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Review Article

Tumor-responsive dynamic nanoassemblies for boosted photoimmunotherapy

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ABSTRACT

Photoimmunotherapy (PIT) is an emerging therapeutic approach that integrates phototherapy and immunotherapy to eliminate primary tumors under an appropriate dosage of local light irradiation, while simultaneously preventing tumor metastasis and recurrence by activating the host antitumor immune response. Tumor-responsive dynamic nanoassemblies (TDNs) have evolved from being a mere curiosity to a promising platform for high-performance PIT. However, the dynamic nano-bio interaction between TDNs and tumor microenvironment remains poorly understood, which shall be critical for precise control of TDNs assembling/disassembling behavior and superior PIT efficacy. To deepen the understanding of the structure–function relationship of TDNs, this review introduces the rational design, nano-bio interactions, and controllable functionalities of cutting-edge TDNs for enhanced PIT. Moreover, the synergetic mechanism between TDNs-based PIT and immunomodulatory agents-mediated immunomodulation is particularly emphasized. Finally, the challenges and future perspectives in this emerging field are assessed.

KEYWORDS

photoimmunotherapy, tumor-responsive dynamic nanoassemblies, immunosuppressive tumor microenvironment

1 Introduction

As non-invasive therapeutic modalities with spatio-temporal controllability, phototherapies, such as photothermal therapy (PTT) and photodynamic therapy (PDT), employ photosensitive agents to generate hyperthermia via nonradiative decay or reactive oxygen species (ROS) through intersystem crossing to destroy the tumor cell [1–3]. These therapies have shown remarkable progress in both pre-clinical and clinical settings for the treatment of primary tumors. In addition to the direct killing of tumor cells, phototherapy further triggers immunological responses via inducing immunogenic cell death (ICD) [4–6]. In this process, the tumor cells killed by phototherapy can release tumor-associated antigens (TAAs) and damage-associated molecular patterns, wherein TAAs can be captured by antigen-presenting cells such as dendritic cells (DCs), and then being presented to adaptive immune cells for initiating the immune attack [7–9]. Nevertheless, phototherapy alone may not completely eradicate tumors since the tumor-driven evolution of immunosuppression could lead to a high incidence of distant metastasis of tumor cells [2, 10].

To reach the ultimate goal of eradicating both primary and metastatic tumors simultaneously, the integrative systems of phototherapy and immunotherapy (termed photoimmunotherapy, PIT) for synergistic effects have been developed and verified both in preclinical studies and clinical trials [11]. For example, the epidermal growth factor receptor (EGFR)-targeted PIT agent (ASP-1929, Rakuten Medical Inc.) for the treatment of nasopharyngeal carcinoma was first approved and registered for clinical application by the Japanese Pharmaceuticals and Medical Devices Agency in 2020 [12, 13], and early findings have revealed its superiority over conventional second-line and third-line therapeutic patterns for recurrent head and neck cancers [14]. The immunostimulatory properties of phototherapy provide an opportunity to boost their antitumor immunity for the therapeutic potential of eliminating metastatic tumors [15]. Therefore, PIT represents a promising strategy that not only destroys primary tumors, but also activates the systemic immune

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response to clean up residual tumor cells and inhibit distant metastasis.

Although PIT has shown promising antitumor outcomes in preclinical studies and clinical trials, there are still some potential limitations that may impede its clinical translation. For instance, the non-specific accumulation of photosensitizers and/or immunomodulatory agents after systemic administration could reduce the overall therapeutic effect and induce adverse events [16–18]. Besides, the immunosuppressive tumor microenvironment (TME) of solid tumors hinders the immune activation and immune cell infiltration, resulting in the poor immunotherapeutic efficacy of PIT agents [19–21]. To address these challenges, innovative tumor-responsive dynamic nanoassemblies (TDNs)-based PIT agents that are composed of three basic parts: stimuli-responsive groups, immunomodulatory agents, and photosensitizers are developed. On the one hand, these stimuli-responsive groups enable the PIT agents to achieve controlled structural alternation and on-demand "cargo" release in tumor sites, enabling tumor-specific treatment with reduced side effects. On the other hand, TDNs can promote the tumor-specific enrichment of immunomodulatory agents (e.g., immune adjuvants, immune checkpoint inhibitors, and TME modulators) and modulate the tumor immune microenvironment, which helps to relieve the immunosuppressive TME through inhibiting the immune response and affecting immune cells infiltration. Consequently, TDNs-based PIT represents an attractive platform for programming the pharmacokinetics and location of photosensitizers/immunomodulators to improve the tumor-targeting capability, enhancing the antitumor efficacy with reduced systemic side effects.

However, despite the therapeutic advantages of TDNs, there is still a lack of comprehensive understanding regarding the dynamic nano-bio interaction between TDNs and tumor immune microenvironment, which shall be critical for the in-depth insight into the therapeutic mechanism of PIT and the precise control of the *in vivo* assembling/disassembling behaviors of TDNs for improved PIT efficacy. Especially, although various reviews have introduced the mechanism and application of PIT [16, 22], none focuses on the TDNs-based PIT and its potential immunomodulation. In this review, we first aim to the design and fabrication of cutting-edge TDNs for enhanced PIT (Fig. 1). Furthermore, the synergetic mechanism between TDNs-based PIT and its immunomodulation is particularly emphasized. The precise control of the subtle assembling/disassembling behavior and the immunomodulatory functions of TDNs offers an in-depth insight of PIT mechanism, facilitating the design of next-generation TDNs-based PIT agents. Finally, the challenges and prospects for further scientific research and practical applications of TDNs-based PIT are presented.

2 Design and fabrication of TDNs-based PIT agents

Conventional PIT agents may cause systemic immune overreaction due to the off-target effect and associated toxicity [23], severely compromising their therapeutic effectiveness. Taking advantage of the unique physiological properties of the neoplastic tissues, the incorporation of TME stimuli (e.g., pH, ROS, glutathione (GSH), hypoxia, and enzyme)-responsive groups into PIT agents can effectively minimize the off-target immunotoxicity and maximize the therapeutic efficiency. In this section, we introduce the design and fabrication of TDNs-based PIT agents from the perspective of materials chemistry.

2.1 pH-based TDNs

In contrast to normal cells energized mainly via oxidative phosphorylation, tumor cells draw energy from the anaerobic glycolysis to survive [24]. Through such oncogenic metabolism, tumor cells generate large amounts of lactate, which contributes to the enhanced acidification of extracellular TME below that of normal tissues [25, 26]. At the subcellular level, pH variations are even more dramatic. For instance, the pH values in late endosomes and lysosomes can drop to 4.5–5.5 [27]. Thus, the difference in pH values is an attractive trigger for controlled drug delivery in PIT.

The pH-mediated dynamic response of nanoassemblies is usually achieved through the incorporation of pH-sensitive functional groups, which undergo the chemical bond-breaking and/or protonation process in an acidic environment. A number of pH-labile chemical bonds (e.g., imine groups, hydrazone groups, and ester groups) can be utilized for the designed fabrication of TDNs with tunable pH sensitivity [28]. For instance, Liu et al. reported a pH-responsive semiconducting polymer nano-immunomodulator (SPNI) for tumor-specific PIT, which consisted of the near-infrared (NIR)-absorbing semiconducting polymer complex and Toll-like receptor 7 agonist (imiquimod: R837) via an acid-labile Schiff base linker (Fig. 2(a)) [29]. Once SPNI reached the acidic conditions, the imine groups would be

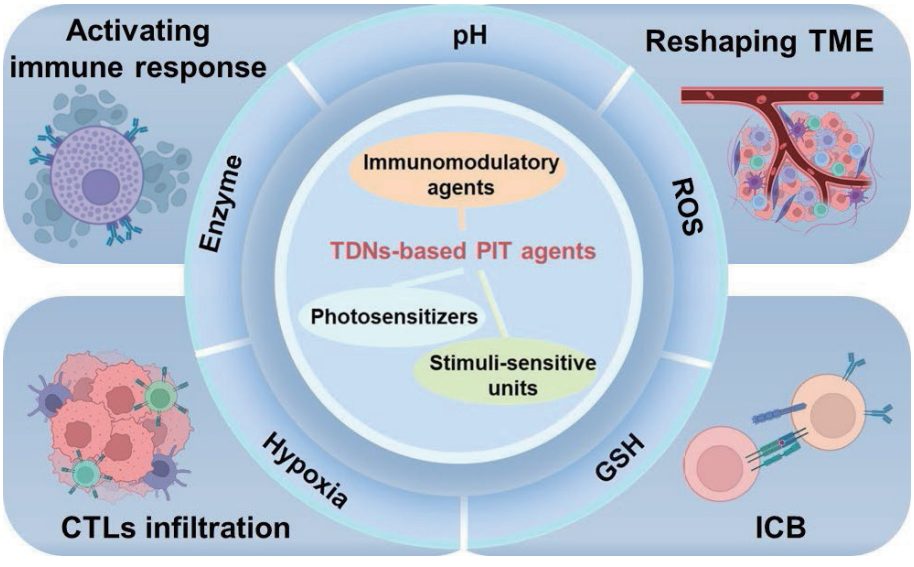

Figure 1 Schematic illustration of TDNs-based PIT agents for immunomodulation through enhancing the activation of the immune response, improving the infiltration of CTLs, and reshaping the immunosuppressive TME and immune checkpoint blockade (ICB).

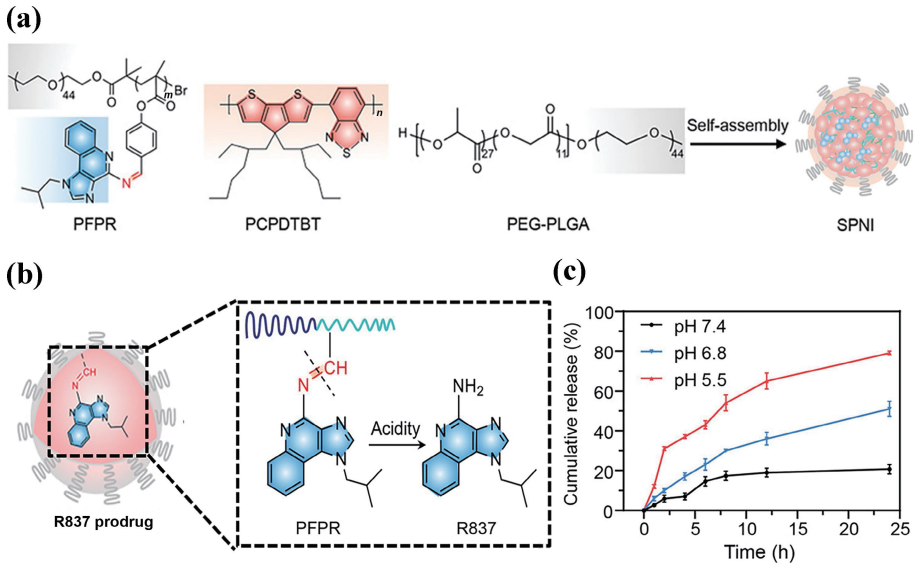

Figure 2 pH-responsive TDNs for PIT. (a) The synthetic procedure of the pH-responsive SPNI via self-assembly. (b) Schematic illustration of pH-triggered R837 release from the SPNI. (c) Cumulative release of R837 at different pH conditions (pH = 5.5, 6.8, and 7.4). Reproduced with permission from Ref. [29], © Wiley-VCH GmbH 2022.

hydrolyzed, leading to an ~ 4-fold and 2.5-fold on-demand release of the R837 at 24 h when pH was 6.8 and 5.5 compared with that in pH = 7.4 (Figs. 2(b) and 2(c)). The amount of mature DCs in the primary tumor and tumor-draining lymph nodes treated by SPIN plus laser irradiation (808 nm, 300 mW/cm^2) was about 1.7 and 1.8 times higher than those treated with R837, respectively. Moreover, Jin et al. conjugated doxorubicin (DOX) and indocyanine green (ICG) via a hydrazone bond to fabricate pH-responsive nanoassemblies (DOX-hydrazone-ICG) for targeted delivery of small-molecule PD-L1 inhibitor (BMS202) [30]. The introduction of the hydrazone bond into the nanosystem not only reduced the off-target toxicity, but also realized tumor-specific therapy with improved therapeutic efficacy for the elimination of primary and metastatic breast tumors. Besides, the pH-responsive functional groups (e.g., imidazole, tertiary amine, and histidine) that undergo the protonation process in acidic conditions can also be utilized for the construction of pH-responsive dynamic nanoassemblies [31, 32]. For instance, Zheng et al. developed an immunomodulatory nano-photosensitizer (NeINP) consisting of a photosensitive core and an acid-responsive polymeric shell [33]. Once accumulated at the tumor site, the tertiary amine groups in NeINP would be protonated and resulted in the swelling of NeINP, thus achieving the on-demand release of small-molecule immunomodulators for efficient PIT.

Moreover, some inorganic materials are also sensitive to acidic conditions and thus can be used as pH-responsive units in TDNs. For instance, calcium carbonate can be degraded in the acidic TME, based on this, Liu et al. designed a pH-responsive nanoplatform (Mn@$CaCO_3$/ICG@siRNA) for PIT [34]. In detail, $CaCO_3$ and ICG were utilized to coat MnO_2 nanoparticles for constructing a core–shell structure (Mn@$CaCO_3$/ICG), then siRNA was modified on Mn@$CaCO_3$/ICG by electrostatic interaction. Once accumulated to the acid TME, $CaCO_3$ degraded into Ca^{2+} ions and CO_2, thereby causing the disintegration of the nanoplatform. Subsequently, the exposed MnO_2 nanoparticles catalyzed H_2O_2 into oxygen, enhancing the therapeutic efficiency of PDT. Additionally, the tumor-specific release of siRNA acted as an immunomodulator to block immune evasion. Together, the Mn@$CaCO_3$/ICG@siRNA nanoplatform exhibited an amplified synergistic effect of the enhanced PDT and strong immune response under laser irradiation (808 nm, 0.5 W/cm^2). In fact, many other types of metal oxide (e.g., iron oxides and manganese oxides) also possess pH-responsiveness [35, 36]. The rational design shall enable the fabrication of novel metal oxide based-TDNs that can act as both pH-sensitive and functional diagnostic/therapeutic units for efficient PIT.

Overall, the acidic microenvironment, as a typical feature of most tumors, is often exploited to construct TDNs-based smart PIT agents. However, for tumor immunotherapy, tumor acidity may work as a double-edged sword. On the one hand, low pH promotes the disassembly of pH-responsive dynamic nanoassemblies for targeted cargo release including immunomodulators. On the other hand, the acidic TME contributes to the immunosuppressive TME, which limits the efficacy of immunotherapy [37]. To address the above issues, TDNs that can relieve tumor acidity may be further developed.

2.2 Redox-based TDNs

The design and construction of redox-responsive dynamic nanoassemblies are mainly based on the difference in the redox potential gradient (100–1000 folds) between the extracellular and intracellular regions. The overproduced ROS and the highly reducing component GSH in the tumor cells have inspired researchers to exploit tumor-specific ROS- and/or GSH-responsive dynamic nanoassemblies for efficient antitumor treatment.

2.2.1 ROS-based TDNs

ROS-responsive dynamic nanoassemblies are constructed by introducing ROS-responsive groups, which include thioketal groups, sulfide groups, and thioether groups [38]. The dynamic nanoassemblies containing thioketal are one of the most widely investigated TDNs. When exposed to excessive ROS, the thioketal groups of TDNs can be oxidized to sulfoxide and sulfone groups, leading to the collapse and disassembly of nanoassemblies [39]. For instance, Xu et al. developed a ROS-responsive nanoplatform (TB/PTX@RTK, (TB: photosensitizer, PTX: paclitaxel)) consisting of aggregation-induced emission (AIE) photosensitizer (TPA-BDTP, TB), PTX, and ROS-sensitive cRGD-modified PEG-TK-PLGA (RTK, PEG: poly(ethylene glycol), TK: thioketal, PLGA: polylactic acid-glycolic acid) [40]. Upon laser irradiation (white light, 100 mW/cm^2), the thioketal linker in RTK could be cleaved by the ROS generated by TB, resulting in a 1.6-fold PTX release compared to that in the non-responsive group for

48 h. The interleukin-12 (IL-12) level in TB/PTX@RTK plus laser-treated tumor-bearing mice was significantly higher than that in other groups, indicating the promotion of DCs maturation for activating anticancer immunity. It is noteworthy that previous studies showed that the excess amounts of ROS might also disrupt the normal function of adjacent immune modulators [41], which seriously hinders the therapeutic outcomes of PIT. Thus, the rationally designed ROS-responsive TDNs should be able to avoid excess ROS and preserve the activity of immune modulators. For example, Zhang et al. created a ROS-responsive biocompatible hydrogel for sustainable PIT, which was prepared by loading chlorin e6 (Ce6) and anti-CD47 antibody (aCD47) onto a conjugated polymer poly(deca-4,6-diynedioic acid) (PDDA) (Fig. 3(a)) [42]. Upon laser irradiation (640 nm, 5 mW/cm^2), the ROS generated by Ce6 degraded PDDA to succinic acid (Fig. 3(b)), thereby removing the harmful ROS to protect the activity of aCD47 from ROS-induced damage. This ROS-responsive hydrogel completely inhibited the metastasis in the 4T1 tumor-bearing mice by the sustainable synergistic combination of PDT and immunotherapy.

2.2.2 *GSH-based TDNs*

The significant variations of the GSH level between tumor intracellular (2–10 mM) and extracellular (2–20 μM) microenvironments inspire the design of GSH-responsive dynamic nanoassemblies for precise PIT [43]. One typical strategy is the introduction of disulfide bonds to develop cross-linked PIT agents [44]. For instance, Sun et al. designed a GSH-responsive supramolecular prodrug-based nanoplatform (HCJSP) for the treatment of pancreatic cancer (Fig. 4(a)). HCJSP could deliver bromodomain-containing protein 4 inhibitor (JQ1) and pyropheophorbide a (PPa) by host–guest interaction between the supramolecular prodrug nanosystems (AD-SS-JQ1 and AD-SS-PPa) and the β-cyclodextrin-grafted hydronic acid (HA-CD) [45]. Benefiting from the CD44 receptor-mediated tumor targeting, HCJSP could be selectively internalized into tumor cells. Thereafter, the disassembly of AD-SS-JQ1 and AD-SS-PPa triggered by endogenous GSH facilitated the controlled intracellular release of JQ1 and PPa. Upon laser irradiation (671 nm, 200 mW/cm^2), HCJSP could activate a dramatic immune response and induce long-term immune memory to inhibit tumor recurrence and metastasis.

Furthermore, since reductive GSH can react with certain metallic materials, the GSH-sensitive metal-organic framework (MOF) with a high loading capacity of diagnostic and therapeutic agents is also developed for PIT [46]. For example, Fan et al. constructed a GSH-responsive nanocarrier (ICG-CpG@MOF, CpG: cytosine-phosphate-guanine) for synergistic antitumor PIT (Fig. 4(b)) [47]. The response of MOF (MIL101-NH$_2$) to GSH could be observed through the changes of particle size and color (Figs. 4(c) and 4(d)). The GSH-responsive MOF acted as the core of the nanocarrier and was dual-dressed with ICG and CpG. Once accumulated in the GSH-enriched TME, ICG-CpG@MOF would be degraded due to the reduction of Fe^{3+} to Fe^{2+}, leading to on-demand release and significant enrichment of ICG and CpG at tumor sites. Upon laser irradiation (808 nm, 1.5 W/cm^2), the PDT/PTT mediated by ICG destroyed tumor cells and induced the release of TAAs. Next, TAAs and CpG could trigger the transition of tumor cells from immune "cold" to "hot" by activating the host immune system.

In conclusion, ROS/GSH-responsive groups or certain metallic materials are utilized to fabricate the redox-responsive TDNs. However, an accurate ROS or GSH- responsive concentration of these responsive groups is not clearly detected and only exists in a wide response range. Therefore, it is necessary to enhance the responsive accuracy through a further study on the responsive behavior of TDNs at the target site.

2.3 Hypoxia-based TDNs

Hypoxic TME is defined as a condition where the partial pressure of oxygen is below 10 mmHg, compared to 40–60 mmHg in most normal tissues [48]. The distinct partial oxygen pressure between tumors and normal tissues can be utilized to develop hypoxia-responsive dynamic nanoassemblies. The commonly used strategy is imparting the hypoxia-responsive bonds (e.g., azobenzene, 2-nitroimidazole, and quinone) to the nanoassemblies, which can be intracellularly cleaved in hypoxic tumor sites [49]. Im et al. fabricated a hypoxia-responsive Ce6-doped-azobenzene-glycol chitosan (GC)-PEG mesoporous silica nanoparticle (CAGE) (Fig. 5(a)) [50]. The azobenzene linker was used to attach GC and PEG to the surface of Ce6-doped mesoporous silica nanoparticles (CAP). Under the stimulations of intrinsic tumor hypoxia and PDT-induced oxygen depletion, the azobenzene linker could be cleaved, which would trigger PEG detachment for the retention of

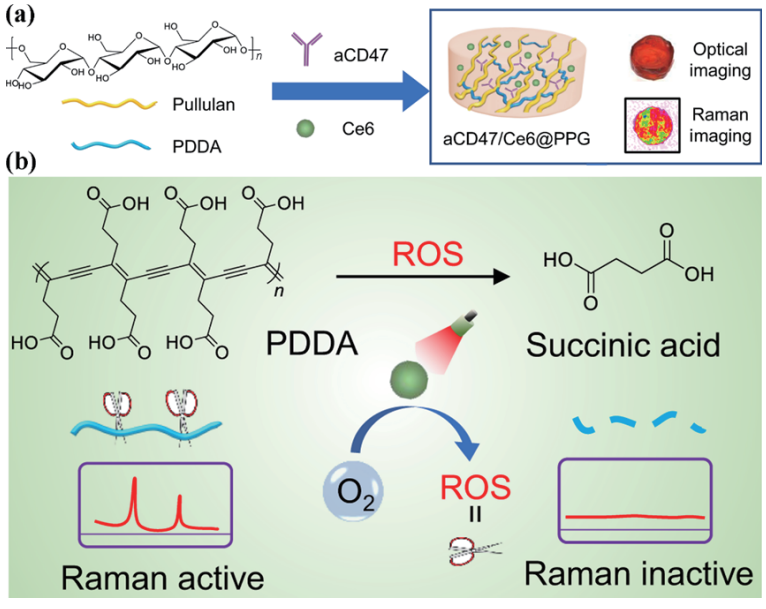

Figure 3 ROS-responsive TDNs for PIT. (a) The synthetic procedure of the aCD47/Ce6@PPG (PPG: poly(propylene glycol)) hydrogel. (b) Schematic illustration of the Raman-traceable and ROS-responsive degradation of aCD47/Ce6@PPG hydrogel. Reproduced with permission from Ref. [42], © Zhang, Y. Y. et al. 2022.

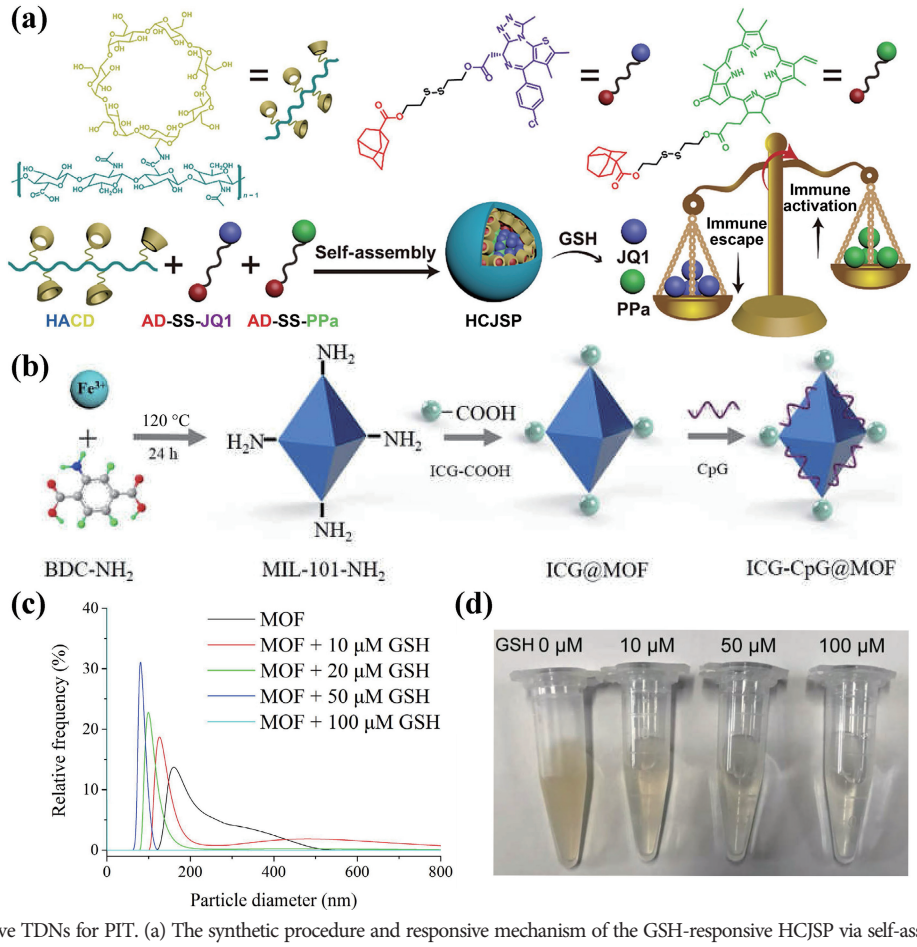

Figure 4 GSH-responsive TDNs for PIT. (a) The synthetic procedure and responsive mechanism of the GSH-responsive HCJSP via self-assembly. Reproduced with permission from Ref. [45], © Sun, F. et al. 2021. (b) The synthetic procedure of the GSH-responsive ICG-CpG@MOF. (c) GSH-triggered particle size change and (d) the degradation of functionalized MOF. Reproduced with permission from Ref. [47], © Fan, Z. J. et al. 2020.

mesoporous silica nanoparticles and the burst release of GC/CpG. The population of activated DCs treated by the hypoxia-responsive group was 2.3-fold higher than that of the non-response group due to the photodynamic effect of PS and the delivery of CpG. The tumor inhibition rate in the hypoxia-responsive CAGE/CpG group was 2.1-folds higher than that in the non-response group under the laser irradiation (660 nm, 200 mW/cm^2) due to the tumor-specific accumulation of Ce6 and CpG. In addition, TDNs modified by 2-nitroimidazole derivatives could convert to hydrophilic state from hydrophobic state in hypoxic conditions. For instance, Liu et al. designed a 2-nitroimidazole-contained hypoxia-responsive polymeric micelle (IDMs) through the incorporation of the chemotherapy drugs DOX, photosensitizer ICG, immunoadjuvant CpG, and immune checkpoint inhibitors anti-cytotoxic T lymphocyte antigen 4 (aCTLA-4) (Fig. 5(b)) [51]. The hypoxia-responsive copolymer that consisted of 6-(2-nitroimidazole)hexylamine (NIDH) moieties could transform to be hydrophilic after bio-reduction and then released these payloads in the hypoxic TME. Based on the tumor-specific responsiveness, IDMs exhibited 3.5-fold enrichment in tumor sites than that of free ICG/DOX groups. The polymeric micelles fabricated could give combination therapeutic regimens for accurate tumor therapy, such as precise tumor diagnosis and efficient eradication of various degrees of malignancy, such as primary tumors, distant tumors, and metastatic cancers.

Although a number of strategies for the treatment of hypoxic tumors have already been developed, it is still challenging for the clinical transition of hypoxia-based TDNs. Because the hypoxic microenvironments of solid tumors are far from the blood vessels, TDNs must have excellent penetrating ability to overcome the dense extracellular matrix (ECM) and high interstitial fluid pressure for an adequate concentration in the deep hypoxic regions. Therefore, the development of size-reducible TDNs in response to the hypoxic TME is expected to be a viable platform to overcome the above limitation.

2.4 Enzyme-based TDNs

The efficiency of PIT can be further enhanced by utilizing the tumor-related specific enzymes (e.g., hyaluronidase [52], matrix metalloproteinase [53], and esterase [54]). For instance, Sun et al. designed a metalloproteinase-2 (MMP-2)-responsive peptide-photosensitizer conjugate (PPC) for PIT, which was prepared by the co-assembly of the photosensitizer Purpurin 18 (P18), the motif FFKYG, the MMP-2 degradation domain PLGLAG, and the PD-L1 antagonist peptide CVRARTR (Fig. 6(a)) [55]. Once accumulated in the tumor sites with overexpressed MMP-2, the junction of PPC (between PLG and LAG) could be gradually degraded, triggering the release of CVRARTR and P18-FFKYGPLG. The PPC and P18-FFKYGPLG could further undergo self-assembly to form the nanofiber structure, which enhanced the local retention for controlled release of the PD-L1 antagonist and promoted the efficacy of mild PTT. The synergistic PTT and antagonist modulated the immunosuppressive TME and enhanced the systemic immune effect. Besides, Sun et al. engineered the photosensitizer IRDye800CW with camptothecin (CPT)-conjugated HA shell (P@CH) for improved PIT (Fig. 6(b)) [56]. 95% of CPT in P@CH was released when treated with hyaluronidases via responsive degradation. The combination of P@CH-based synergistic therapy and immune checkpoint blockade therapy could achieve long-term protection with almost no tumor recurrence and metastasis in mice.

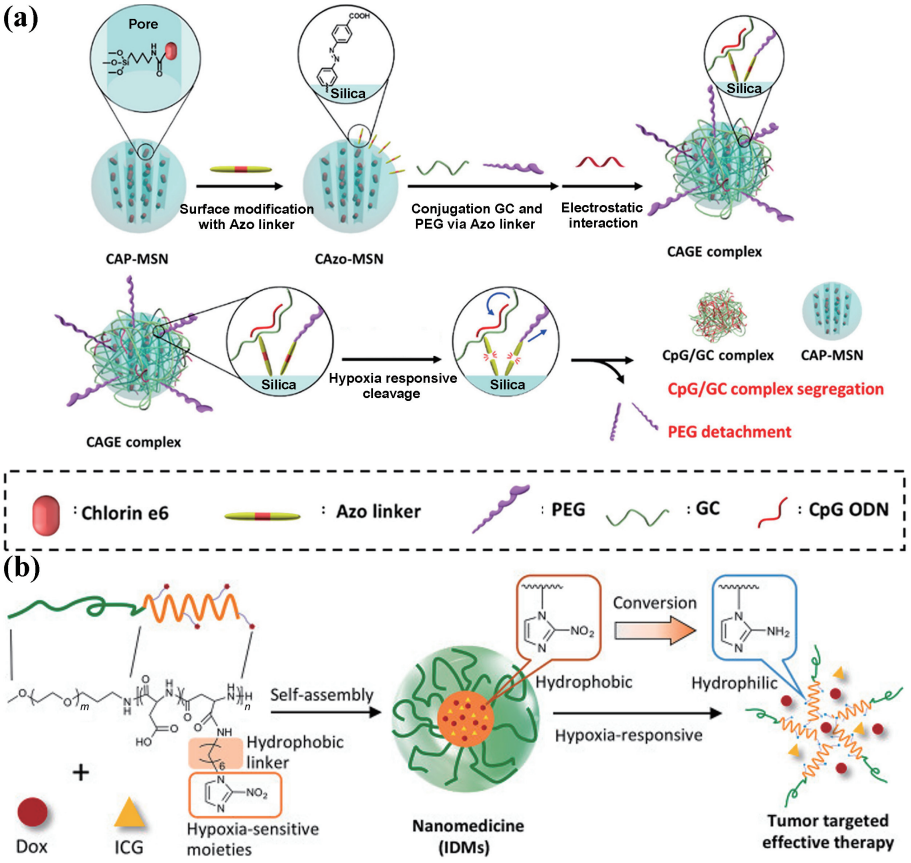

Figure 5 Hypoxia-responsive TDNs for PIT. (a) The synthetic procedure and responsive mechanism of the hypoxia-responsive CAGE. Reproduced with permission from Ref. [50], © American Chemical Society 2018. (b) Scheme of collaborative synthetic procedure of nanomedicine (IDMs) and hypoxia-responsive tumor-targeted therapy. Reproduced with permission from Ref. [51], © Elsevier Ltd. 2021.

Although enormous progress has been made in the fabrication and application of enzyme-responsive nanosystems, we should be aware that the same enzyme family (e.g., MMP) commonly has analogous catalytic mechanisms, which results in similar substrate preferences [57]. After the activation of enzyme-responsive nanosystems in the TME, it is still challenging to identify whether this responsive process is indeed produced by a specific enzyme but not by a complex process induced by a series of enzymes of the same family. Therefore, it is necessary to address substrate specificity with a rational design to ensure precise enzyme-specific activation and accurate treatment.

In conclusion, based on the unique features of TME (e.g., low pH, abnormal redox level, hypoxia, and overexpressed enzymes), various types of TDNs have been developed for enhanced PIT (the typical examples of TDNs-based PIT agents are summarized in Table 1). Despite the significant achievements made in TDNs-based PIT, critical challenges still exist and cannot be ignored. For instance, the dynamic responsiveness of TDNs *in vitro* may not reflect the actual *in vivo* biological situations, which are considerably more complex than the *in vitro* simulated situations [58, 59]. Therefore, a deeper and more comprehensive understanding is necessarily required to further investigate the responsive mechanisms of TDNs *in vivo*.

3 Nano-bio interactions between TDNs and TME for immunomodulation

The host immune response can be impeded by a number of immunosuppressive pathways, which usually result in tumor immune escape and unsatisfactory therapeutic outcomes [60]. For example, tumor cells can secrete immunosuppressive cytokines and recruit immunosuppressive cells to hamper the antitumor immune response, ultimately leading to an immunosuppressive TME [61]. Besides, the abnormal metabolism of tumor cells leads to a unique TME (e.g., hypoxia, acidity, overexpressed enzymes, and excess ROS), which plays a significant role in tumor initiation and development [62]. Given the foregoing, diverse studies have proved that TDNs can act as a blank "canvas" onto which immunomodulators may be mapped, allowing the unique TME to serve as biomarkers for tumor-specific delivery of immunomodulators to improve the immune response and alleviate the off-target effects [63]. In this section, the representative strategies for enhancing immunotherapy driven by TDNs-based PIT are presented. In particular, the inherent nano-bio interaction between TDNs and TME for subtle immunomodulation, and the unique advantages of TDNs that boost antitumor immunity are discussed.

3.1 TDNs for boosting the activation of immune response

Phototherapy has been reported to trigger the ICD of tumor cells to release TAAs [64]. The acquisition, processing, and transportation of TAAs are crucial steps in the initiation of immune responses [65]. Under the activation of immunostimulatory molecules, such as TAAs, DCs tend to mature and undergo several changes, including the enhanced efficiency of lymphatic drainage and antigen presentation [66]. However, the systemic immune response induced merely by the phototherapy is relatively weak, and its strength and magnitude severely limit efficient tumor suppressors [67]. By tumor-specific accumulation and TME-triggered on-demand cargo release, the rational design of TDNs incorporated with molecular ICD inducers can be utilized to boost the immune response. The effective delivery of ICD inducers using TDNs holds great

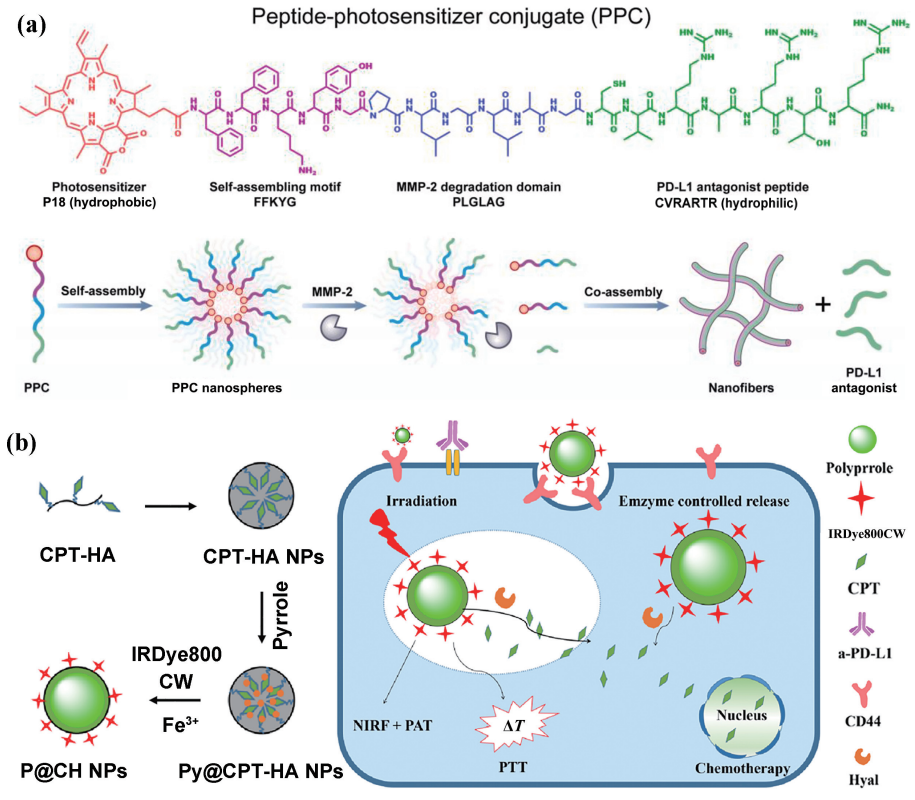

Figure 6 Enzyme-responsive TDNs for PIT. (a) The synthetic procedure and responsive mechanism of the enzyme-responsive PPC. Reproduced with permission from Ref. [55], © Sun, Y. N. et al. 2023. (b) The synthetic procedure and responsive mechanism of the enzyme-responsive P@CH NPs. Reproduced with permission from Ref. [56], © Sun, W. et al. 2019.

Table 1 The list of typical TDNs-based PIT agents

Nanoparticle	Stimuli	Phototherapy agent	Immunotherapy agent	Response	References
SPNI	pH	Poly(cyclopentadithiophene-alt-benzothiadiazole)	R837	Bond cleavage	[29]
aCD47/Ce6@PPG	ROS	Ce6	aCD47	Degradation	[42]
HCJSP	GSH	PPa	JQ1	Bond cleavage	[45]
ICG-CpG@MOF	GSH	ICG	CpG	Degradation	[47]
CAGE	Hypoxia	Ce6	CpG	Bond cleavage	[50]
IDMs/CpG/aCTLA-4	Hypoxia	ICG	CpG/aCTLA-4	Hydrophilic/ hydro-phobic conversion	[51]
PPC	Enzyme	Purpurin 18	CVRARTR	Bond cleavage	[55]
PPy@CPT-HA-IRDye800CW/ anti-PD-L1	Enzyme	IRDye800CW	Anti-PD-L1	Degradation	[56]

potential for enhancing antitumor immune responses. For instance, Im et al. designed a hypoxia-responsive nanocarrier (CAGE) for delivering CpG to increase TAAs presentation and promote DCs maturation (Fig. 7(a)) [50]. In the *in vitro* drug release experiments, the released CpG from CAGE in hypoxic conditions was significantly higher than that in normoxic conditions. Moreover, the fluorescent intensity of carboxyfluorescein succinimidyl ester (CFSE, as an indicator to evaluate the release of TAAs) in the tumor cells treated with CAGE was almost 6-fold higher than that of MSN under the laser irradiation (660 nm, 100 mW/cm^2) (Figs. 7(b) and 7(c)), indicating that CAGE loaded with CpG could significantly increase the release of TAAs from tumor cells. Due to the targeted delivery of CAGE/CpG in hypoxic TME, the synergetic therapy mediated by CAGE and immunomodulatory CpG greatly improved the population and maturation ratio of tumor infiltrating DCs, and efficiently promoted TAAs presentation for immune activation.

The fatal immune toxicity of immunotherapy may be induced by the exaggerated immune response due to the acute elevation of systemic inflammatory cytokines [68]. TDNs prevent the random dissemination and minimize systemic exposure of ICD inducers, which avoid potential adverse effect. For instance, Li et al. designed a pH-responsive biomimetic nanosystem coloaded with R837 and gold nanoparticles [69]. Once accumulated in acidic TME, the pH-responsive shell was shed to ensure the on-demand release of R837 for improved immune response, which could achieve long-term inhibition of tumor and avoid adverse effects on normal tissue.

3.2 TDNs for strengthening the suppression of immune escape

Generally speaking, immune checkpoints act as crucial negative regulatory pathways that inhibit the overactivation of T cells and regulate the immune response to prevent the incidence of autoimmune diseases [70]. However, tumor cells exploit these mechanisms to evade immune response [71]. Fortunately, researchers have discovered that antibody-mediated immune checkpoint blockade can disrupt these receptor/ligand interactions and overcome tumor immune resistance [72, 73].

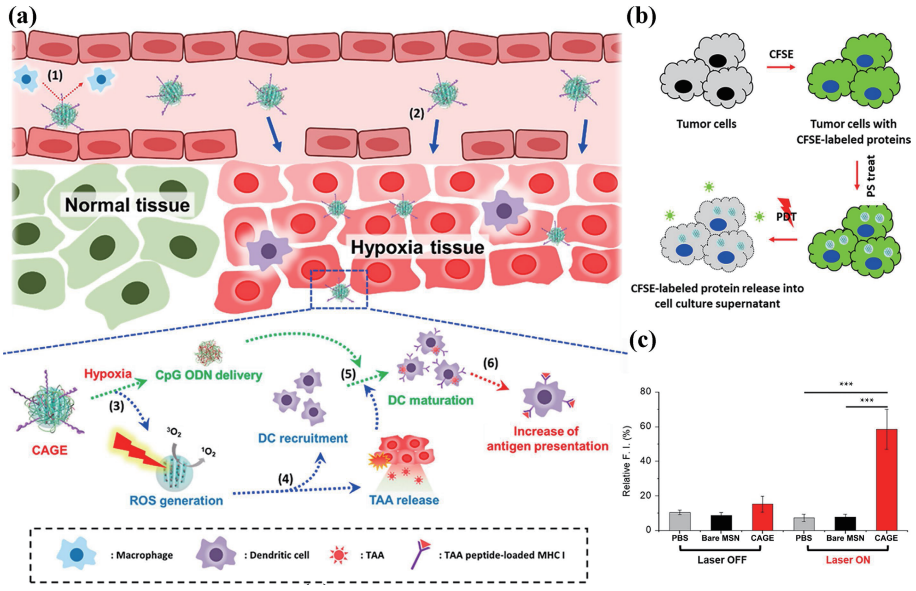

Figure 7 Mesoporous silica-based nanocarrier (GAGE) combined with immune adjuvants for enhancing the activation of the immune response. (a) Schematic illustration of the therapeutic mechanism of hypoxia-responsive GAGE to enhanced antigen presentation. (b) Schematic illustration of tumor proteins release experiment. (c) The release profile of tumor proteins investigated by CFSE fluorescence. Reproduced with permission from Ref. [50], © American Chemical Society 2018.

Immune checkpoint inhibitors (e.g., indoleamine 2,3-dioxygenase (IDO) inhibitor and PD-1/PD-L1 inhibitors) stimulate the inherent immune systems to recognize and eradicate tumor cells avoiding from immune escape, and have been approved by the USA Food and Drug Administration (FDA) for the treatment of various malignant tumors [74–76]. However, non-specific enrichment of immune checkpoint inhibitors may cause immune-related toxicity in the nontarget organs [77, 78]. To address this, TDNs have been rationally designed and developed for the loading and selective delivery of immune checkpoint inhibitors into tumor tissues. Till now, there have been several attempts in the utilization of IDO blockade as assembling units of TDNs [79, 80], which can be considered as a promising strategy to synergistically promote the immune response. For example, Liu et al. fabricated a GSH-responsive porphyrin-based nanoliposome (IND@RAL), which was constructed by the self-assembly between PPa-disulfide bond-phospholipid conjugate and IDO inhibitor (Fig. 8(a)) [81]. Once exposed to the reductive TME, IDO inhibitor could be released due to the disintegration of nanoliposomes caused by the breakage of the disulfide bond, thereby resulting in the reversal of the immunosuppressive TME (Fig. 8(b)). As a consequence, the combination of PDT-mediated phototoxicity and IDO inhibitor-mediated immunoregulation in IND@RAL-treated groups exhibited a 3-fold and 1.7-fold growth inhibition in primary and distant tumors compared with that in non-GSH activatable liposome-treated groups (Figs. 8(c) and 8(d)). Furthermore, there was no obvious pathological damage in the main organs of the mice treated by IND@RAL, which might be result from the tumor-specific accumulation of IND@RAL for reduced side effects. In addition, Liu et al. developed an enzyme-responsive prodrug nanoplatform (mPEG-Pep-IDOi/ICG NPs) to deliver IDO inhibitor for effective PIT [82]. Once accumulated in TME, the enzyme-responsive disassembly of PEG shells led to the targeted release and enhanced penetration of ICG and IDO into the tumor tissues. More importantly, the cytokines (IFN-γ, TNF-α, IL-6, and IL-2) levels in the mice treated by mPEG-Pep-IDOi/ICG NPs-based synergistic therapy were obviously higher in the mice executed by other treatments, indicating the vigorous immune response activated by mPEG-Pep-IDOi/ICG NPs. Importantly, no obvious physiological toxicity was detected in mPEG-Pep-IDOi/ICG NPs-treated mice.

The over-expressed PD-L1 on tumor cells makes the tumor cells invisible to CTLs and allows them to evade immune surveillance. Since the PD pathway plays a critical role in regulating CTLs activity, the binding of PD-1 or PD-L1 can interrupt the inhibitory interaction and restore T cells function. Based on this, Peng et al. developed a GSH/MMP-responsive supramolecular assembly (DTX-IR820-CF27), which utilized peptides CF27 and N'-bis(acryloyl)cystamine (BISS) to generate self-cross-linking of nanoparticles with NIR dyes IR-820 and supramolecular assembled-DTX [83]. The peptide CF27 was composed of tumor-targeting peptide sequence (Lyp-1), the tumor-responsive unit, and PD-L1 inhibitor. The on-demand release of PD-L1 inhibitor prevented tumor immune escape by blocking the PD-1/PD-L1 signaling, dramatically enhancing tumor immunity [84]. Therefore, DTX-IR820-CF27-mediated PTT (808 nm, 1 W/cm^2), chemotherapy, and immune checkpoint blockade achieved efficient inhibition of both primary and secondary tumors.

3.3 TDNs for the regulation of immunosuppressive TME

Immunosuppressive cells in TME promote the tumor immune evasion and immune surveillance escape, playing a pivotal role in tumorigenesis and malignant development [85, 86]. Moreover, many studies have revealed that the physiological properties of TME (e.g., hypoxia and dense ECM) facilitate the immunosuppression [87–89], significantly contributing to the growth, reproduction, and metastasis of tumor cells. Additionally, the majority of tumors exhibit an immunologically "cold" phenotype because of the insufficient infiltration of CTLs in tumor tissues [90]. The immunosuppressive properties of TME seriously hamper the normal functioning of the host immune system. Herein, TDNs represent a simple and efficient platform for the regulation of immunosuppressive TME.

3.3.1 Suppression of immunosuppressive cells

The expression of immunosuppressive cells (e.g., regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages) often leads to a reduced immune response in PIT [91]. To address this, the most straightforward way to boost immune activation is to reduce the infiltration of

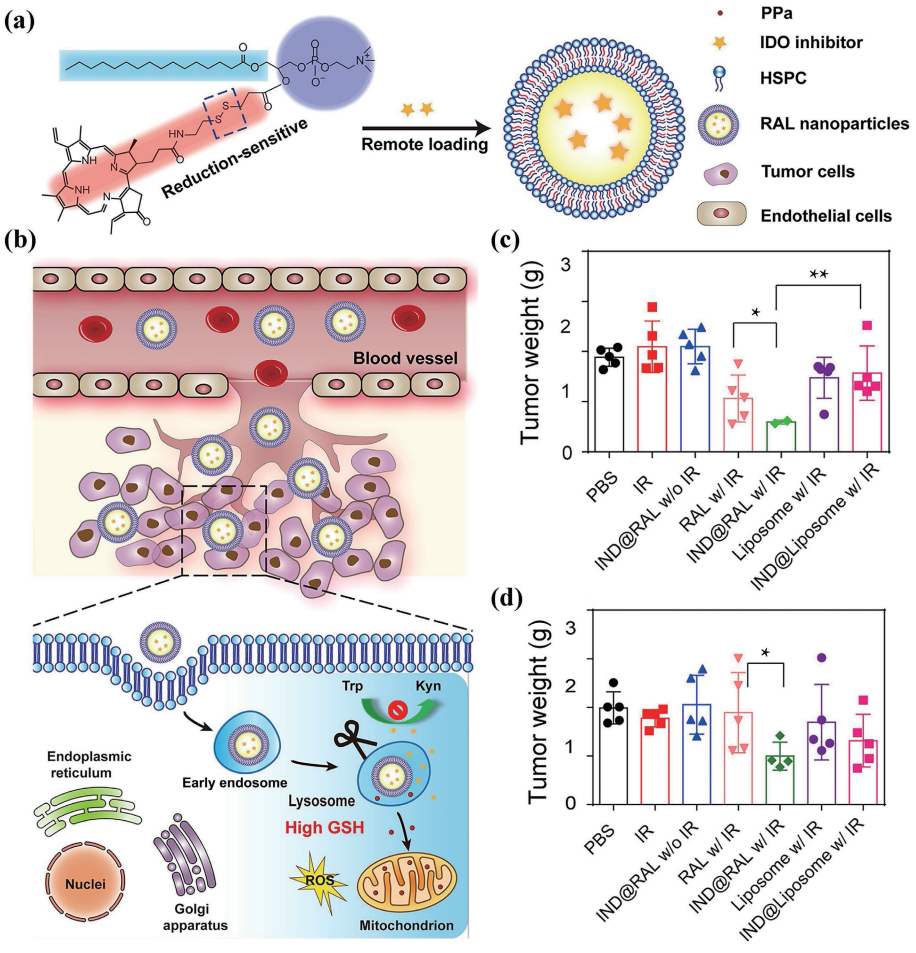

Figure 8 Porphyrin-based nanoliposome (IND@RAL) combined with immune checkpoint inhibitors for the remodeling of immunosuppressive TME. (a) The synthetic procedure of the GSH-responsive IND@RAL. (b) Schematic illustration of IND@RAL-mediated synergistic treatment of PDT and immunotherapy for high-performance antitumor effect. (c) The average weights of primary tumors and (d) distant tumors at the end of different treatments. Reproduced with permission from Ref. [81], © American Chemical Society 2019.

immunosuppressive cells. However, the random distribution of immunomodulators for immunosuppressive cells depletion may induce an overactivated immune response, resulting in autoimmune diseases and cytokine storms [92]. TDNs provide an attractive option to avoid unwanted systemic side effects. For example, Chen et al. designed a GSH-responsive photodynamic immunomodulator (ICy-NLG) for the highly specific PIT [23], which inhibited the infiltration of regulatory T cells and promoted the proliferation of CTLs. The GSH-responsiveness of ICy-NLG made it possible to precisely control the biodistribution of immunomodulators *in vivo*, thereby avoiding the potential physiological toxicity.

3.3.2 *Alleviation of tumor hypoxia*

The tumor hypoxia tends to increase the relative expression level of hypoxia-inducible factor-1α (HIF-1α), which selectively upregulates the expression of PD-L1 by binding with hypoxia response elements to initiate tumor escape and hamper immune responses [93]. Besides, hypoxic TME can also upregulate the level of immune-checkpoint proteins on the surface of tumor cells to favor tumor immune evasion [94].

More importantly, hypoxic TME severely impairs the therapeutic efficacy of PDT due to the insufficient oxygen supply [95]. To overcome this problem, Jing et al. designed a pH-sensitive nanosystem (SPM-P/C) by using photosensitizer Ce6 and a catalase gene (pDNA-cat)-encoded plasmid DNA as cores, while the shell was a pH-responsive detachable PEG [96]. Once the acidic TME triggered the shedding of the PEG coating, tumor cells transfected with pDNA-cat could express catalase to catalyze the conversion of overexpressed hydrogen peroxide to oxygen and thus remodeling TME. Therefore, PDT-induced ICD was enhanced by relieving hypoxia, promoting the maturation of DCs and the infiltration of CTLs in tumors. The mice treated with SPM-P/C plus laser irradiation (670 nm, 400 mW/cm^2) showed the most significant infiltration of $CD8^+$ T cells. Moreover, the infiltration of $CD8^+$ T cells in tumors was 17.0% in mice treated with SPM-P/C plus laser irradiation (670 nm, 400 mW/cm^2), significantly higher than that in non-responsive groups (12.0%). Besides, our group reported an anisotropic photocatalytic agent (gold/end-ceria nanorods (GCNRs)) via selectively capping ceria nanosheets (CeO_2 NSs) onto the ends of gold nanorods (GNRs) for plasmonic catalysis-mediated TME modulation [97] (Fig. 9(a)). Upon NIR laser irradiation (808 nm, 300 mW/cm^2), an efficient electron-hole spatial separation along the longitudinal axis of GCNRs occurred due to the end-deposition morphology. The hot electrons could transfer from GNRs to CeO_2 NSs, boosting the peroxidase (POD)- and oxidase (OXD)-like activities of GCNRs via Ce^{4+}–Ce^{3+} shift and oxygen vacancies generation in the acidic TME. Thus, the GCNRs could generate abundant ROS for ICD induction (Figs. 9(b) and 9(c)). In the meantime, the hot holes could drive oxygen-evolution half-reaction (OER, $2H_2O + 4h^+ \rightarrow O_2 + 4H^+$), alleviating tumor hypoxia in an on-demand and H_2O_2-independent manner to repolarize tumor-associated macrophages (TAMs) toward an antitumoral M1-type (Figs. 9(d)–9(f)). Hence, the hot electronics/holes in GCNRs could concurrently modulate the TME and induce significant infiltration of cytotoxic T cells into tumors, inhibiting the growth and metastasis of tumors (Figs. 9(g) and 9(h)).

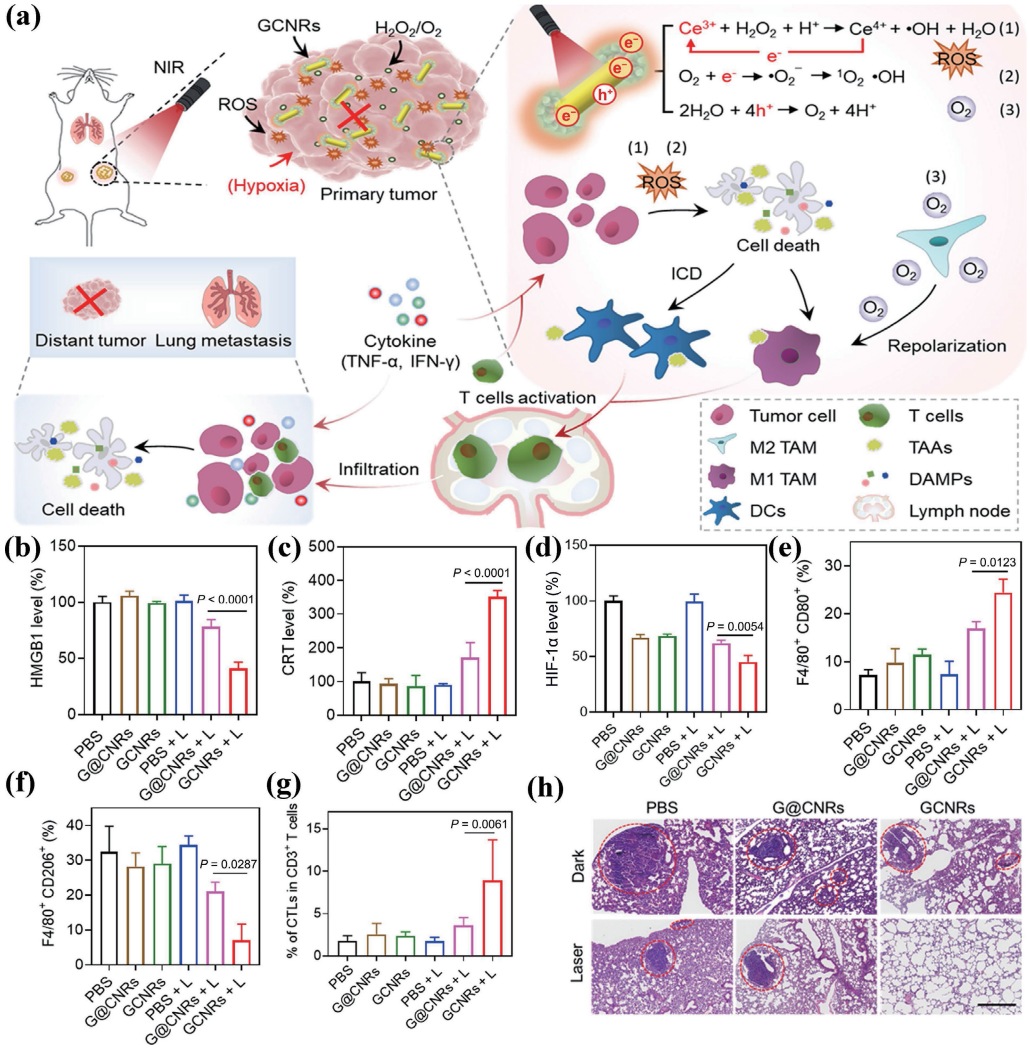

Figure 9 Anisotropic GCNRs combined with TME modulator for the alleviation of tumor hypoxia. (a) Schematic illustration of catalysis-mediated TME modulator for the inhibition of tumor growth and metastasis. Relative mean intensity of 4T1 cells incubated with (b) HMGB1-marker, (c) CRT-marker, and (d) HIF-1α-marker after six treatments. Relative mean proportion of (e) M1-TAM (stained with F4/80CD80) and (f) M2-TAM (stained with F4/80CD206) analyzed by flow cytometry after six treatments. (g) Proportions of tumor-infiltrating CTLs among CD3 cells. (h) H&E staining images of pulmonary metastasis mice after six treatments. Reproduced with permission from Ref. [97], © Elsevier Ltd. 2023.

3.3.3 *Degradation of the dense extracellular matrix*

In solid tumors, the dense ECM not only impedes the penetration of PIT agents, but also hinders immune-related cells to infiltrate the tumor tissues [98]. As the essential element of the ECM, hyaluronan (HA) is highly expressed in tumors to support the growth of tumors [99]. The hyaluronidase is widely utilized to degrade the HA in ECM, resulting in enhanced penetration of PIT agents and increasing the infiltration of CTLs in tumor tissues [100]. In addition, since HA is an important component of connective tissues, the degradation of HA in normal tissues causes potentially toxic effects [61]. To solve the above problems, Liu et al. developed a pH-responsive polymer-mediated coating strategy for tumor-specific delivery of hyaluronidase [101]. Once accumulated at the acidic TME, the pH-sensitive linker between hyaluronidase and dextran was broken, which triggered the release of hyaluronidase for the degradation of the ECM to enhance the antitumor immune response. Moreover, pretreating tumor tissue with hyaluronidase represents a simple way to degrade the overexpressed HA in the ECM before the systemic injection of PIT agents, which is expected to enhance the penetration of PIT agents and increase the infiltration of CTLs in tumor tissues. For instance, Yang et al. developed a HA-coated nanosystem by electrostatic interaction for CD44-targeted PIT [102]. Before the tail vein injection of the nanosystem, hyaluronidase was preinjected into the tumor lesions to degrade ECM, which facilitated the accumulation of the nanosystem and the infiltration of immune cells into the tumor sites.

In conclusion, by virtue of the unique biochemical properties of TME, TDNs-based PIT agents have shown excellent prospects for the enhancement of immune activation, the suppression of immune escape, and the regulation of immunosuppressive TME. Although many current *in vivo* studies have shown encouraging antitumor outcomes, it is worth noting that the complex microenvironment of human malignancies cannot be accurately simulated by the animal tumor models that are currently in use, and the majority of TDNs that exhibit beneficial therapeutic effects in animal models may not have the same positive effects in humans, which hinder the clinical transformation of TDNs. On the premise of not excessively increasing the complexity of the materials, more delicate coordination of the proportion and composition of various functional components will greatly promote the repeatability, scale-up production, and performance improvement of TDNs. In addition, stepping up the application of TDNs from small animals (i.e., mice) to large animals (e.g., rabbits and orangutans) will also benefit their further clinical translation.

4 Conclusions and future perspective

With the rapid development of nanotechnology, TDNs have

demonstrated excellent potential in tumor-specific PIT. This potential is realized through the ingenious combination of stimuli-responsive compounds, immunomodulatory agents, and photosensitizers in TDNs-based PIT agents. These agents can be activated by various stimuli present in the TME, such as pH, ROS, GSH, hypoxia, and enzyme. By controlling the pharmacokinetics and location of photosensitizers and immunomodulators, these smart agents enhance PIT efficacy, resulting in improved activation of the immune response, enhanced infiltration of cytotoxic T lymphocytes, reshaping of the immunosuppressive TME, or immune checkpoint blockade.

However, despite the significant progress made in TDNs-based PIT, there are still several limitations that remain to be addressed. First, due to the limited tissue penetration of light, phototherapy is generally more suitable for superficial cancers such as melanoma, osteosarcoma, and squamous cell carcinoma, which usually leads to insufficient immune activation in the treatment of deep-seated tumors. The utilization of advanced light sources, such as flexible fiber optic [103] and implantable light-emitting-diode devices [104], as well as the integration of NIR photosensitizer [105] or upconversion [106]/down-conversion [107] nanoparticles into TDNs may bring opportunity for stimulating the immunity of deep-seated tumors for clinical translation. Second, healthy immunity should be carefully regulated to achieve robust immunotherapy with low systemic toxicity. The insufficient immunity may result in a suboptimal therapeutic outcome, while excessive immunity might induce toxic side effects on the host. Owing to the capability to activate the host immune response with spatiotemporal controllability, phototherapy is a promising candidate to achieve the appropriate immune response. Accordingly, the further development of imaging agent integrated TDNs-based visible PIT system [108, 109], which enables *in vivo* real-time monitoring of immunotherapy, is highly desirable to realize accurate light-controlled immune response regulation. Third, it is rather challenging to scale-up the fabrication of TDNs-based PIT agents for clinical translation. As a matter of fact, most of the current approaches for constructing nanoparticle assemblies are still based on empirical knowledge [110]. In addition, with the introduction of diverse modules into TDNs-based PIT agents, the complexity and difficulty of clinical transformation might be increased. In order to achieve the large-scale and high-quality synthesis of TDNs-based PIT agents, much tentative labor needs to be devoted to further exploring the assembling/disassembling mechanism of these "smart" nanoassemblies. Last but not least, the biocompatibility and long-term toxicity of PIT agents should be systematically verified [111, 112]. In order to reduce the potential side effects of nanosystems, it may be a viable strategy to employ FDA-approved biomaterials as the building blocks for the fabrication of PIT agents. With the deepening understanding of PIT and continuous development of TDNs, it is anticipated that the TDNs-based PIT will eventually achieve the translation from bench to bedside.

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