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Stable triangle: nanomedicine-based synergistic application of phototherapy and immunotherapy for tumor treatment

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Abstract

In recent decades, cancer has posed a challenging obstacle that humans strive to overcome. While phototherapy and immunotherapy are two emerging therapies compared to traditional methods, they each have their advantages and limitations. These limitations include easy metastasis and recurrence, low response rates, and strong side effects. To address these issues, researchers have increasingly focused on combining these two therapies by utilizing a nano-drug delivery system due to its superior targeting effect and high drug loading rate, yielding remarkable results. The combination therapy demonstrates enhanced response efficiency and effectiveness, leading to a preparation that is highly targeted, responsive, and with low recurrence rates. This paper reviews several main mechanisms of anti-tumor effects observed in combination therapy based on the nano-drug delivery system over the last five years. Furthermore, the challenges and future prospects of this combination therapy are also discussed.

Introduction

The World Health Organization has focused on malignant tumors, which are the leading cause of human death. According to data released by the International Agency for Research on Cancer (IARC), there were approximately 19.3 million new cancer cases and 10 million deaths worldwide in 2020 [1]. Finding an effective treatment for malignant tumors has become an urgent problem in the medical field. Currently, traditional treatment methods such as surgery, radiotherapy, and chemotherapy were used for patients. However, surgical resection often results in extensive trauma and fails to inhibit metastatic lesions. Subsequently, patients require adjuvant therapies such as chemotherapy and radiotherapy after surgery. Unfortunately, these treatments lack specificity in targeting cancer cells and also harm normal cells. Still, the challenges of resistance remain unresolved, rendering traditional methods ineffective in treating tumors. Over the past few decades, researchers have tirelessly explored alternative tumor therapies. New generation treatments, including gene therapy [2], chemodynamic therapy (CDT) [3], immunotherapy [4], and phototherapy [5], have gained significant attention in recent years.

Phototherapy encompasses two effective and minimally invasive treatment strategies for primary tumors:

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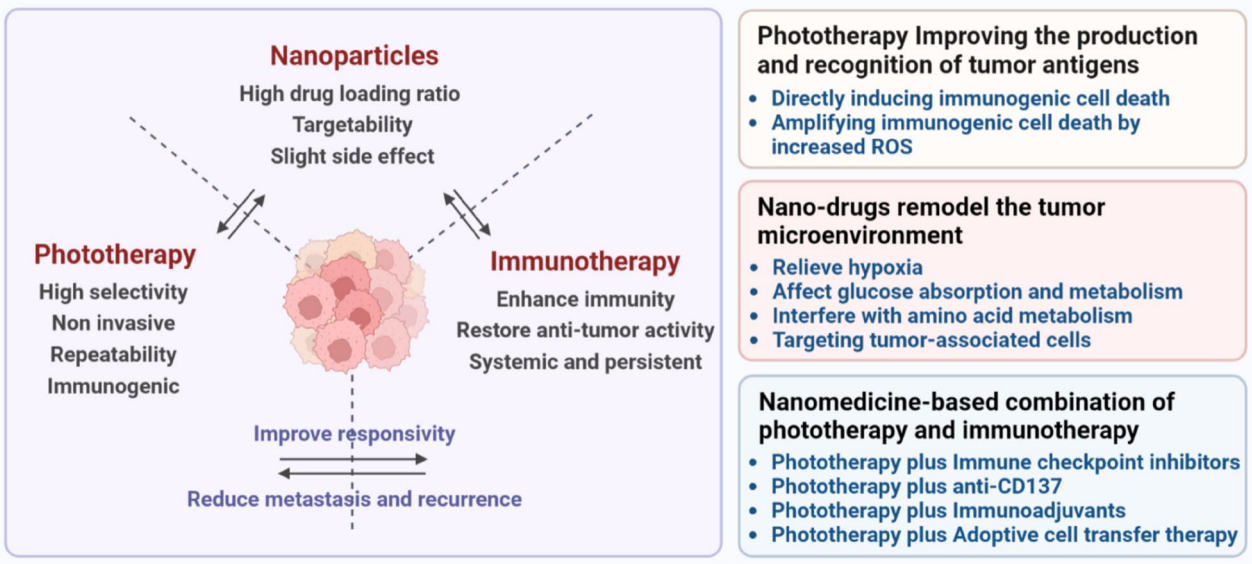
Graphical abstract



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photodynamic therapy (PDT) and photothermal therapy (PTT). PDT involves the application of a photosensitizer (PS) followed by appropriate light exposure. Upon light excitation, the PS could generate reactive oxygen species (ROS). PDT-mediated ROS production is based on two kinds of photoreactions according to the photophysical and photochemical basis: type I (electron transfer) reaction mainly produces superoxide anions, hydrogen peroxides and hydroxyl radicals, while type II (energy transfer) mechanism mainly produce singlet oxygen. These ROS could attack cancer cells and lead to the destruction of organelles, such as mitochondria, nuclei, and lysosomes, ultimately causing cell death [6, 7]. As far back as the 1970s, Dr. Dougherty's experimentation with injecting hematoporphyrin derivatives (HpD) and using laser irradiation to eliminate solid tumors in experimental animals served as the foundational technical prototype for what we now recognize as PDT [8]. Subsequently, HpD and photofrin emerged as the early photosensitive drugs utilized in numerous clinical trials, exhibiting initial efficacy in treating lung cancer, rectal cancer, bladder cancer, and basal cell carcinoma [9–12]. However, a notable drawback of these early treatments is their tendency to accumulate in the skin, leading to heightened sensitivity to sunlight and subsequent dermatitis in patients [13]. Photothermal Therapy (PTT) employs targeted photothermal conversion materials at tumor sites, converting light energy into heat upon exposure to laser radiation. This process effectively eradicates tumor cells by generating high temperatures [14–16]. However, conventional photothermal conversion materials exhibit low targeting efficiency, often causing heat diffusion and thermal damage to surrounding tissues during treatment. Recent advancements involve the localized application of photothermal conversion materials and the utilization of controllable near-infrared radiation to adjust the hyperthermia induced by PTT, thereby minimizing non-target tissue damage. Several phase I trials, concentrating on bladder cancer treatment, have affirmed the safety and potential clinical application of PTT [17, 18]. Yet, a significant drawback of phototherapy is the poor penetration effect of the excitation light source, resulting in insufficient light energy reaching the target site and consequently limited clinical efficacy. Consequently, phototherapy finds predominant use in superficial or hollow tissues and organs, such as melanoma, bladder cancer, and breast cancer [19]. In addition, ROS exhibit a short lifetime and diffusion distance, diminishing the antitumor effectiveness of PDT; elevated tissue temperatures prompt the overexpression of heat shock proteins, fostering heat resistance in cancer cells, thereby weakening the efficacy of PTT. These factors also restrict the therapeutic outcomes and clinical application of phototherapy [20]. It's noteworthy that standalone phototherapy might not completely eradicate tumors, potentially leading to residual tumors, recurrence, drug resistance, immune evasion, and even metastasis [21].

The human immune system possesses powerful mechanisms to eliminate foreign substances within the body. Immunotherapy is a type of cancer treatment that aims

to stimulate or enhance the immune system's anti-tumor response. In recent years, significant advancements have been made in the development of immunotherapies, including immune checkpoint therapy, cytokine therapy, adoptive cell therapy, and cancer vaccines [22]. Immunotherapy has been recognized as a promising approach in the fight against tumors over recent decades, significantly advancing the field of anti-tumor strategies. However, despite these advancements, immunotherapy remains in its nascent stages of development, and the performance of singular immunotherapy interventions in clinical applications has not met initial expectations. This shortfall can be attributed to the intricate nature of immunotherapy, involving intricate interactions among immune cells and cancer cells, as well as various associated pathways, proteins, and cytokines. Several factors contribute to the limited success observed in recent decades, including: (i) inadequate antigen recognition; (ii) failures in immune checkpoint mechanisms; and (iii) insufficiencies in creating inflammatory and immune responses within the microenvironment. The immune response rate varies significantly among individuals, leading to ineffective treatment in some cases. Additionally, there is a risk of immune-related adverse events (irAEs) associated with immunotherapy [23]. Furthermore, the complex preparation process of immunotherapy contributes to its high cost, imposing a significant financial burden on patients.

A new cancer treatment strategy is emerging by combining immunotherapy with phototherapy. This combined approach leads to the immediate death of a large number of tumor cells, triggering adaptive immunity. It involves the redistribution and activation of immune effector cells, the expression and secretion of cytokines, and the transformation of memory T lymphocytes. These effects have a further impact on the tumor microenvironment. By combining these therapies, it becomes possible to overcome issues such as recurrence caused by phototherapy, the low response rate, and slow onset of immunotherapy. This dual strategy aims to control tumor growth effectively, achieving two goals simultaneously.

Nanomaterials, due to their unique physical and chemical properties, are considered ideal carriers for combined therapy [24–26]. Nano-drug delivery systems offer several advantages, including improved water solubility of drugs, enhanced targeting efficiency, and increased cell uptake. Additionally, they possess characteristics such as ultra-small volume, large specific surface area, and high drug loading capacity. Nanoparticles exploit the enhanced permeability and retention (EPR) effect, enabling them to passively target tumor sites and concentrate drugs locally, thus enhancing the therapeutic effect [27–29]. Although recent studies indicated that nanoparticles accumulated in tumor site by other mechanisms, it is true that nanomedicine-based therapy did result in the enhanced biodistribution in tumor site [30–32]. Furthermore, nano-preparations have the potential to reduce drug dosage, minimize toxic and side effects, and improve drug stability [33–35].

Nanomaterial-based phototherapy offers the potential to not only directly eliminate tumors but also induce a sustained anti-tumor immune response, referred to as photoimmunotherapy. This synergistic approach has the ability to enhance the effectiveness of both therapies and overcome their inherent limitations, thus paving the way for a new direction in current anticancer treatment (Fig. 1). In this paper, we provide a comprehensive review

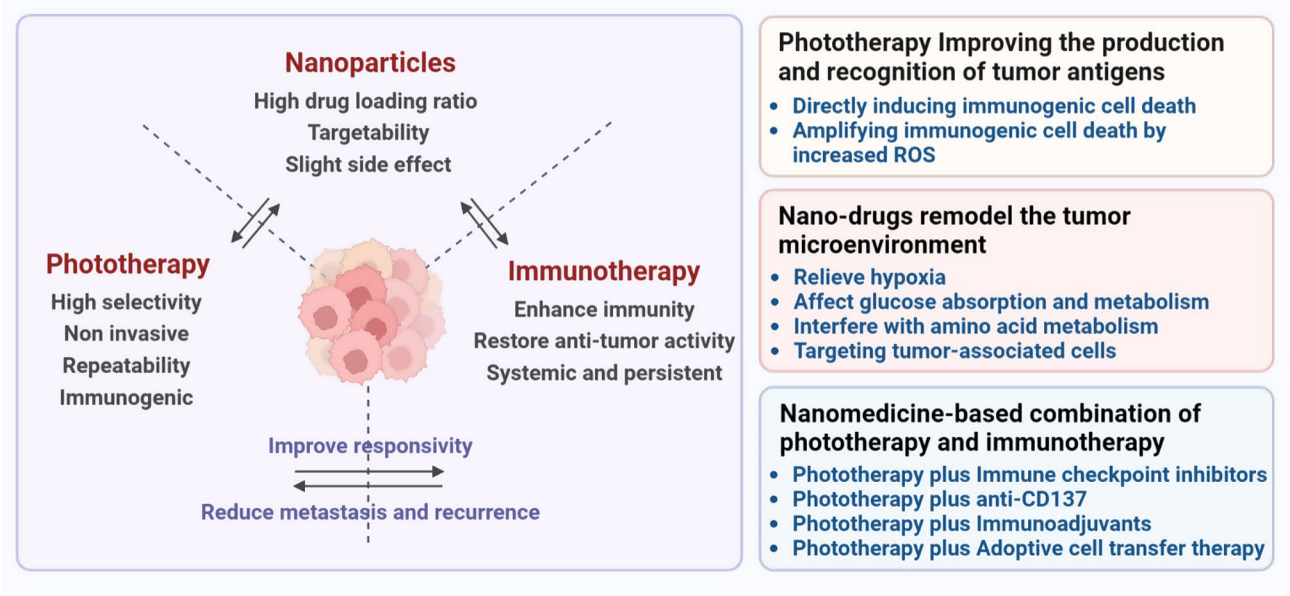

Fig. 1 The characteristics and synergistic application of nanoparticles, phototherapy, and immunotherapy

of the latest advancements in photoimmunotherapy utilizing nanomaterials. We also discuss the challenges faced in this field and explore future prospects for further development.

Phototherapy improving the production and recognition of tumor antigens

Tumor antigens can be broadly categorized into two groups: tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs) [36]. TSAs are exclusively expressed on tumor cells, while TAAs are expressed to a lesser extent in normal tissue cells. The challenge in immunotherapy for solid tumors lies in the inadequate antigenicity and the difficulty in antigen recognition. Phototherapy presents a potential solution to these issues by addressing both problems and supporting sensitization immunotherapy. By combining phototherapy with immunotherapy, the antigenicity of tumors can be enhanced, and the immune system can be better primed to recognize and target tumor cells effectively [37]. This approach has the potential to overcome the limitations of immunotherapy in solid tumors and improve treatment outcomes.

Directly inducing immunogenic cell death

The concept of immunogenic cell death (ICD) was initially proposed in 2005. In a study conducted by Noelia Casares et al. [38], tumor cells were exposed to doxorubicin (DOX), which led to cell apoptosis and triggered a durable immune response. Unlike other forms of cell death, ICD represents a specific type of regulated cell death (RCD). When tumor cells succumb to external stimuli, they transition from a non-immunogenic state to an immunogenic state, initiating an anti-tumor immune response. ICD is characterized by the release of TAAs, damage-associated molecular patterns (DAMPs), and pro-inflammatory cytokines from the deceased cells. These factors aid in the presentation of TAAs by immune cells and elicit an antigen-specific immune response [39]. TAAs have the capacity to enhance antigen-specific T cell responses, while the release of DAMPs serves as a "danger" signal for immune stimulation, enhancing the uptake of tumor antigens by dendritic cells (DCs) and inducing their maturation. This, in turn, activates T cells to initiate anti-tumor immunity. Several immunogenic factors associated with apoptotic cell death have been identified as DAMPs, including calreticulin (CRT), adenosine triphosphate (ATP), high mobility group protein 1 (HMGB-1), and heat shock proteins (HSPs) [40]. Although certain chemotherapy drugs can induce ICD when used individually, it is important to note that these drugs often exhibit significant toxicity and side effects on normal tissues and cells in clinical settings. Adverse reactions such as vomiting and bone marrow cell damage may occur. Additionally, drug resistance and low induction efficiency in vivo limit their widespread utilization in cancer therapy.

Phototherapy is widely recognized as a treatment that can induce ICD and enhance systemic immune responses. One advantage of phototherapy is that it can elevate the local temperature of tumor sites through the accumulation of photosensitizers and laser irradiation. This thermal ablation of the tumor leads to immunogenic cell death, resulting in the release of TAAs and the formation of an in situ tumor vaccine with a broad spectrum. Sobhana et al. developed a therapeutic nanocomposite comprising an ultra-small core component, CuS, with encapsulated indocyanine green (ICG), a photosensitizer, and folic acid (FA), a targeting agent [41]. This nanocomposite exhibited excellent absorption of a wide range of near-infrared (NIR) wavelengths and demonstrated a high conversion rate from light energy to heat energy, effectively killing HeLa cells. Upon exposure to 808 nm laser radiation, the cells exhibited DNA damage and double strand breaks. Additionally, phototherapy-induced ICD was observed, as evidenced by the translocation of CRT to the cell surface and the release of HMGB1 and ATP into the extracellular environment. Furthermore, the nanocomposite exhibited remarkable photoacoustic (PA) imaging capabilities, making it a promising candidate for "nanotheranostic" applications.

Amplifying immunogenic cell death by increased ROS

In addition, several studies have indicated that ROS generated during phototherapy not only possess high toxicity for killing tumor cells but also induce endoplasmic reticulum stress, leading to ICD in tumor cells and synergistically enhancing the anti-tumor effect with immunotherapy [42–45]. In view of this, researchers loaded catalase (CAT) and anti-GITR antibody (DTA-1) with Treg targeting ability into photosensitive PDA-ICG nanoparticles (Fig. 2A-C) [46]. The resulting PDA-ICG@CAT-DTA-1 nanoparticles exhibited intrinsic local hyperthermia and increased ROS production within tumors (Fig. 2D). This formulation caused a significant decrease in $FOXP3^+$ regulatory T cells and an increase in $CD4^+$ effector T cells by 4.3 times and 1.5 times, respectively. Furthermore, it promoted the production of CRT (Fig. 2E), thus enhancing the ICD effect. Therefore, while inhibiting the primary tumor locally, it also suppressed the growth of distant tumors. However, a challenge arises due to the short half-life of ROS, which can only diffuse within a limited range of 10–20 nm, resulting in decreased ROS accumulation under endoplasmic reticulum stress [47]. To overcome this limitation, Li et al. developed reduction-sensitive nanoparticles that can effectively target the endoplasmic reticulum (ER) [48]. This nanosystem consists of ER-targeting pardaxin (FAL)

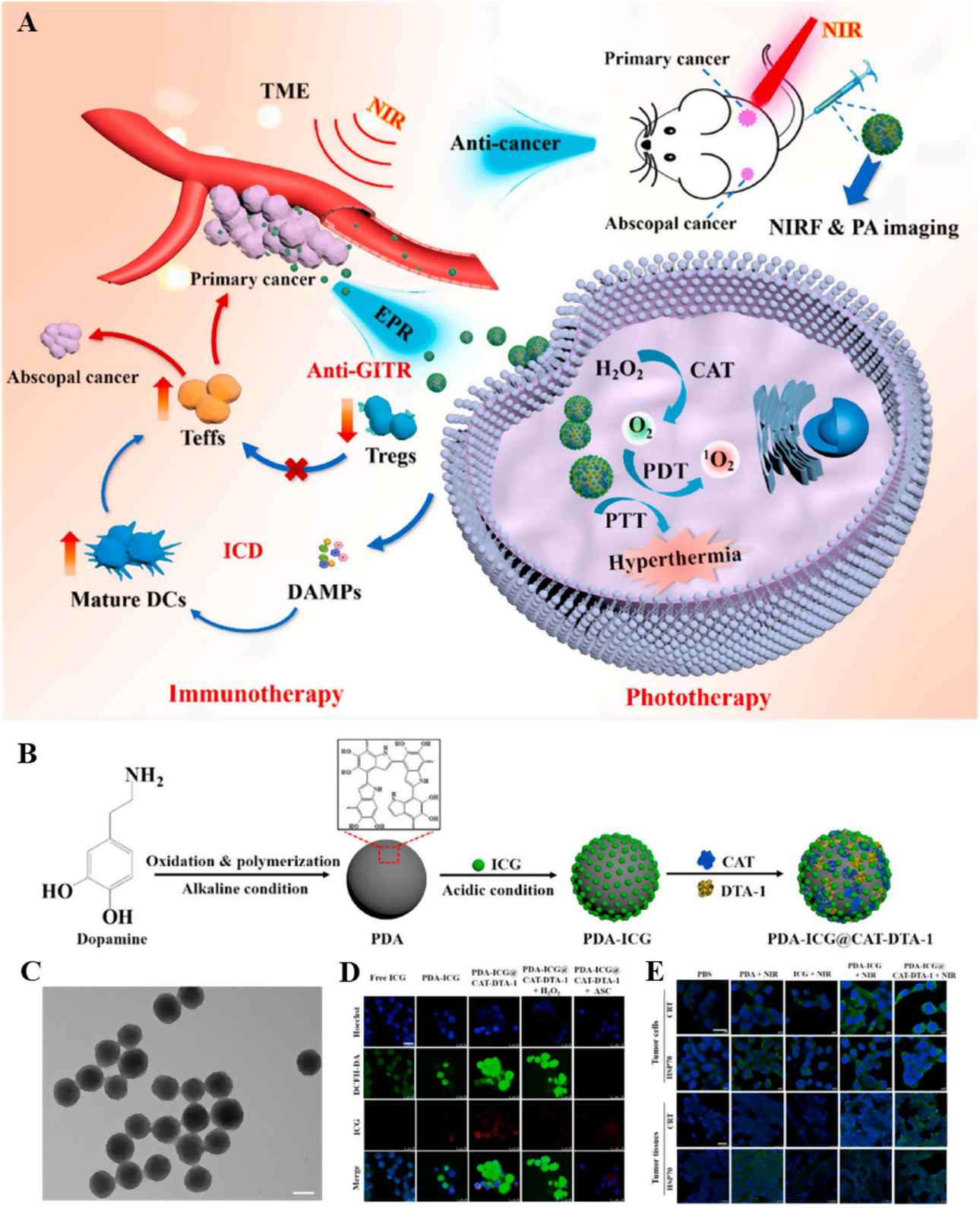

Fig. 2 Phototherapy inducing immunogenic cell death. (**A**) Schematic illustration of PDA-ICG@CAT-DTA-1 nanoparticles based on phototherapy and immunotherapy. (**B**) Schematic diagram of preparation process of PDA-ICG@CAT-DTA-1. (**C**) TEM image of PDA-ICG@CAT-DTA-1. (**D**) Intracellular ROS generation with different treatments under laser irradiation. (**E**) Immunofluorescence staining of CRT and HSP70 in tumor cells in vitro and tumor sections in vivo (Adapted with permission from reference [46])

peptide-modified hollow ICG-conjugated gold nanospheres (FAL-ICG-HAuNS) along with oxygen-delivering hemoglobin (Hb) liposomes (FAL-Hb-lipo). Upon combined administration, researchers observed notable dendritic cell maturation and stimulation of immunogenic functions (IL-6^{high}/IL-10^{absent}) in lymph nodes and tumors. Additionally, the number of activated $CD8^+$ T cells and immune-promoting cytokines increased, while the amount of Treg cells decreased. This confirms that targeted ER can continuously generate ROS through the PDT/PTT reaction, thus promoting the immunotherapy effect of ICD.

Nano-drugs remodel the tumor microenvironment

The tumor microenvironment exhibits several distinctive biochemical characteristics, such as a low pH value and elevated levels of ROS and glutathione (GSH) [49, 50]. These harsh conditions can significantly impact the functionality of immune cells and facilitate the initiation and progression of tumors. Nanomedicine-based treatment could exert considerable effect to modify the changed tumor microenvironment. In this section, we introduced the effect of nanomedicine-based treatment on tumor microenvironment and the enhanced therapeutic outcome and the synergistic effect with other therapies.

Relieving hypoxia

The hypoxic environment is a crucial factor within the tumor microenvironment. It is widely known that hypoxia is prevalent in around 90% of solid tumors. The rapid proliferation of tumor cells leads to increased oxygen consumption, while the newly formed blood vessels within the tumor are dysfunctional and fail to efficiently deliver oxygen, thus limiting oxygen diffusion into the tumor tissues. Studies have demonstrated that hypoxia promotes essential processes in cancer cells, such as invasion, extravasation, and metastasis, making it a significant obstacle to effective cancer immunotherapy [51]. Oxygen is the third important factor in PDT process besides PS and light, and the hypoxic nature of the tumor microenvironment severely hinders its application [52]. Currently, there are many strategies to solve the insufficient oxygen supply at the tumor site, and we introduce them in the following section.

Increasing in in situ oxygen generation

Tumors often exhibit higher levels of hydrogen peroxide (H_2O_2) compared to normal tissues. Taking advantage of this characteristic, the first strategy to increase oxygen involves catalytically decomposing endogenous H_2O_2 within the tumor to generate in situ oxygen and alleviate hypoxia. For instance, Shi et al. employed a liposome cavity to encapsulate MBDP (a lysosome-targeted near-infrared photosensitizer) and DOX (chemotherapy agent) to enhance the synergistic effects of chemotherapy and PDT [53]. Additionally, catalase was loaded to alleviate tumor hypoxia and promote an anti-tumor immune response. The inclusion of CAT expedites the PDT process and generates $^1O_2$. Moreover, it modulates immune cytokines to reverse the immunosuppressive TME and support anti-tumor immunity, leading to significant tumor cell death. However, this strategy may not be suitable for PTT since CAT is thermally unstable due to its inherent biological enzyme characteristics.

In recent years, a class of nanomaterials with unique physical properties and catalytic activity, resembling natural enzymes, has emerged and is referred to as nanoenzymes. Examples of such nanomaterials include graphene, iron oxide, palladium nanocrystals, and molybdenum diselenide (MoSe2). Wang et al. utilized MoSe2, known for its high photothermal conversion efficiency (59.28% at 808 nm), to prepare a nanoenzyme called MoSe2-PVP [54]. This nanoenzyme exhibits superior catalytic activity and thermal resistance compared to natural catalase. When combined with Ce6, MoSe2-PVP promotes efficient generation of $^1O_2$ under 660 nm laser irradiation. Moreover, the degradation products of MoSe2-PVP under weakly acidic and high H_2O_2 conditions can activate antigen-presenting cells and enhance the killing effect of cytotoxic T cells. Combining MoSe2-PVP/Ce6 with PD-1 antibody effectively increases effector memory T cells and natural killer (NK) cells, demonstrating enhanced effects compared to standalone PTT or PDT. Another example involves iron carbide nanoparticles (NPs) possessing photothermal conversion properties (50.5% at 1064 nm), which induce the production of hydroxyl radicals (•OH) and subsequently ROS in acidic environments [55]. The Fenton-like reaction with copper ions serving as CDT agents enhances the peroxidase-like activity of iron carbide NPs, leading to increased ROS production. These pH/temperature-responsive particles also release the adjuvant R848 and effectively reverse the state of the tumor microenvironment.

A second strategy for increasing in situ oxygen levels involves decomposing water within the body to generate oxygen. Wang et al. employed FeS_2 and CoS2 to construct FCs@PEG nanosheets with combined photothermal and photocatalytic capabilities [56]. This nanocomposite enables two pathways for oxygen generation (Fig. 3A). Firstly, when irradiated at 1064 nm, the photoexcited pores exhibit strong oxidizing capacity, enabling the oxidation of water (H_2O) to produce oxygen (O_2). Secondly, FCs@PEG mimics the functions of catalase and peroxidase (POD), catalyzing the conversion of hydrogen peroxide (H_2O_2) into O_2 and •OH. Furthermore, the hyperpyrexia-induced energy assists in generating photogenerated electrons, which possess reduction abilities to

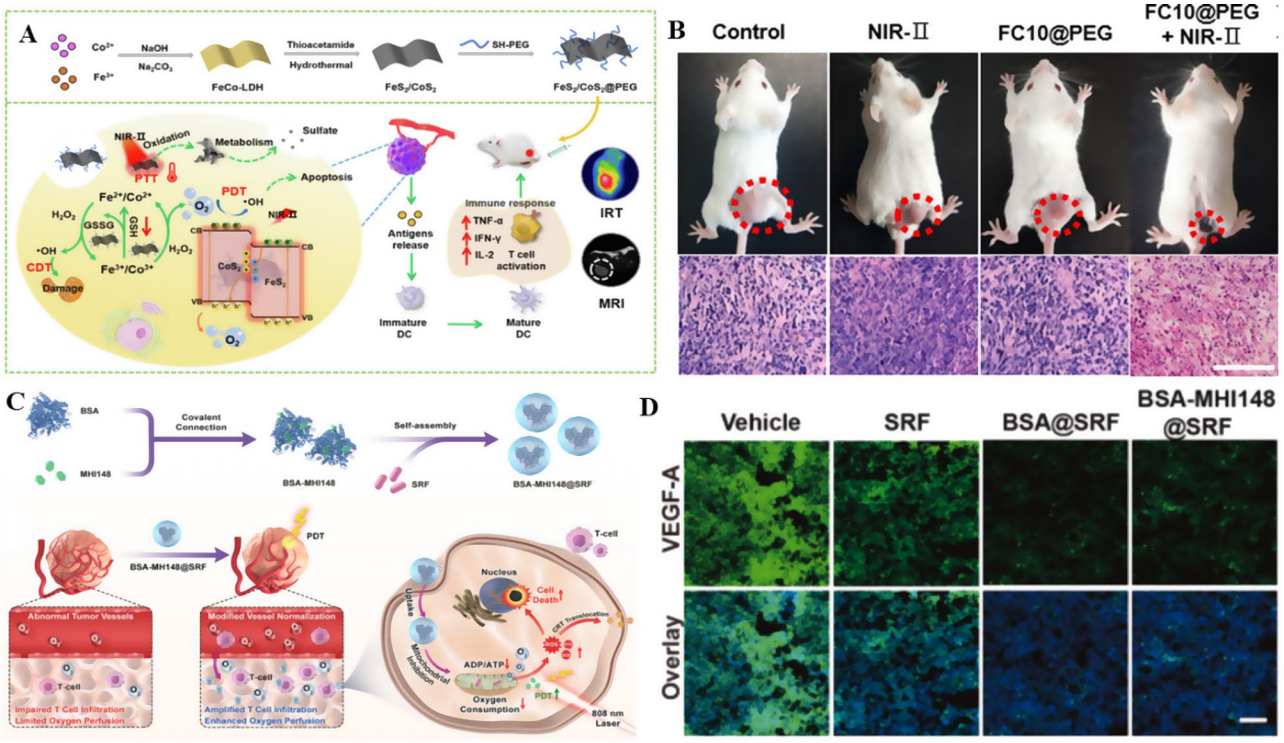

Fig. 3 Nano-drugs improve hypoxic microenvironment at tumor site. (**A**) Schematic illustration of FeS_2/CoS_2@PEG NSs for efficient PTT/PDT/CDT. (**B**) Photographs of mice and H&E staining of tumors after two weeks treatments (Adapted with permission from reference [56]) (**C**) Schematic illustration of the synthesis route of BSA-MHI148@SRF nanoparticles and the mechanism illustration of enhancing tumor photodynamic immunotherapy by re-oxygenation and immune re-sensitization strategy mediated. (**D**) Representative fluorescence images of VEGF-A expression in tumor tissues (Adapted with permission from reference [68])

capture dissolved oxygen and produce ROS. Additionally, FCs@PEG acts as a glutathione oxidase (GSHOD), depleting intracellular GSH and promoting oxidative stress. Animal experiments have demonstrated the efficacy of the synergistic therapy involving PTT, PDT, and CDT, resulting in significant anti-cancer effects and an immune response against tumors (Fig. 3B).

Directly delivering oxygen

Hemoglobin (Hb) within red blood cells serves as a proficient oxygen transport agent. However, due to its limited oxygen-carrying capacity in blood, recent focus has centered on the development of nano-carriers adept at efficiently transporting oxygen. These oxygen-rich nanocarriers demonstrate the capability to deliver oxygen within tumors, subsequently elevating the oxygen levels within these regions. Notable existing nano-carriers capable of self-supplying oxygen include Hb, perfluorocarbon (PFC), and metal-organic skeleton (MOF) [57]. Chen et al. pioneered the hybridization of Hb with intermolecular disulfide bonds to fabricate the chlorine c6-coated (C@HPOC) hybrid protein oxygen nanocarrier [58]. This innovative approach targetedly delivered oxygen-bearing C@HPOC, mitigating tumor hypoxia. Simultaneously, increased oxygen levels enhanced $^1O_2$ production at the tumor site, thereby augmenting PDT efficacy. Furthermore, nanoparticles facilitated a systemic anti-tumor immune response, elevating the ratio of mature DCs, activated T lymphocytes, and NK cells in the tumor and tumor-draining lymph nodes, thereby stimulating anti-metastasis effects. While Hb has conventionally served as a natural oxygen carrier, the emerging PFC, recognized by the FDA as bionic blood due to its high oxygen capacity, is gaining widespread use [59]. PFC demonstrates high chemical stability and commendable biocompatibility. Unlike Hb, PFC's advantage lies in the significantly increased solubility of oxygen molecules, which, although minimally soluble in water, exhibit twentyfold higher solubility in perfluorocarbons. Wang et al. presented an intriguing nanoparticle oxygen carrier employing the photosynthetic microbe Chlorella to produce oxygen, while leveraging perfluorocarbons to concentrate oxygen, ensuring a continuous oxygen supply [60]. Continuous PDT further augmented DC activation, upregulated IL-12p70, a crucial marker of innate immunity, and bolstered anti-tumor immune responses.

Inhibiting cell respiration to reduce oxygen consumption

Cellular respiration is the fundamental process wherein all living cells decompose organic substances into

carbon dioxide and water, utilizing oxygen participation to release energy. Normal cells predominantly rely on mitochondrial oxidative phosphorylation to generate energy. Consequently, a strategic approach to alleviate hypoxia involves the inhibition of mitochondrial respiration, effectively reducing tumor oxygen consumption [61]. The FDA-approved antimalarial drug atovaquone selectively hampers mitochondrial electron transport, diminishes pyrimidine biosynthesis, and induces a sudden decline in mitochondrial membrane potential, impeding the reproduction of Plasmodium [62]. Zhang et al. introduced a novel treatment strategy for lung cancer using a light-enhanced nanoenzyme probe (AP-HAI) [63]. The ultra-small platinum nanoenzyme nPt generates •OH, contributing to tumor cell death. Under laser irradiation, Photothermal Therapy (PTT) facilitated by the photothermal converter AuP and IR780 effectively enhanced the H_2O_2 catalytic reaction. The encapsulated atovaquone successfully disrupts the tumor's respiratory metabolism, thereby preserving oxygen levels. This combined approach of nanoenzyme action and reduced oxygen consumption by atovaquone significantly amplifies the generation of Reactive Oxygen Species (ROS), synergizing with cancer catalytic therapy/ICD-based immunotherapy.

Inhibiting critical bioactive molecules in the anoxic pathway

Hypoxia-inducible factor-1 (HIF-1), functioning as a pivotal regulator governing cellular equilibrium and the expression of hypoxia-related genes, orchestrates the transcription of various target genes, significantly impacting tumor proliferation, metastasis, and the initiation and progression of tumors [64]. Despite being overexpressed in normal oxygenated cells, the protein level of HIF-1 remains low due to proteasome degradation, yet it can sustain stable expression in hypoxic cells. HIF-1 also participates in reshaping cancer cell metabolism, involving, among other processes, glucose, lipid, and amino acid metabolism [65]. Cai et al. devised MOF-based nanoparticles loaded with the HIF signaling inhibitor acriflavine and the immune adjuvant CpG [66]. A surface coating of hyaluronic acid specifically targets the overexpressed CD44 receptor, wherein acriflavine impedes the heightened survival signal induced by hypoxia after PDT, thereby inhibiting HIF-1α-mediated survival and metastasis. Moreover, these nanoparticles trigger a host immune response, synergistically amplifying the therapeutic impact of PDT.

Vascular endothelial growth factor (VEGF) and its receptor VEGFR, a tyrosine kinase receptor, play a crucial role in tumor angiogenesis. Hypoxia promotes the secretion of VEGF, which negatively impacts dendritic cell maturation, T lymphocyte proliferation, and upregulates the expression of programmed cell death protein 1 (PD-1) on CD8+T lymphocytes. This, in turn, inhibits the activation of immune cells. Therefore, inhibiting VEGF production can promote vascular normalization, improve tumor perfusion, and facilitate the transportation of activated immune cells to tumor sites, thereby enhancing immunotherapy [67]. Zhou et al. developed BSA-MHI148@SRF nanoparticles, consisting of sorafenib (SRF) and bovine serum albumin (BSA) modified with the near-infrared photodynamic material MHI148 (Fig. 3C) [68]. SRF is an inhibitor of serine/threonine kinase and receptor tyrosine kinase on tumor blood vessels. The BSA-MHI148@SRF nanoparticles exhibit rapid accumulation in tumors and exert anti-tumor effects through multiple mechanisms. These include: (i) SRF reducing tumor oxygen consumption by inhibiting mitochondrial respiration. (ii) Inhibiting VEGF to normalize tumor blood vessels, enhancing oxygen supply (Fig. 3D), and suppressing PD-L1 expression, thereby significantly reversing the immunosuppressive microenvironment within the tumor. (iii) Inducing production of ROS and enhancing ICD, while promoting T cell infiltration and enhancing tumor cell killing ability.

Affecting glucose absorption and metabolism

It is widely known that tumor cells primarily rely on glucose as their main energy source. Cutting off the glucose supply to tumor cells can be achieved through a treatment strategy known as starvation therapy [69]. Glucose oxidase (GOx) efficiently oxidizes glucose in tumor tissues, producing gluconic acid and H_2O_2. However, the hypoxic microenvironment of tumor tissues often limits the application of GOx. The emergence of photosensitive nanoenzymes has addressed this limitation, enabling the combination of oxygen supply, glucose consumption, and photothermal conversion in starvation therapy [70]. Wang et al. developed nanoenzymes by covalently linking three precious metals (gold, platinum, silver) with GOx, resulting in AuPtAg-GOx with catalase-like activity [71]. In tumors, AuPtAg-GOx can catalyze H_2O_2 to generate O_2 and efficiently consume glucose under aerobic conditions, thus achieving successful starvation therapy. Simultaneously, starvation therapy reduces ATP levels in tumors, indirectly inhibiting the synthesis of heat shock proteins (HSPs). This approach significantly enhances the sensitivity and efficacy of mild PTT. Importantly, mild PTT can promote the infiltration of immune cells, reversing the "cold" tumor state. Therefore, the integration of AuPtAg-GOx with α-PD-L1 can effectively enhance the effects of immune checkpoint blockade therapy and synergistically enhance the outcomes of ST, PTT, and immunotherapy. In addition to glucose oxidase-based approaches, another potential strategy for modulating glucose metabolism in tumor cells is through the use of glucose transporter 1 (GLUT1) inhibitors. Tumor cells

heavily rely on the GLUT1 transporter to uptake glucose [72, 73]. Miura et al. synthesized a glucose-coupled photosensitizer that targets GLUT1 [74]. Upon light induction, this photosensitizer inactivates GLUT1 protein and mediates PDT-induced cell toxicity through the EGFR/MAPK signaling pathway. However, this approach has not yet been applied in the field of photoimmunotherapy.

Abnormal energy metabolism in tumor cells enables their unlimited proliferation. The Warburg hypothesis highlights the abnormal glucose metabolism observed in tumors. Instead of relying on oxidative phosphorylation, cancer cells enhance anaerobic glycolysis to obtain energy, even in the presence of oxygen [75]. Targeting glucose metabolism offers a promising approach to control tumor growth and metastasis.

Metformin (Met), a medication commonly used for treating diabetes, has shown remarkable potential in tumor immunotherapy [76–78]. It not only reduces tumor hypoxia by decreasing oxygen consumption but also impacts memory CD8+T cells [79, 80]. Luo et al. designed a tumor vaccine that actively modulates immune cells [81]. They encapsulated tumor antigen, Met, and gold nanospheres within a PLGA microsphere carrier. Under NIR laser irradiation, the carrier shell expands, leading to the release of the encapsulated components. The release of Met down-regulates the NADH/NADPH ratio, activates AMPK, and shifts glycolysis towards fatty acid oxidation. This metabolic transformation enhances T cell survival and promotes the differentiation of CD8+T cells. Additionally, Met reduces the expression of PD-1, thus increasing its potential application in the field of immunotherapy.

In another study, the research group introduced 2-deoxy-D-glucose (2DG) to synergistically target glucose metabolism [82]. 2DG is a synthetic glucose analogue and the most extensively studied inhibitor of glucose metabolism. It acts as a competitive inhibitor of glucose by competing with glucose for hexokinase. Once inside the cell, 2DG is phosphorylated into 2DG-6-P, which cannot undergo further metabolism. The accumulated 2DG-6-P inhibits hexokinase and phosphoglucose isomerase, thereby interfering with glycolysis [73]. In this particular paper, laser irradiation was performed before and after 2DG injection to further inhibit glycolysis. By inhibiting glycolysis, 2DG indirectly reduces the synthesis of heat shock proteins HSP70 and HSP90. It also promotes endoplasmic reticulum stress (ERS) and synergistically enhances PTT-induced ICD. The intermittent administration of 2DG, along with the PTT mode, successfully increased the production of CD8+T cells and significantly inhibited primary tumor growth and metastasis.

In the later stages of glycolysis, pyruvate is converted into lactic acid by lactate dehydrogenase instead of being oxidized by the mitochondrial tricarboxylic acid cycle. This metabolic shift leads to the establishment of a glucose-deficient and lactic acid-rich immunosuppressive tumor microenvironment. This environment enables tumor cells to evade normal apoptotic processes and enhances their proliferation and migration capacities [83, 84]. Building upon this understanding, Yang et al. designed a self-assembled photothermal "nanodot" that electrostatically adsorbs lactate oxidase (LOX) [85]. LOX catalyzes the decomposition of lactic acid, producing H_2O_2. This approach reduces lactic acid efflux and alleviates the abnormal metabolism of tumor cells. The "nanodot" effectively promotes ICD through photothermal ablation of mouse breast tumors. Furthermore, it triggers the secretion of pro-inflammatory cytokines, recruits "immune-hot" cells, and reshapes the immunosuppressive TME. When combined with immune checkpoint blockade, CD8+T cell activity is restored, lung metastasis is completely eliminated, and hepatocellular carcinoma in Hepa1-6 mice is cured.

Interfering with amino acid metabolism

Another nutrient on which tumor cells depend for survival is glutamine, which is about 10–100 times as much as other amino acids for proliferating tumor cells [86]. Normal glutamine metabolism in cells can generate GSH, a well-known antioxidant. However, during phototherapy, the high levels of GSH in tumors can rapidly neutralize the ROS generated by PDT, thus diminishing its therapeutic efficacy. To address this issue, Mai et al. developed a carrier-free nano booster called C6SN. This nano booster self-assembles by combining the glutaminase inhibitor C968 and the photosensitizer Ce6 [87]. Upon release, C968 inhibits glutamine metabolism, preventing GSH from consuming the ROS produced during PDT. This inhibition amplifies intracellular oxidative stress, promoting ICD. Additionally, the treatment results in increased numbers of mature dendritic cells and related cytokines in mouse lymph nodes, as well as a reversal of the macrophage phenotype. Consequently, more cytotoxic T lymphocytes are recruited and activated. This strategy effectively reshapes the immunosuppressive tumor microenvironment, achieving the dual purpose of inhibiting primary and distant tumors.

The combination of ferroptosis and amino acid metabolism is a common approach due to their association with GSH depletion. Glutathione Peroxidase 4 (GPX4) serves as a core regulator in ferroptosis, and its activity reduction can mediate lipid peroxidation, effectively inducing cancer cell death. Xie et al. developed a metal-phenol nanosystem loaded with the PD-L1 inhibitor GW4869 to restore T cell function and enhance ferroptosis in tumor cells [88]. The nanosystem consisted of a phenolic polymer coordinated with the ferroptosis inducer Fe^{3+},

forming a metal-phenol network with excellent light absorption and heat conversion properties at 808 nm (Fig. 4A). Under acidic conditions, GW4869 was released, leading to the activation of anti-tumor immunity through dendritic cell maturation and T cell activation. Activated CD8+T cells proliferated and secreted interferon-gamma (IFN-γ), resulting in the down-regulation of cystine transport mediated by SLC7A11/SLC3A2. This, in turn, caused a decrease in GSH levels, inactivation of GPX4, and increased lipid peroxidation. Additionally, PTT-induced ICD and the hydroxyl radicals produced by the Fenton reaction of iron further promoted this cycle process, sustaining an anti-tumor immune response and reducing metastasis. While some studies have indicated that ferroptosis alone can evade immune responses by inhibiting immune cells in the tumor microenvironment, at least in this particular study [89], the combination of ferroptosis and phototherapy demonstrated excellent fluorescence/photoacoustic (FL/PA) tracking imaging capabilities and achieved a satisfactory immune effect (Fig. 4B&C).

Indoleamine 2,3-dioxygenase (IDO) expressed on antigen-presenting cells acts as both an immune checkpoint protein and a key rate-limiting enzyme in tryptophan metabolism. IDO converts tryptophan to kynurenine, regulating the cellular concentration of tryptophan and creating a "tryptophan starvation state," which in turn mediates the differentiation of T cells into regulatory T cells (Tregs) [90]. 1-methyl-DL-tryptophan (1-MT) is the first discovered competitive inhibitor of IDO. In human and mouse experiments, the administration of D-1-MT (also known as NLG8189) has been shown to eliminate tryptophan consumption, leading to T cell proliferation and activation [91]. Yang et al. developed nano-bullets coated with erythrocyte membranes for co-delivery of the photothermal agent IR1061 and the IDO-1 inhibitor 1-MT [92]. The erythrocyte membrane coating helps evade immune system clearance, prolongs circulation, and reduces in vivo drug leakage (Fig. 4D). Under near-infrared laser irradiation, PTT-induced ICD assists in the recruitment of CD8+cytotoxic T lymphocytes. Heat-sensitive nitric oxide (NO) donors released during the process normalize tumor vessels and relieve hypoxia. Simultaneously, 1-MT interferes with tryptophan metabolism pathways and reprograms the immunosuppressive tumor microenvironment into an immunostimulating phenotype in collaboration with NO. This combined approach improves the therapeutic efficacy against primary breast cancer and metastatic tumors. Additionally, another small-molecule IDO inhibitor called NLG919 has shown promising results in regulating tryptophan metabolism [93–95]. However, despite

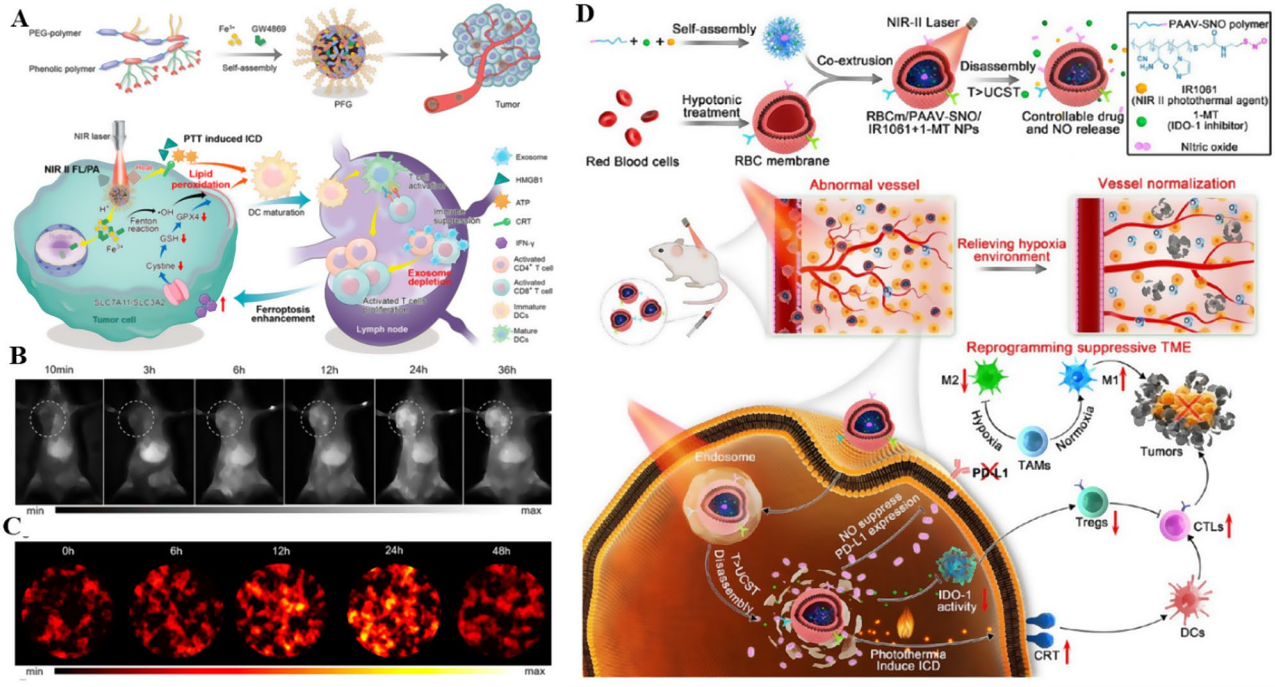

Fig. 4 Nano-drug delivery systems regulate abnormal tumor metabolism. (**A**) Photoimmune mechanism of PFG MPNs in alleviating exosomal immunosuppression, enhancing ferroptosis and immune stimulation. (**B**) NIR II fluorescence imaging of B16F10 tumor-bearing mice after intravenous injection of PFG MPNs (λ_{ex} = 808 nm). (**C**) Photoacoustic imaging of tumor region (λ_{ex} = 808 nm) (Adapted with permission from reference [88]) (**D**) Schematic diagram of the structure, release process, and reprogramming of the tumor immunosuppressive microenvironment of erythrocyte membrane camouflage nano-bullet (Adapted with permission from reference [92])

these successes in the laboratory setting, the failure of IDO inhibitors in phase III clinical trials several years ago indicates that there is still a long way to go before these inhibitors can be successfully applied in clinical practice [96].

Amino acid metabolism plays a crucial role in tumor growth, and certain amino acids such as arginine, serine, and asparagine have been found to have significant effects. L-arginine (L-Arg) supplementation has been shown to prolong the survival of T cells, enhance the formation of memory T cells, and improve tumor killing [97–99]. However, to date, arginine has primarily been used as a NO donor. For example, Feng et al. designed a GSH-responsive "nano-bomb" called L-Arg/MB@MP [100]. Under PDT, this nano-bomb generates a large amount of ROS, some of which oxidize L-Arg to produce NO. The released NO not only regulates vasodilation but can also be used for gas therapy (GT). This combination therapy of PDT and GT induces G2/M cell cycle arrest, amplifies the anti-tumor immune response, and depletes GSH levels.

Targeting tumor-associated cells

The tumor microenvironment consists of various cell types, including tumor cells, immune cells, fibroblasts, and epithelial cells [101]. The interactions between these cells and tumor cells play a critical role in the growth and progression of tumors.

Tumor-associated macrophages

Macrophages, which are the most abundant immune cells in the tumor microenvironment, play a significant role in immune evasion according to compelling evidence. Typically, macrophages are classified into two populations with distinct functional characteristics: M1 and M2, which are polarized from naive macrophages (M0) [102]. M1 macrophages are known for their production of numerous ROS, NO, and cytokines such as IL-12 and TNF-α. They possess robust antigen presentation capabilities and can induce a Th1 immune response, making them effective in tumor eradication [103]. On the other hand, M2 macrophages express mannose and galactose receptors and secrete anti-inflammatory cytokines like IL-10 and TGF-β [104]. They modulate and promote a Th2 immune response while participating in immune regulation and angiogenesis. Tumor-associated macrophages exhibit characteristics similar to M2 macrophages since they are exclusively found in the tumor environment and do not belong to either M1 or M2 populations [105]. The polarization of TAMs is believed to be driven by the tumor's rapid cell proliferation, resulting in a hypoxic and glucose-deficient microenvironment [106]. Further investigations have revealed that TAMs hinder the activation of CD8+T cells, expedite the recruitment of Tregs, and collaborate with other cells like myeloid-derived suppressor cells to suppress anti-tumor immune responses [107].

So far, the development of drugs against tumor-associated macrophages has primarily been divided into three strategies: (i) Repolarizing TAMs from the M2 phenotype to the M1 phenotype (Fig. 5); (ii) Promoting apoptosis of TAMs; (iii) Reducing TAM recruitment by the tumor microenvironment and promoting their depletion [108, 109]. The overarching idea is to increase the M1/M2 ratio, reverse the immune state of the tumor, and prevent metastasis. Yang et al. constructed PVP-modified BiFeO3/Bi2WOs nanoparticles (BFO/BWO-PVP NPs) to alleviate hypoxia and reshape the immunosuppressive TME through PDT and radiotherapy [110]. Under 660 nm irradiation, the percentage of M2-TAMs (CD45+F4/80+CD206+) was three times lower than that of the control, while the percentage of M1-TAMs (CD45+F4/80+CD80+) was 2.3 times higher than that of the control. After combined RT, these percentages increased to 4.4 times and 2.6 times, respectively. These results confirmed that BFO/BWO-PVP NPs decomposed into O_2 through H_2O_2, thereby relieving tumor hypoxia in situ. O_2, as a functional gas molecule, can also alleviate hypoxia-induced inhibition of hypoxia-inducible factor-1α (HIF-1α) in vivo, effectively repolarizing TAMs from the M2 phenotype to the M1 phenotype. Cooperation with RT to activate and recruit cytotoxic lymphocytes (CLTs) can further enhance immune memory, inhibit tumor recurrence, and metastasis.

Epigenetic regulation by inhibiting class IIa histone deacetylases (HDACs) is a promising method for utilizing the anti-tumor potential of macrophages, as it can repolarize M2-TAMs into M1-TAMs by modifying their epigenetic profile [111]. Biomimetic nanoparticles carrying the TAM repolarizer TMP195 were used to reshape the inflammatory microenvironment after PTT [112]. The results demonstrated that the proportion of M1-TAMs increased to 52.0%, while the proportion of M2-TAMs decreased to 27.8%. Consequently, the tumor elimination rate increased from 10% after PTT to 60%.

Cancer-associated fibroblasts

Cancer-associated fibroblasts constitute the primary components of the tumor matrix and play a critical role in tumor invasion. In normal tissues, non-malignant fibroblasts regulate the structure and function of tissues and facilitate tissue repair by producing the extracellular matrix, including collagen. However, in cancerous tissues, which can be likened to a persistent wound, fibroblasts undergo continuous activation [113]. These "activated" fibroblasts are referred to as cancer-associated fibroblasts or tumor-associated fibroblasts (TAFs). CAFs possess the ability to remodel the ECM, promote

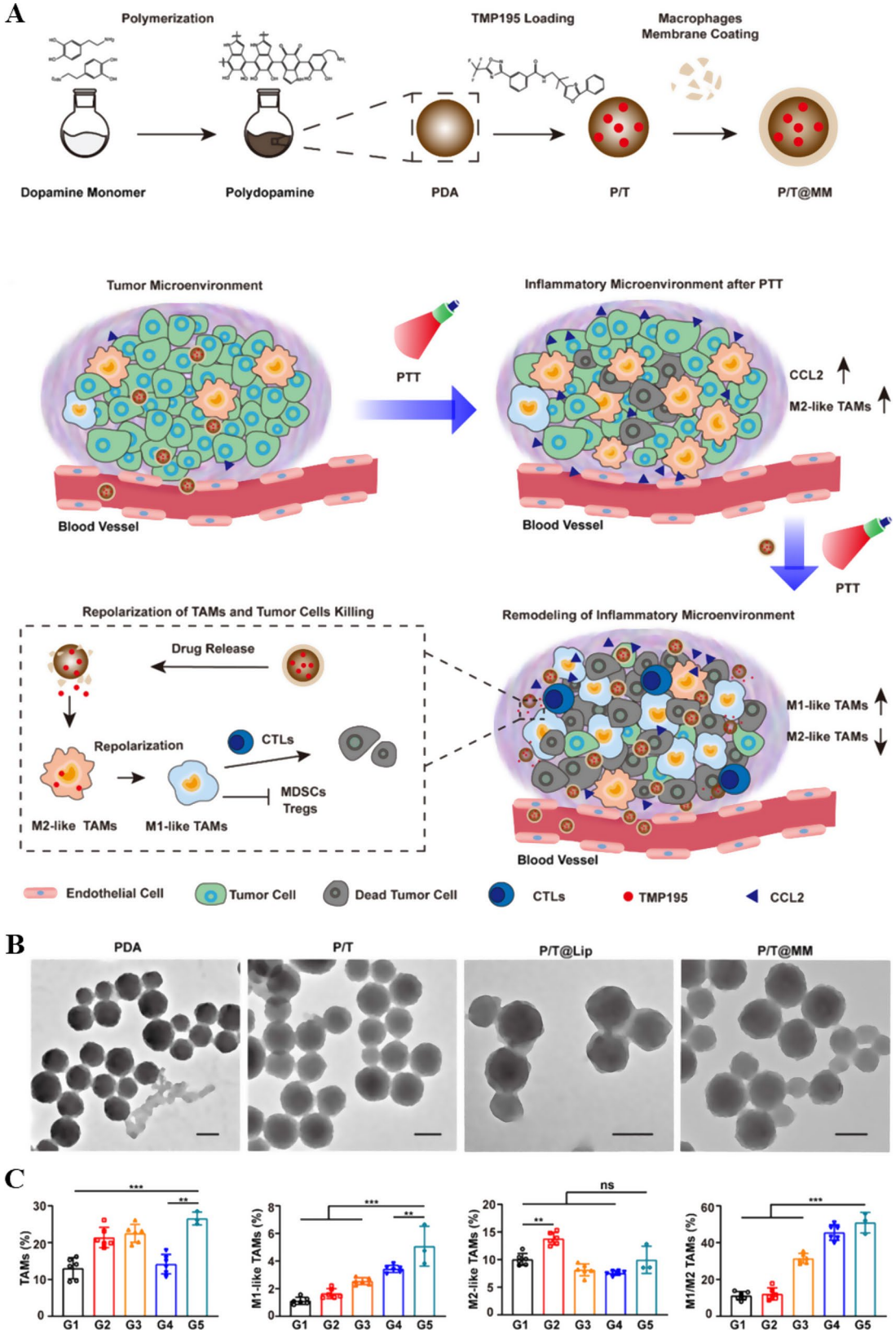

Fig. 5 Strategies for repolarization TAM based on nanomaterials. (**A**) Schematic illustration of preparation and antitumor strategy of P/T@MM NPs. (**B**) TEM images of different groups of nanoparticles. (**C**) Quantification of TAMs, M1-like TAMs, and M2-like TAMs, and the ratio of M1/M2 TAMs infiltrated in tumor tissues (Adapted with permission from reference [108])

tumor growth, angiogenesis, inflammation, and metastasis, as well as contribute to immune evasion and drug resistance. For instance: (i) CAFs can generate matrix metalloproteinases (MMPs) and plasminogen activators that degrade the ECM, leading to a disruption of ECM remodeling and facilitating tumor cell invasion; (ii) CAFs induce the secretion of stromal cell-derived factor-1 (SDF-1), which in turn stimulates the production of VEGF. This promotes angiogenesis and exacerbates hypoxia; (iii) Moreover, CAFs increase tissue fluid pressure and form a dense barrier within the tumor tissue. Consequently, nanocarriers are unable to penetrate deeper into the tumor sites, leading to a decrease in the EPR effect [114–118]. Overall, CAFs play a significant role in shaping the tumor microenvironment and facilitating tumor progression by modulating ECM, promoting angiogenesis, and impeding effective drug delivery to tumor sites [119].

Alba et al. conducted a study where they developed nanoparticles to normalize the stiffness of cholangiocarcinoma tumors rich in cancer-associated fibroblasts [120]. They observed that these nanoparticles exhibited preferential targeting towards CAFs, and by depleting CAFs through PTT, the tumors completely regressed. However, depleting CAFs may exacerbate immunosuppression and promote tumor growth. To address this concern, Li et al. proposed an alternative strategy of reprogramming CAFs instead of depleting them, aiming to reduce the tumor extracellular matrix [121]. They encapsulated indocyanine green (ICG) and calcipotriol (Cal), which induce the inactivation of CAFs, within tumor cell-derived cell microparticles (MPs) for targeted delivery to tumor tissues (Fig. 6A). The Cal/ICG@MPs effectively regulated myofibroblasts, shifting them to a resting state and reducing collagen content. This led to a decrease in α-smooth muscle actin (α-SMA) expression and collagen fiber deposition (Fig. 6B), facilitating ECM remodeling and subsequent penetration of Cal/ICG@MPs into tumors. This strategy successfully enhanced CD8+T cell antigen-mediated activation-induced cell death induced by CAFs, activated CD8+T cell-mediated anti-tumor immunity, and triggered long-term immune memory. Additionally, homologous targeting mechanisms can be employed for specific CAF targeting. Li et al. utilized activated fibroblast membrane-coated nanoparticles, which exhibited stronger tumor accumulation compared to cancer cell membrane-coated nanoparticles [122]. This approach involved combining PDT and PTT for NIR fluorescence/PA cancer diagnosis and treatment. These studies demonstrate different strategies for targeting CAFs, either depleting them or reprogramming them, to modulate the tumor microenvironment and enhance anti-tumor immune responses, ultimately improving cancer treatment outcomes.

Cancer-associated fibroblasts exhibit a distinct biological phenotype, and their surface molecular markers include fibroblast activation protein (FAP), α-SMA, vimentin, among others [123, 124]. FAP, specifically, is a type II membrane-bound glycoprotein belonging to the serine oligopeptidase family. It is minimally expressed or absent in normal tissues but shows high specificity and expression on the surface of CAFs, making it a commonly used marker for identifying CAFs [125]. Due to its enzymatic activity, FAP is involved in the degradation and remodeling of the tumor matrix, facilitating the detachment of tumor cells from the primary site, and promoting distant metastasis. Additionally, FAP can induce the conversion of macrophages from an M1 phenotype to an M2 phenotype, thereby promoting the growth and migration of tumor cells and tumor-associated macrophages through the PTEN/AKT and MEK/ERK signaling pathways [126]. In a study by Yu et al., a FAP-α-responsive and heat-sensitive liposome was developed to overcome the delivery and treatment challenges associated with the fibrotic matrix in pancreatic cancer [127]. In the presence of FAP-α and laser irradiation, small albumin nanoparticles (approximately 10 nm) loaded with BMS-202 (an immune checkpoint inhibitor)were released from the liposome, which had a size of about 120 nm. Mild hyperthermia not only facilitated the release and effectiveness of BMS-202 but also enhanced tumor blood perfusion and the recruitment of immune cells. Following treatment, drug accumulation in pancreatic cancer increased, immune responses were significantly enhanced, and the risk of tumor metastasis decreased.

Natural killer cells (NK cells)

NK cells represent a prominent subset of innate lymphocytes that play a crucial role in mediating anti-tumor and antiviral responses without the requirement for prior sensitization to target cells. They are vital immune cells within the human body. NK cells serve as a double-edged sword, as they are involved not only in anti-tumor, antiviral, and immune regulatory functions but can also contribute to hypersensitivity reactions and autoimmune diseases in certain cases [128]. NK cells possess the ability to recognize target cells and directly lyse them by releasing toxic granules such as perforin and granzyme through exocytosis. They can also induce apoptosis in target cells by activating the expression of FAS ligand (FASL) and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on NK cells. Additionally, activated NK cells can recruit other immune cells and elicit a secondary immune response by synthesizing and secreting cytokines such as IFN-γ, tumor necrosis factor-alpha (TNF-α), and chemokines [129]. NK cells engage in various levels of crosstalk with dendritic cells, macrophages, and T cells. While NK cells can induce apoptosis in

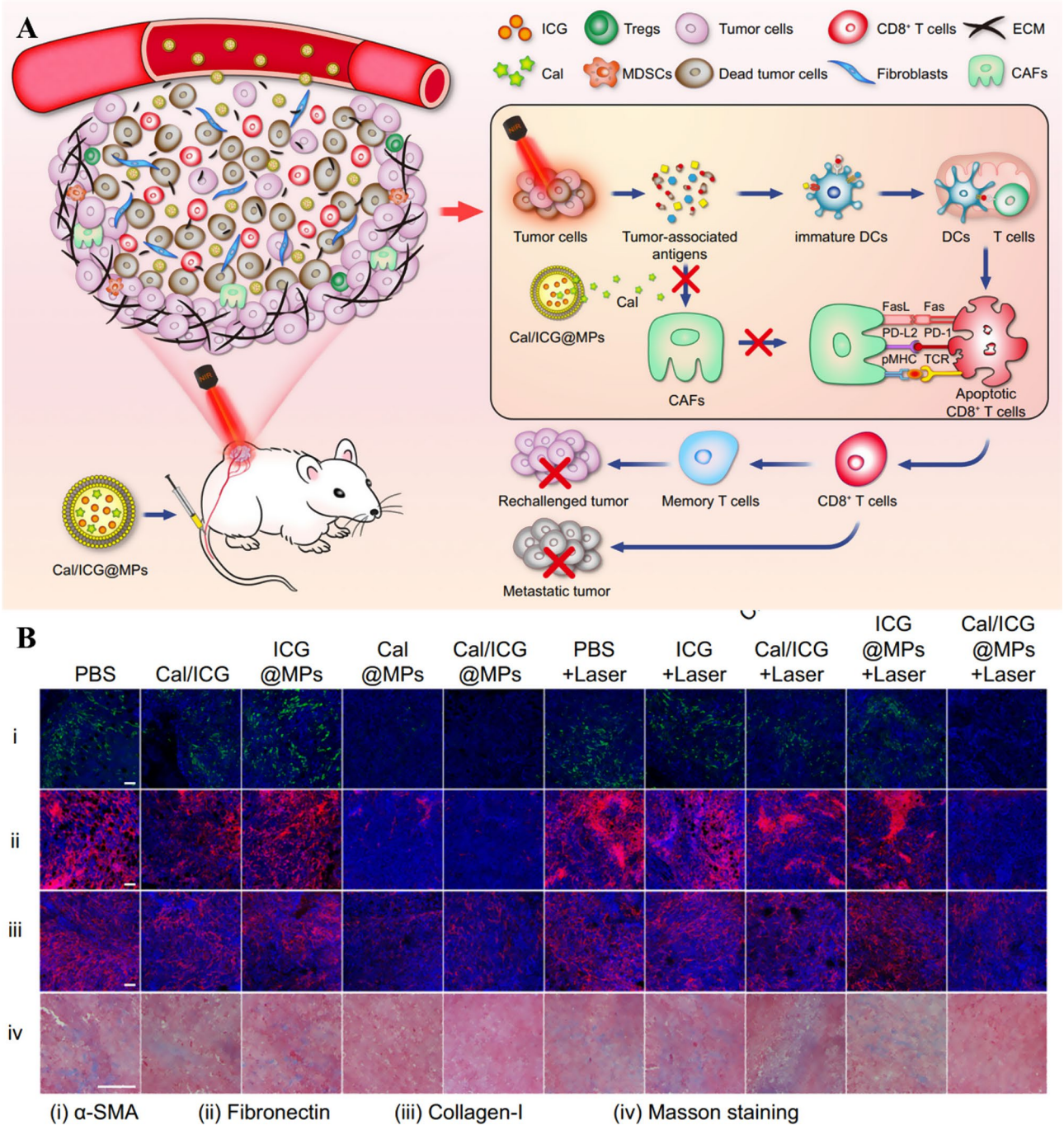

Fig. 6 Effects of nano-drug delivery systems on cancer-associated fibroblasts (CAFs). (**A**) Schematic illustration of Cal/ICG@MPs as an effective drug for regulating CAFs to improve the efficacy of PTT. (**B**) Immunofluorescence staining of α-SMA, fibronectin, and collagen-I, and Masson's trichrome staining of collagen in tumor sections of stroma-rich H22 tumor-bearing mice after treatment (Adapted with permission from reference [121])

immature DCs, in activated NK-DC co-culture experiments, the production of TNF-α increases at low NK/DC ratios, which promotes DC maturation [130, 131].

NK cell response to established and advanced solid tumors is often insufficient. To achieve effective NK cell-based immunotherapy, two prerequisites need to be addressed: improving the targeting and infiltration of NK cells into tumors and restoring/enhancing NK cell functionality [132]. NK cell immunotherapy is associated with the activation and recognition of the NK group 2, member D (NKG2D) receptor on the surface of NK cells and its ligands (NKG2DLs) expressed on tumor cells. Malignant tumors can evade NK cell recognition and clearance by shedding and lysing NKG2DLs, such

as MICA and MICB, thus promoting immune evasion. Consequently, small molecule inhibitors can be utilized to block the shedding of MICA/MICB on tumor cell surfaces and reactivate the anti-tumor immune function of NK cells. Liu et al. developed a dual-responsive biological nanosystem based on matrix metalloproteinase-2 (MMP-2) and laser stimulation for NK cell-mediated immunotherapy of melanoma (Fig. 7A) [133]. The nanosystem internally encapsulated SB-3CT, which is known to regulate NKG2DL expression and shedding, thereby enhancing cancer cell recognition by NK cells. SB-3CT and Ce6 (a photosensitizer) were released in response to the MMP-2-rich tumor microenvironment and 660 nm laser irradiation. SB-3CT mitigated tumor immune escape by antagonizing MMP-2 and promoting the NKG2D/NKG2DL pathway. The photoimmunotherapy mediated by this nanosystem induced cytotoxicity, significantly enhanced NK cell infiltration into tumors by up to 148 times, and upregulated the expression of MICA and ULBP-1, resulting in synergistic inhibition of tumor growth. Similarly, in a study by Wang et al., a combination of low molecular weight citrus pectin expressing β-galactoside-binding protein galectin-3 and PDT was employed to reduce the affinity of major histocompatibility complex (MHC) proteins to NKG2D [134]. This approach effectively achieved immunotherapy for melanoma.

Indeed, recent research has revealed that NK cells possess immune memory functions, representing a significant breakthrough in our understanding of their capabilities. It was traditionally believed that immune memory was a distinctive feature of mammalian T cells and B cells. However, the discovery of immune memory in NK cells has expanded their potential application in the field of immunology [135]. This newfound understanding means that NK cells can exhibit a stronger and more efficient response upon encountering the same pathogen for a second time. This memory response allows NK cells to mount a rapid and targeted immune defense, contributing to the clearance of pathogens and providing enhanced protection against reinfection. Interestingly, human and mouse memory NK cells can be induced by IL-12, IL-15, and IL-18 stimulation, which provides a good opportunity for the future development and clinical application of cytokine-induced memory-like (CIML) NK cells in the field of anticancer [136, 137].

Myeloid-derived suppressor cells

Myeloid-derived suppressor cells represent a heterogeneous group of immature myeloid cells that serve as precursors for macrophages, dendritic cells, and granulocytes. They are a significant component of the immunosuppressive network. In pathological conditions like tumors and inflammatory infections, MDSCs remain in an undifferentiated state due to impediments in the mechanisms of mature differentiation. MDSCs possess the ability to effectively suppress T cell activity and diminish the production of IFN-γ by consuming metabolites essential for maintaining T cell function. Through the upregulation of PD-L1 expression and the production

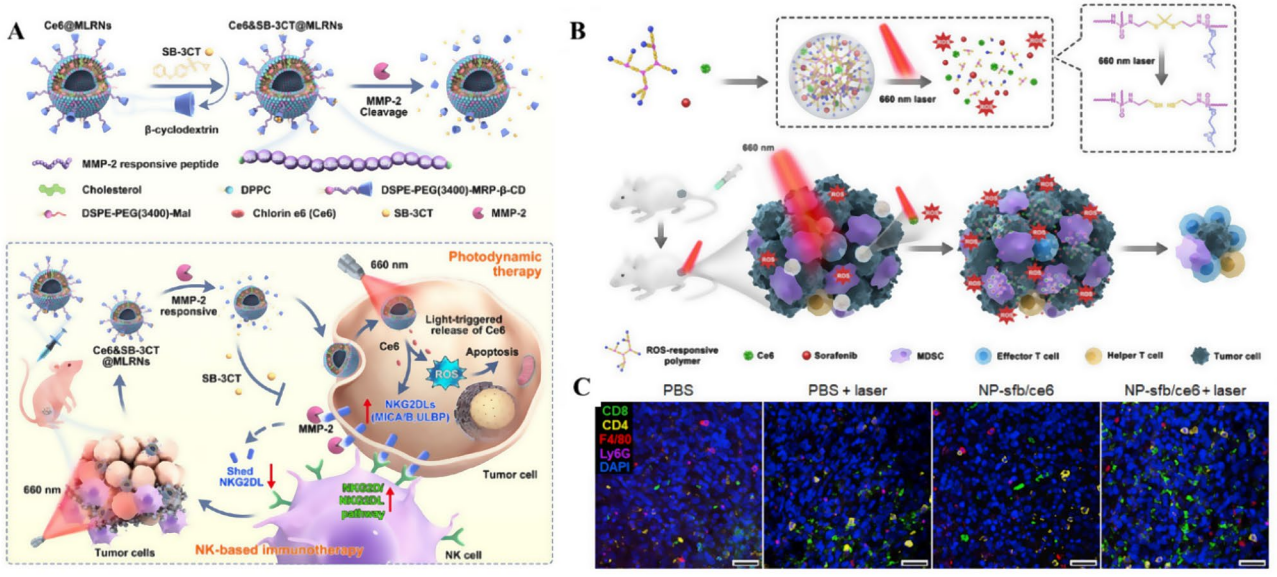

Fig. 7 Effects of nano-drug delivery systems on other tumor-associated cells. (**A**) Schematic illustration of preparation technology of Ce6&SB-3CT@MLRNs, dual-responsive drug release and mechanism of improving photodynamic immunotherapy for tumor (Adapted with permission from reference [133]) (**B**) Schematic illustration of ROS-activated cascade release of sorafenib synergistically enhances the antitumor effects of PDT. (**C**) CLSM images show the distribution of effector T cells, helper T, TAMs and MDSCs in tumor sections at the end of the tumor inhibition experiment (Adapted with permission from reference [138])

of Arg-1, iNOS, and ROS, MDSCs induce immunosuppression. Furthermore, they communicate with NK cells, leading to the inhibition of NK cell activity, which contributes to the immune evasion of malignant tumors [139, 140]. Additionally, MDSCs participate in extracellular matrix remodeling and promote mesenchymal-epithelial transformation, thereby facilitating tumor metastasis. Overall, targeting MDSCs holds great promise in alleviating immunosuppression, reshaping the immunosuppressive microenvironment, and supporting cancer immunotherapy in the future.

Several strategies for targeted MDSC therapy are currently being investigated, including selective elimination, induction of maturation, blocking of function, and inhibition of amplification [141, 142]. One drug used for selectively scavenging MDSCs is gemcitabine (GEM), which specifically inhibits the activation of the JAK/STAT3 pathway, thereby impeding the generation of MDSCs while sparing other T cells. In a study by Chen's team, they employed a photosensitizer-based porous metal-organic framework (pMOF) as the core of the therapy [143]. They electrostatically adsorbed a shell of DNA-gemcitabine prodrug (DGLs) and enveloped it with a periosteum-targeted DNA aptamer for active targeting. PDT was utilized to enhance tumor penetration of the nanoparticles by inducing cross-linking destruction and matrix degradation. This approach led to a reduction in the number of MDSCs by nearly 40% and an increase in the M2/M1 ratio.

In certain studies, PDT alone has been associated with an immunosuppressive effect, accompanied by increased expression of Tregs and myeloid-derived suppressor cells. This may be attributed to PDT inducing the expression of cyclooxygenase-2 (COX-2) through the platelet-activating factor (PAF) pathway. COX-2 is an important factor in the accumulation and activation of MDSCs. To mitigate the immunosuppression induced by PDT, selective COX-2 inhibitors are utilized to inhibit the function of MDSCs and improve the therapeutic efficacy against solid tumors (Fig. 7B and C) [138, 144]. Sunitinib, a known compound, has been demonstrated in previous studies to reduce the accumulation of MDSCs in peripheral blood, restore T cell function, and block VEGFRs. It indirectly reverses the immunosuppressive state of MDSCs. Domvri et al. combined sunitinib with Norvaline, which can correct T cell subsets and restore immune balance [145]. Copper sulfide nanocarriers, with their high photothermal conversion efficiency, facilitate the biodegradation and scavenging of MDSCs after depletion or functional inactivation under laser irradiation. This approach enables the reactivation of the immune response in lung tumors, leading to an increase in cytotoxic T lymphocytes, a reduction in MDSC infiltration, downregulation of immunosuppressive Foxp3+Treg cells, and alleviation of tumor immunosuppression. Additionally, the acid ceramidase inhibitor LCL521 has shown promise in reversing the tumor-impeding effects of PDT by Tregs and MDSCs while effectively restoring immune function [146].

Nanomedicine-based combination of phototherapy and immunotherapy

Phototherapy plus Immune checkpoint inhibitors

The principle of immune checkpoint blocking therapy is rooted in the activation mechanism of T cells, which are pivotal immune cells for tumor restriction. Immune checkpoints are present on the surface of T cells, while their corresponding ligands are expressed on the surfaces of tumor cells and myeloid suppressor cells. Upon activation, immune checkpoints hinder the presentation of antigens to T cells, thereby suppressing the immune function of T cells. Consequently, T cells are unable to effectively eliminate tumor cells, allowing the tumor cells to evade immune surveillance [147]. Immune checkpoint inhibitors (ICIs) work by blocking the interaction between immune checkpoints and their ligands, thereby restoring the cytotoxic function of tumor-specific T cells and reactivating immune cells to exert an anti-tumor effect. Several ICIs have gained approval from the Food and Drug Administration (FDA) for treating various cancers, including melanoma, Hodgkin's disease, head and neck cancer, bladder cancer, and non-small cell lung cancer [148]. The elucidation of the immune function of Cytotoxic T-lymphocyte antigen-4 (CTLA-4) in the 1990s marked the beginning of the emergence of more ICIs. Examples include the well-known Programmed cell Death protein 1/Programmed cell Death Ligand 1 (PD-1/PD-L1) pathway, as well as Lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin domain and mucin domain-3 (TIM-3), T cell Immunoglobulin and ITIM Domain (TIGIT), and others [149]. Despite the significant impact of ICI development on cancer treatment strategies, it is important to note that only a minority of patients (approximately 10–40%) experience long-term responses to certain tumors (such as liver cancer), while some cancers, like pancreatic cancer, exhibit limited or no response to ICB therapy [150–152].

Currently, the most widely used antibodies in clinical practice for immune checkpoint blockade therapy are PD-1/PD-L1 antibodies (e.g., Pembrolizumab, approved in 2014) and CTLA-4 antibodies (e.g., Ipilimumab, approved in 2011). Duan and his colleagues hypothesized that phototherapy could enhance the immunogenicity of tumors, thereby rendering them sensitive to ICB therapy [153]. This hypothesis aimed to expand the application of ICB therapy to metastatic cancers. Subsequent experiments confirmed that the combination of PDT with anti-PD-L1 antibodies promoted the infiltration of

CD8+T cells into tumors and induced apoptosis in vivo. Photosensitive nanoparticles addressed the limitation of 4T1 tumors not responding to anti-PD-L1 therapy and effectively eliminated primary tumors while controlling unirradiated distal tumors. Following, an increasing number of studies have investigated the combination of photothermal nanoparticles with ICIs to prevent tumor recurrence and metastasis [154–159]. For instance, Wang and colleagues developed up-conversion nanoparticles (UPNPs) loaded with dual photosensitizers (ICG and rose bengal) for selective PTT [160]. They coated DSPE-PEG-mal to enhance the capture ability of tumor-derived proteins as antigens (Fig. 8). When combined with anti-CTLA-4 therapy, which is known to have a clinical response rate of less than 10% in triple-negative breast cancer, the response rate increased to 34% in animal experiments, and more than 80% of mice survived for an extended period. Upon NIR laser irradiation, the UPNPs demonstrated excellent photothermal and photodynamic capabilities, simultaneously releasing DAMPs to trigger ICD and induce T cell activation throughout the body. These studies highlight the potential of combining phototherapy with ICIs as a promising approach to enhance treatment outcomes and promote immune responses against tumors.

Phototherapy plus anti-CD137

In addition to ICIs, the tumor necrosis factor receptor/ligand superfamily also plays a crucial role in reactivating "dormant" T cells. Among these, CD137 is a member of the tumor necrosis factor receptor superfamily and can transmit co-stimulatory signals to T cells, leading to their proliferation, survival, and memory formation [161, 162]. Rather than focusing on immune checkpoints like PD-1 and CTLA-4 to reverse T cell immunosuppression, antiCD137 mAb (aCD137) targets and activates CD137 (4-1BB) [163]. Engagement of this co-stimulatory molecule, expressed on activated T cells and various immune cells, triggers activation of CD4+and CD8+T cells, aiding in tumor clearance. Urelumab and utomilumab, two aCD137 antibodies in clinical development, function by activating CD137 on immune effector cells [164]. However, while aCD137 has shown promise in early clinical trials, its broader application has been limited. This suggests that a strategy reliant solely on T cell activation, lacking antigen targets for activated T cells, might be inadequate for comprehensive tumor eradication. Cano-Mejia et al. utilized Prussian blue nanoparticles (PBNPs) for photothermal treatment of neuroblastoma, demonstrating that their administration is immunogenic and significantly improves survival rates in neuroblastoma-bearing mice [165]. Nevertheless, these effects are not robust enough to entirely eradicate distal neuroblastoma tumors or metastases. Consequently, the researchers combined the PTT with anti-CD137 (aCD137) treatment to specifically target and activate CD137 for photothermal treatment of SM1 melanoma [166]. This combination approach resulted in systemic immune activation, upregulation of immunostimulatory molecules related to antigen presentation, generation of CD4 and CD8+T cell memory, and reduction of hepatotoxicity. By harnessing the potential of CD137 activation in conjunction with phototherapy, this research aimed to enhance the immune response against melanoma and overcome the insensitivity to traditional ICI treatment. The combination strategy demonstrated promising results in terms of systemic immune activation and the development of durable immune memory, providing a potential avenue for improving melanoma treatment outcomes.

Phototherapy plus immunoadjuvants

Immunoadjuvants are substances that can enhance or modify the body's specific immune response to antigens in a non-specific manner. Adjuvants can be immunogenic or non-immunogenic. When injected with an antigen, immunoadjuvants offer several benefits, such as improving the stability of the immunogen, reducing the required dosage of the immunogen, and prolonging the duration of action [167]. In certain cases, PTT alone may not be sufficient to completely inhibit tumor growth. However, the addition of immune adjuvants can help address this limitation.

Currently, aluminum adjuvants are the most commonly used immunoadjuvants. Additionally, manganese has also been identified as a "messenger" of immunity. Chen et al. demonstrated the synergistic use of MnO_2, a metal-based photothermal agent, and DOX to improve the efficiency of ICD induction [168]. MnO_2 nanostructures can react with H^+ or GSH in the tumor microenvironment, leading to the formation of Mn^{2+} ions, which act as effective immune adjuvants. In their study, BSA/MnO_2 nanoparticles exhibited high photothermal conversion efficiency, and MnO_2 decomposed in an acidic environment, releasing DOX and enhancing the killing efficacy against 4T1 cells. Importantly, MnO_2 possesses catalase-like activity, facilitating the breakdown of H_2O_2 into O_2 within cells, thereby relieving tumor hypoxia. This feature holds significant promise for future applications.

Dendritic cells express Toll-like receptors (TLRs), which activate genes associated with acquired immunity, promote the maturation of antigen-presenting cells, produce relevant cytokines, and regulate Th1 and Th2 immune responses. To date, eleven members of the TLR family have been identified, with TLRs playing a critical role as immunoadjuvants. Lipopolysaccharide (LPS) is the natural ligand for TLR-4. Ye et al. utilized LPS and GM-CSF (granulocyte-macrophage colony-stimulating factor, an immune stimulator) as a

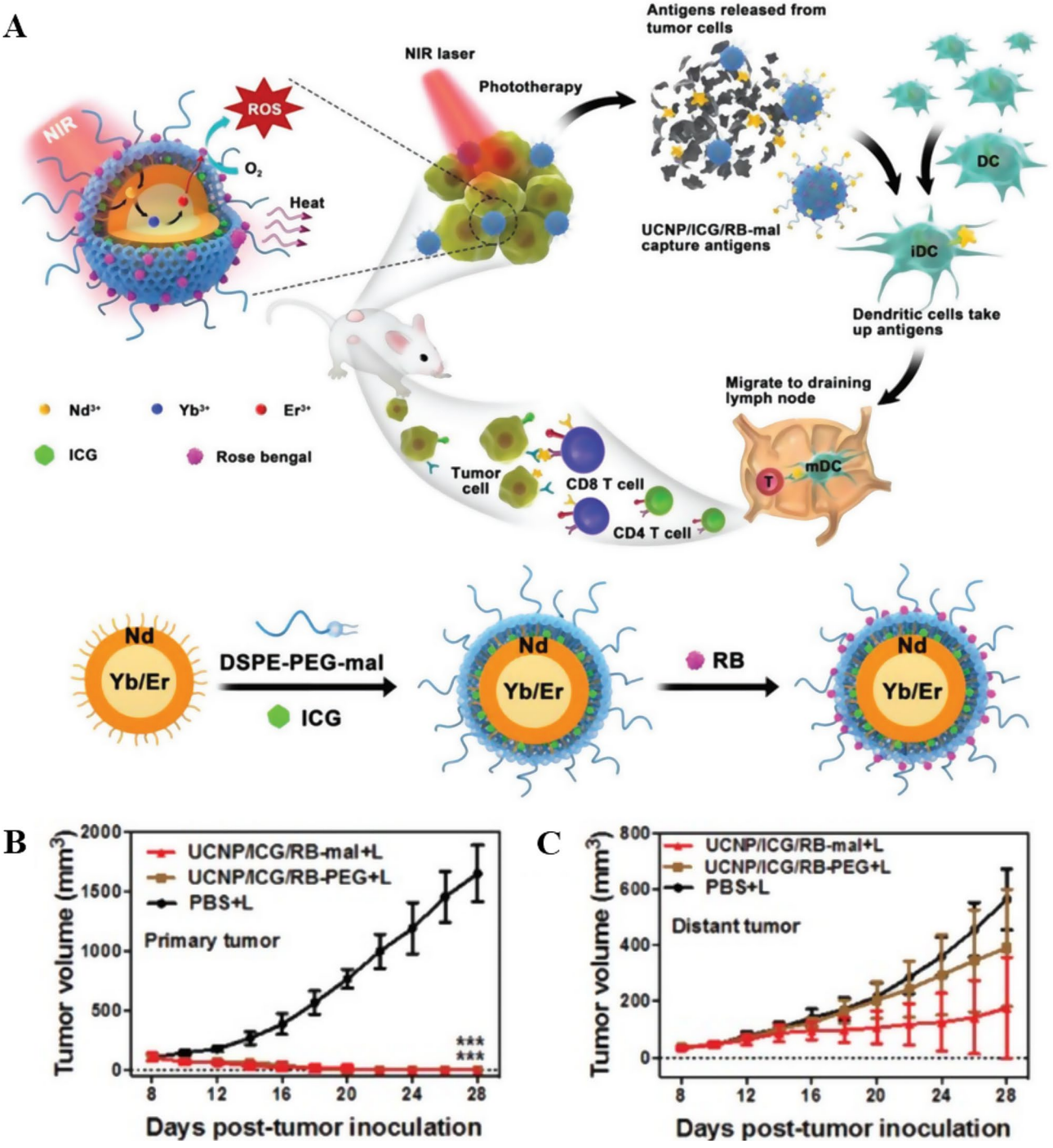

Fig. 8 Strategy for combining phototherapy with immune checkpoint blocking. (**A**) Schematic illustration of mechanism and preparation process of near infrared triggered antigen capture UCNP/ICG/RB-MAL nanoplatform for photoimmunotherapy. (**B**) Growth curve of primary tumor volume in mice with different treatment groups. (**C**) Growth curve of distal tumor volume of mice in different treatment groups (Adapted with permission from reference [160])

combined immunoadjuvant [169]. In their study, they incorporated bionic cancer cell membrane-encapsulated black phosphorus nanovesicles (BPQD-CCNVs) into a thermosensitive hydrogel containing the two adjuvants. After subcutaneous injection and NIR laser irradiation, the hydrogel generated local heat and gradually released LPS and GM-CSF to recruit and activate DCs, thereby inducing a robust immune response. Animal experiments showed a significant increase in the density of CD11c+dendritic cells and the percentage of the T cell proliferation marker Ki67 to varying degrees. Furthermore, the addition of a PD-1 antibody helped restore the

functionality of depleted CD8+T cells, reduced tumor metastasis, minimized the recurrence rate following tumor resection, and prolonged the survival time of mice.

Another commonly used new adjuvant is cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODN), which can stimulate the production of IFN-α/β/γ, IL-12, and IL-18 by DCs, promoting a Th1 immune response [170, 171]. Xu et al. employed black porous silicon (BPSi) as a carrier for DOX and utilized CpG ODN to enhance immunotherapy [172]. By extending the duration of laser irradiation, the immune response was intensified, resulting in the selective upregulation of IL-2, IFN-γ, and TNF-α without causing a cytokine storm.

It is important to highlight that certain nanomaterials, due to their inherent properties, have been found in previous studies to impact the immune response by influencing the function of dendritic cells in antigen presentation. This suggests that nanomaterials can be utilized as immunoadjuvants for tumor treatment. The nano-platform black phosphorus (BP), mentioned earlier, possesses adjustable size, low toxicity, and high biocompatibility, making it an efficient drug delivery carrier [173]. BP nanomaterials not only exhibit excellent photothermal performance but can also serve as a contrast agent for PA imaging, offering promising possibilities for integrated tumor diagnosis and treatment. Moreover, BP itself possesses anti-cancer biological activity, allowing for potential applications in "nano-phosphorus therapy" by affecting cell division progress [174]. In addition, Alessandra et al. also found that carbon nanotubes could regulate the immune response of dendritic cells [175].

Tumor-derived cell membrane fragments can act as specific antigens and trigger antigen-specific immune responses [176–178]. In another investigation, Prussian blue (PB) nanoparticles, docetaxel (DTX), and TLR-7 agonist imiquimod (R837) were loaded into PLGA shells coated with cancer cell membranes, resulting in nanospheres with specific homologous targeting capabilities (Fig. 9) [179]. This enhanced the accumulation and uptake of nanospheres at tumor sites. The incorporation of R837 with TAAs produced by PTT resulted in an increased proportion of CD80+CD86+DCs, stimulated DCs to secrete more cytokines, and exhibited vaccine-like functions. Furthermore, the nanospheres demonstrated enhanced PA imaging and T1-weighted MR imaging effects, emphasizing the efficacy and potential of a multi-pronged cocktail therapy approach.

Furthermore, even in the absence of ICIs or chemotherapy drugs that induce ICD, the combination of immunoadjuvants with PTT can still yield positive treatment outcomes. Chen's research team incorporated the TLR-7/8 agonist resiquimod (R848) into the photothermal nano-shell [180]. This approach promoted dendritic cell maturation, reversed the tumor microenvironment, and transformed the tumor from an "immunosuppressive" state to an "immunogenic" state, thereby eliciting a systemic immune response. Simultaneously, when subjected to 808 nm laser irradiation, low-temperature hyperthermia (at 41–45 °C) minimized heat diffusion, aiding in the eradication of the primary tumor and the establishment of a durable memory immune response.

Overall, these studies underscore the ability of nanomaterials to impact the immune response, paving the way for their utilization as immunoadjuvants for tumors, while also highlighting their potential for integrated diagnosis and treatment strategies. These findings highlight

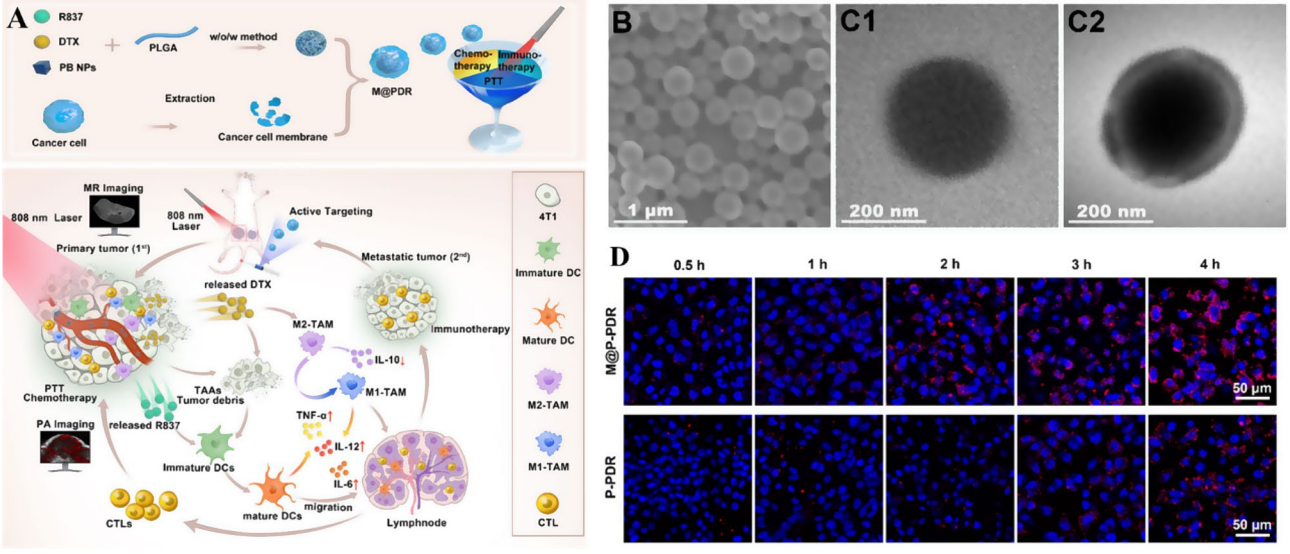

Fig. 9 Strategy for combining phototherapy with immunoadjuvants. (**A**) Schematic diagram of homologous targeting tumor based on M@P-PDR "nano-targeting cell". (**B**) SEM image of M@P-PDR. TEM images of (**C1**) P-PDR and (**C2**) M@P-PDR. (**D**) CLSM images taken by 4T1 cells treated with M@P-PDR and P-PDR nanospheres (Adapted with permission from reference [179])

that the combination of immunoadjuvants with PTT can be effective in tumor treatment even without the use of ICIs or chemotherapy drugs that induce immunogenic cell death.

Phototherapy plus adoptive cell transfer therapy

Adoptive cell transfer therapy aims to assist patients with compromised immune cell function. It involves extracting and isolating immune cells from the patients, activating and expanding them in a controlled environment, and subsequently reintroducing them into the patients' bodies. This process stimulates the body's immune response and enhances the ability to eliminate tumor cells. While adoptive cell transfer therapy has shown promising advancements in treating hematological tumors, it still encounters challenges when it comes to solid tumors [181]. In recent years, CAR-T cell therapy has gained significant attention in research. Currently, CAR-T cell therapy has reached its fifth generation, and the FDA has approved six CAR-T drugs for commercial use [182]. CAR-T therapy, short for Chimeric Antigen Receptor T-cell immunotherapy, involves the isolation of non-specific T cells from patients. Through gene transfection technology, artificial chimeric antigen receptors capable of recognizing tumor antigens are introduced to these cells. They are then cultured and assessed for their functionality before being infused back into the patients. The antigen targeting domain of CARs typically utilizes the Single-chain Fragment variable (ScFv) of a monoclonal antibody. This approach allows for the identification of tumor cells, activation of T-cell immune pathways, and the release of numerous effector factors through immune action to counter T-cell exhaustion. However, the effectiveness of CAR-T cell therapy in treating solid tumors is limited by the dense physical barrier formed by these tumors and the immunosuppressive effects of the tumor microenvironment. Furthermore, as solid tumor antigens are often expressed at varying levels in normal tissues, it is crucial to ensure that CAR-T cells specifically reach the tumor site to avoid causing harm to healthy tissues (on-target/off-tumor toxicity) [181].

The current research involving the combination of nanomaterials, phototherapy, and CAR-T cell therapy is still in its early stages of development. Several studies suggest that mild photothermal effects can disrupt the extracellular matrix of certain tumor cells, induce tumor vasodilation, increase blood flow, reduce solid tumor density, and facilitate the accumulation of CAR-T cells within tumors [183–186]. Zhu et al. focused on the development of a copper-based nanomaterial called HA@Cu2-xS-PEG (PHCN), which specifically targets the HA receptor (CD44) [187]. PHCNs have the ability to decompose endogenous H_2O_2 into highly toxic hydroxyl radicals through a catalytic reaction involving metal ions, thereby inducing programmed cell death. The synergistic effect of photothermal-nanocatalytic mechanisms enhances the catalytic efficiency. Consequently, PHCNs modulate the immunosuppressive tumor microenvironment, improve blood perfusion, enhance the infiltration of CAR-T cells, and ultimately prolong the overall survival time of mice. In another case, Chen et al. developed polylactic acid glycolic acid (PLGA) nanoparticles loaded with ICG nanoparticles, through an oil-in-water emulsification method (Fig. 10A) [188]. By intravenously injecting PLGA-ICG nanoparticles into the tail vein and subsequently irradiating with a 780 nm laser, PTT was found to enhance the anti-tumor effect of CAR-T cells. Specifically, the study demonstrated that CAR-T cells targeting chondroitin sulfate proteoglycan-4 (CSPG4) effectively inhibited tumor growth for up to 20 days (Fig. 10B). Furthermore, hyperthermia-induced destruction of cancer cells triggered an inflammatory reaction, leading to increased secretion of various cytokines, which in turn promoted the recruitment and activation of CAR-T cells.

It is important to note that although these studies provide promising insights, further research is needed to fully understand the potential of nanomaterials combined with phototherapy and CAR-T cell therapy in cancer treatment. Miller et al. have developed plasma gold nanorods (AuNRs) known as "engineering thermal-specific gene switches" to achieve localized tumor heating [189]. Upon reaching a temperature of 40–42 °C, transgene expression is initiated, resulting in increased levels of IFN-γ and TNF-α. In vitro studies have demonstrated a remarkable up-regulation of gene expression by up to 60 times within a heating duration of less than 30 min. In vivo experiments have further validated the feasibility of this approach. Elevated temperatures not only preserve the key functions of CAR-T cells but also enhance their activity, thereby alleviating antigen escape. An intriguing study revealed that the membrane of CAR-T cells exhibits equivalent functional activity and targeting ability as the CAR-T cells themselves (Fig. 10C) [190]. By encapsulating mesoporous silica containing IR780 nanoparticles, CAR-T cell membrane-coated nanoparticles (CIMs) exhibit excellent biocompatibility and photothermal conversion ability. IR780, a widely used photosensitizer, facilitates NIR-II photothermal action, raising the temperature above 50 °C. Additionally, it aids in near-infrared imaging for tumor localization (Fig. 10D). The membrane-coated nanoparticles have shown improved controlled release, prolonged in vivo circulation, and enhanced penetration of tumor stroma. These characteristics make them promising for initiating long-term anti-tumor immunotherapy.

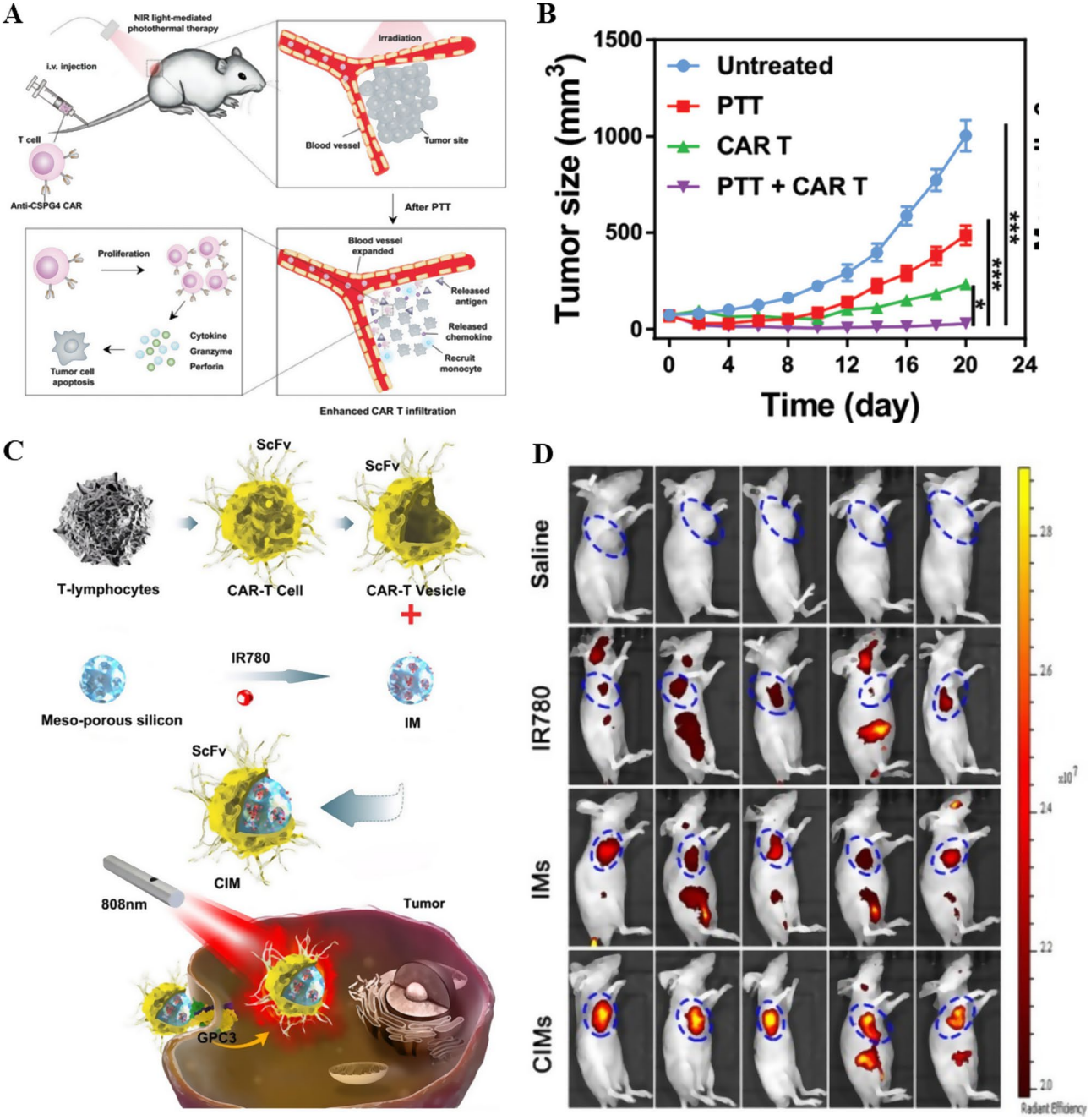

Fig. 10 Strategies of combining phototherapy with CAR-T therapy. (**A**) Schematic illustration of mild heating of tumor promotes adoptive metastasis CAR CSPG4 T cell infiltration and activation enhancement. (**B**) Average tumor growth kinetics in different groups (Adapted with permission from reference [188]) (**C**) Schematic illustration of bionic nanoparticles coated with CAR-T membrane for specific tumor photothermal therapy. (**D**) In vivo imaging of tumor-bearing mice at 24 h post-injection treated with IR780, IMs, and CIMs (Adapted with permission from reference [190])

Summary and future outlook

This review highlights that PTT and PDT based on nano-delivery platforms have the ability to accumulate at the tumor site to exert anticancer effect and simultaneously initiate immune response, achieving synergistically therapeutic outcomes. During PDT, nanoparticles carrying PS accumulate at the tumor site, instigating the production of ROS upon light activation. This ROS generation prompts apoptosis and necrosis of tumor cells. On the other hand, PTT employs a photothermal conversion agent to directly eradicate tumor cells through locally generated heat. Consequently, cell demise initiates an ICD effect, stimulating the production of TAAs, which fosters dendritic cell maturation, amplifies antigen presentation, activates immune cells, and triggers the expression and secretion of cytokines. This, in turn, initiates

adaptive immunity. Furthermore, when combined with traditional immunotherapies such as immune checkpoint blockade, cytokines, and adjuvants, these phototherapy approaches amplify systemic immunity. This leads to improved response rates and treatment outcomes, effectively eliminating tumors both locally and distantly. Additionally, the nano-preparations designed for the tumor microenvironment synergistically counteract the deterioration of the microenvironment when combined with other therapies such as surgery, radiotherapy, and sonodynamic therapy. These combined approaches help reduce the generation and activation of stromal cells and immunosuppressive cells, reverse the tumor's insensitivity to basic immunotherapy, and suppress the formation of tumor metastases.

Indeed, while the combination therapy has shown promising results in the mentioned cases, it is important to acknowledge and address the existing limitations. Firstly, the use of near-infrared II (NIR II) lasers with deeper tissue penetration is advantageous. However, standardization of the power density and irradiation duration of lasers in photoimmunotherapy is necessary to prevent excessive heat diffusion that could damage the skin and surrounding organs. Establishing proper guidelines for laser parameters will be crucial for future clinical applications. Secondly, immunotherapy can be costly, and this may also apply to photoimmunotherapy. For example, current adoptive cell therapy relies on autologous cells, which requires significant time and resources for individualized production. Developing universal models in the future could reduce production time and costs, making these therapies more accessible.

Lastly, while significant progress has been made in the safety, stability, and long-term performance of nano-drugs, it is essential to understand the biodegradation and excretion pathways of nanoparticles in vivo. Although most intravenous nano-drugs demonstrate good biocompatibility and do not cause hemolysis, the specific mechanisms of biodegradation and excretion need further investigation. Furthermore, while the laboratory experiments have shown promise, it is important to consider the differences between animal models, particularly in mice, and human solid tumors. The EPR effect in humans is still a subject of debate, and current nano-drugs on the market may not achieve true and complete tumor targeting. This calls for ongoing research and exploration by scientists to realize effective accumulation of nano-drugs in human solid tumors. Addressing these limitations and continuing research efforts will pave the way for the development and improvement of photoimmunotherapy for clinical applications.

Indeed, mounting evidence supports the notion that phototherapy based on nanoplatforms can enhance anti-tumor immune responses and alleviate the immunosuppressive tumor microenvironment. The progress in this field is evident, as photoimmunotherapy was approved by the U.S. FDA for clinical trials in April 2015. Furthermore, in September 2020, Japan's Ministry of Health, Labor, and Welfare approved the world's first photoimmunotherapy drug for the treatment of head and neck malignant tumors. These milestones signify that the combined approach of PTT and PDT with immunotherapy is gradually entering the realm of clinical translation. It emerges as a promising contender among the next generation of cancer treatment technologies.

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Author contributions
Q.Y. and L.K. conceived the topic and structure of the manuscript. W.C. and T.S. contributed equally to this work. W.C. wrote the original manuscript. T.S. made the figures. C.Q., H.S., and R.C. participated the discussion process. C.X., L.K., and Q.Y. reviewed and edited the last version. All author reviewed the manuscript and approved the name order.

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