approval to the final version of the manuscript.
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