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REVIEW

Nanomedicines Targeting Tumor Cells or Tumor-Associated Macrophages for Combinatorial Cancer Photodynamic Therapy and Immunotherapy: Strategies and Influencing Factors

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Abstract: Immunotherapy is a promising cancer treatment because of its ability to sustainably enhance the natural immune response. However, the effects of multiple immunotherapies, including ICIs, are limited by resistance to these agents, immune-related adverse events, and a lack of reasonable therapeutic targets available at the right time and place. The tumor microenvironment (TME), which features tumor-associated macrophages (TAMs), plays a significant role in resistance owing to its hypoxic microenvironment and lack of blood vessels, resulting in cancer immune evasion. To enhance immunotherapy, photodynamic therapy (PDT) can increase innate and adaptive immune responses through immunogenic cell death (ICD) and improve the TME. Traditional photosensitizers (PSs) also include novel nanomedicines to precisely target tumor cells or TAMs. Here, we reviewed and summarized current strategies and possible influencing factors for nanomedicines for cancer photoimmunotherapy.

Keywords: cancer, tumor-associated macrophages, photodynamic therapy, nanomedicines, immunotherapy

Introduction

Cancer is a disease of the genome that is initiated by somatic instability and progresses through the accumulation of numerous point mutations and structural alterations.[1,2] In the process of tumorigenesis, these diverse alterations can lead to the development of progressively more aggressive and invasive phenotypes, leading to the impairment and exhaustion of essential physical functions.[3] To prohibit tumorigenesis, the immune system can recognize genomic variation, which could give rise to characterized tumor antigens and further elicit humoral and cellular immune responses.[4] However, cancer cells have evolved multiple mechanisms, such as defects in antigen presentation mechanisms, the upregulation of negative regulatory pathways, and the recruitment of immunosuppressive cell populations, to evade immune surveillance, leading to impaired effector function of immune cells and elimination of antitumor immune responses.[5–9] For these reasons, the tumor microenvironment (TME), which involves the infiltration of specialized immune cells, also plays a significant role in cancer immune evasion, indicating that cancer immunity needs more intervention.

Various cells compose the TME and have extremely complicated relationships with cancer cells, especially immune cells that mediate innate and adaptive immune responses. Since the adaptive immune system, which is usually activated by innate immune cells, can undergo immune surveillance and tumor eradication, macrophages and dendritic cells, which

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are innate immune cells, exhibit tumorigenic effects owing to complex cross-talk and different chemokines in the TME. To this end, the modulation of innate immune cells has attracted much attention, and targeting tumor-associated macrophages (TAMs) may be a potential way to enhance the positive innate immune system.

Considering the importance of antitumor immunity, immunotherapy has become a major focus among tumor treatments because it can increase natural immune defenses to eliminate malignant cells and do less harm to normal cells.[10] With diverse traditional methods, including monoclonal antibodies and immune system modulators, which are already valuable for immunotherapy, the clinical utilization of cancer vaccines and immune checkpoint inhibitors (ICIs) has achieved notable benefits as a breakthrough in new treatments.[11–13]However, the effects of multiple immunotherapies, including ICIs, are limited by resistance to these agents, immune-related adverse events, and a lack of reasonable therapeutic targets available at the right time and place.[14,15] In recent years, many studies have attempted to develop new immunotherapies or combination therapies to increase the proportion of beneficiaries, of which therapeutic targeting via immunotherapy with nanomedicine and photodynamic therapy might constitute another breakthrough.[15]

Current Strategies for Enhancing Immunotherapy

Owing to the mechanism that drives the somatic immune system, immunotherapy is associated with high expectations of durable responses, whereas only a minority of patients treated with immune checkpoint inhibitors (ICIs) respond stably and constantly to these agents.[16,17] Resistance to immunotherapy results in 70% of patients being classified as nonresponders or progressing after the initial response to ICIs.[18] To increase the response rate and safety of immunotherapy, strategies such as therapeutic targeting and combination therapies have made breakthroughs in clinical practice. Several types of immunotherapies, including adoptive cell transfer and ICIs, have achieved durable clinical responses, but their efficacy varies, and only subsets of cancer patients can benefit from them.[19] Thus, the underlying mechanisms and additional therapeutic strategies need to be addressed.

According to one recent study, the issue of immune therapy resistance can be resolved by two factors: intrinsic factors of tumors and the dynamic nature of the TME.[20] With respect to tumor immunotherapy, we have focused on how to target tumor cells, such as PD-L1 expression,[21] mutational burden,[22] and deficiencies in antigen presentation,[23] instead of overlooking the modulation of the TME. TME modifiers can indirectly facilitate tumor immunogenicity and antitumor immunity, as components of the TME can influence sensitivity to immunotherapy both individually and in combination.

While the components of the TME include various cells, the extracellular matrix (ECM), the vasculature, and chemokines, all kinds of theoretical and rational combination therapies that enhance efficacy by adjusting the TME have been studied. To optimize the tumor microenvironment, we first need to determine which mediators play key determining roles in pro- or antitumorigenic effects. Thus, we can directly improve the antitumorigenic immune response by blocking inhibitory checkpoints, activating stimulatory pathways, and utilizing adoptive cell transfer therapy (including CAR-T-cell therapy) or vaccines as modulators of the immune microenvironment.[24–27] On the other hand, hampering immune tolerance is the key to reversing resistance to immunotherapy by targeting cellular tumorigenic mediators of tumor immune tolerance, such as MDSCs, Tregs, TAMs, and defective APCs.[28]

In addition, combining immune therapy with conventional treatment modalities, such as targeted ionizing radiation, can improve response rates. It is the radiational mechanism of causing focused cancer cell death and releasing tumor antigens that substantially activate immune cell responses.[29] Like radiation, which is a local choice for combination with immunotherapy, novel photodynamic therapy (PDT) can also cause immunogenic cell death (ICD), a cell death modality that increases innate and adaptive immune responses with the generation of long-term immunological memory.[30] Compared with radiotherapy, PDT benefits from less damage to normal tissue and minimal acquired resistance and is thus regarded as a useful adjunct to local cancer treatment.[31]

Novel Nanomedicines for Photodynamic Therapy Combined with Immunotherapy

As a novel cancer treatment, PDT has gained great attention in recent years. Photosensitizers (PSs), which can be stimulated by light at a specific wavelength, generate high levels of reactive oxygen species (ROS), leading to vascular injury and tumor cell death.[32] To ensure the ability of local tumor ablation, a two-step mechanism to react with oxygen and three determining factors is involved: high-efficiency PSs, laser irradiation at the optimal wavelength, and a sufficient supply of oxygen in the

TME.[33] In addition to destroying tumor tissue directly, PDT-driven cancer immunotherapy involves various mechanisms, such as the secretion of damage-associated molecular patterns (DAMPs);[34] the recruitment of neutrophils or macrophages;[35] and the upregulation of transcription factor expression (NF-κB), heat shock protein 70 (HSP 70)[36] or cytokines (IFN-γ, IFN-α).[37] PDT can increase tumor immunogenicity via ICD to induce an immune response.

However, the antitumorigenic immune response caused by PDT is usually mild. To take advantage of its limited immune effects, we reviewed and summarized current progress (Table 1) in photodynamic therapy combined with immunotherapy, revealing diverse novel nanomedicines that perform essential ligation functions. The use of specific nanoparticles can prolong retention time in tumor sites and achieve targeted delivery, thus reducing toxicity.[38] In combination with multimodality therapy, nanoplatforms can also mediate the optimal immune response, with all kinds of immunomodulators working together.

PDT in Combination with Immunotherapy

PDT combined with ICIs such as anti-PD-1/PD-L1 antibodies or IDO inhibitors and other immunotherapeutic agents to modulate the tumor microenvironment could be a potential approach to amplify the immune response induced by PDT in combination with immunotherapy (Table 1).

PDT in Combination with Anti-PD-1/PD-L1 Agents

Although blocking the PD-1/PD-L1 pathway is effective, its durable response rate remains low, which leads to resistance to PD-1/PD-L1 blockade therapy. Recent studies have shown that PDT can increase PD-L1 expression on tumors and thus augment PD-L1 blockade therapy.[59] Zinc pyrophosphate (ZnP) nanoparticles imbued with the photosensitizer pyrolipid (ZnP@pyro), which ensures longer circulation in the blood and greater accumulation in tumor cells than free pyrolipid does, can activate apoptosis and necrosis in tumor cells when they are exposed to light.[39] The study found that both the CLSM images and flow cytometry data confirmed that ZnP@pyro only caused CRT exposure when exposed to radiation, suggesting that photodynamic therapy (PDT), and not pyrolipid itself, is responsible for inducing immunogenic characteristics in 4T1 tumor cells. With the dual purpose of concurrently enhancing intracellular ROS production via PDT and ICD, an organic–inorganic scaffold was devised to load a honey bee venom melittin (MLT) peptide and chlorin e6 (Ce6), designated Ce6/MLT@SAB.[45] Compared with free MLT, this system could reduce hemolysis and improve Ce6 penetration of cancer cells compared with single Ce6. However, immune-related adverse events were found to be a potential risk with the overloading of anti-PD-L1 antibodies in nanomedicine.[40] To precisely regulate the amount of anti-PD-L1 agent used in nanomedicine, a molecular engineering approach involving the use of an anti-PD-L1 peptide (APP) in place of an anti-PD-L1 antibody was developed. The molecular structure was used to estimate the exact APP loading (48.4 wt%), and the resulting molecule, IR780-M-APP, was able to self-assemble into nanoparticles (NPs). Owing to its inherent aggregation-caused quenching (ACQ) effect, PdPc (OBu)8 in the water phase causes H-aggregate production and FUCL quenching. The upconversion luminescent phthalocyanine photosensitizer PdPc(OBu)^8 into the lipid bilayer was designed to reduce aggregation-induced quenching and improve water solubility and biocompatibility, promoting the development of immunotherapy combined with upconversion-based PDT for precision tumor therapy.[55]

A milieu of hypoxia within the tumor reduces the effectiveness of photodynamic therapy because of insufficient bioreaction with oxygen for the generation of ROS. Advanced nanomedicines can address tumor hypoxia by integrating different self-sustaining oxygen approaches. As an innovative nanophotosensitizer, Fe-TBP, a metal–organic framework operating at the nanoscale, can sensitize cells to effective PDT and overcome tumor hypoxia, thereby priming noninflamed tumors for cancer immunotherapy.[41] Under both normoxic and hypoxic conditions, Fe-TBP, which is composed of iron-oxoclusters and porphyrin ligands, promoted PDT. Considering the lack of blood vessels in the TME, a dual "unlocking" strategy was proposed to address hypoxia by combining engineered hybrid nanoparticles (named ZnPc@FOM-Pt) with dexamethasone (DXM).[53] The novel nanoparticle was composed of disulfide bond-doped organosilica hybrid F127 micelles (named FOM), Pt nanoparticles added to the surface of FOM, and a hydrophobic ZnPc photosensitizer. In addition, the prodrug of bromodomain-containing protein 4 inhibitor (BRD4i) JQ1, which is intended to inhibit the expression of c-Myc and PD-L1, is a crucial regulator of tumor glycolysis and immune evasion. A novel approach using JQ1 was proposed to improve photoimmunotherapy for pancreatic cancer through the inhibition of both

Table 1 Photodynamic Nanomedicine in Combination with Immunotherapies

Photosensitizer and Immunotherapeutic Agents	Delivery System	Therapeutic Target	Characteristics	Model	Ref.
Photosensitizer pyrolipid + anti-PD-L1 antibodies	Zn-pyrophosphate NPs	Tumor and PD-L1	Long Circulation and High Tumor Accumulation	4T1 and TUBO murine breast cancer (Balb/c mice)	[39]
IR780 + anti-PD-L1 peptide	NPs	Tumor and PD-L1	Precise control of the loading content of anti-PD-L1 agent	B16F10 (C57BL/6)	[40]
Nanophotosensitizer (Fe-TBP) + anti-PD-L1 antibodies	nMOFs	Tumor and PD-L1	Overcoming tumor hypoxia	Bilateral CT26 (Balb/c mice)	[41]
Ppa + JQ1	Supramolecular prodrug nanoplatform	Tumor and BRD4i	Inhibiting PDT-mediated immune evasion through down-regulating expression of c-Myc and PD-L1	Panc02 cell (C57BL/6)	[42]
PEGylated Ppa + reduction-sensitive IDO inhibitor (NLG919)	Prodrug vesicle	MMP-2 in TME and IDO	Designing a tumor-microenvironment-sheddable prodrug vesicle	CT26 and 4T1 (Balb/c mice)	[43]
HPPH + IDO inhibitor indoximod	pH-responsive nanovesicles	Endoplasmic reticulum in tumor and IDO	Achieving endosomal escape to release cargos in the cytoplasm	B16F10 (C57BL/6)	[44]
Photosensitizer chlorin e6 (Ce6) + honey beevenom melittin (MLT) peptide + anti-PD-1 antibodies	Organic–inorganic nanocarrier	Tumor and PD-1	Inducing ICD and activating DCs by MLT to enhance the ICD effect	4T1 (Balb/c mice)	[45]
Ppa + IDO inhibitor (NLG919)	Redox-activatable liposome	Tumor and IDO	Inducing ICD and reversing of suppressive tumor microenvironment	4T1 (Balb/c mice)	[46]
Chlorin derivative + IDO inhibitor (INCB24360)	Chlorin-based nMOFs	Tumor and IDO	Increased T cell infiltration in the tumor microenvironment	CT26 (Balb/c mice) and MC38 (C57BL/6)	[47]
Photosensitizer PpIX + IDO inhibitor (1MT)	Chimeric peptide NPs	TME and IDO	Releasing 1MT in response to caspase-3	CT26 (Balb/c mice)	[48]
Photosensitizer ICy-NH2 + IDO inhibitor (NLG919)	NPs	Tumor and IDO	Good biosafety and biocompatibility	4T1 (Balb/c mice)	[49]
Photosensitizer tetrakis (4-carboxyphenyl) porphyrin (TCPP) + TLR7 agonist (L-7)	NPs	Tumor and TLR7	Activating host antitumor immune responses through the co-delivery of adjuvant and tumor antigen.	B16F10 (C57BL/6)	[50]
Photosensitizer chlorin e6 (Ce6) + IDO inhibitor (1MT)	MSUCN-based nanocarriers	Tumor and IDO	Able to emit light at multiple wavelengths and actively target tumor cells	HeLa and A549 (Vitro)	[51]
Photosensitizer tetrakis (4-carboxyphenyl) porphyrin (TCPP) + STING agonists (ADU-S100)	3D NPs	Tumor and STING	Preparing STING agonist (ADU-S100)-functionalized porphyrin-based nanoparticles (NP-AS)	4T1 (Balb/c mice)	[52]
Photosensitizer zinc phthalocyanine (ZnPc) + anti-PD-L1 antibodies	Engineered hybrid nanoparticles	Tumor and PD-L1	Enhancing nanomedicine delivery efficacy and hypoxia relief	4T1 (Balb/c mice)	[53]
Photosensitizer MDK Nb-PCP NPs + anti-PD-1 antibodies	Novel light-activated nanoparticles	TME and PD-1	Achieving multimodal imaging and remodeling the immunosuppressive TME	KPC and AsPC-1 (C57BL/6)	[54]
Frequency upconversion luminescence (FUCL) phthalocyanine nano-photosensitizers PdPc (OBu)8 + anti-PD-L1 antibodies	The nano-photosensitizer platform PdPc NPs	Tumor and PD-L1	Reducing the aggregation-caused quenching and improving water solubility and biocompatibility	4T1 (Balb/c mice)	[55]
Photosensitizer chlorin e6 (Ce6) + M1 exosomes	NPs	TME and TAMs	Enhancing the photodynamic performance of Ce6 and reprogramming M2 macrophages at tumor site	C26 (FVB/N female mice)	[56]
Photosensitizer TPA-BD + anti-PD-L1 antibodies	Combo-NP	TME and PD-L1	Addressing the issue of tumor hypoxia by normalizing the tumor vasculature	OCM1 and B16F10 (C57BL/6)	[57]
Photosensitizer tetrakis (4-carboxyphenyl) porphyrin (TCPP) + STING agonists (SR-717)	nMOFs	Tumor and STING	Reversing immunosuppressive tumor microenvironment and enhancing endogenous STING activation	4T1 (Balb/c mice)	[62]

cancer glycolysis and adaptive immune resistance.[42] Pretreatment of tumors with DXM has been shown to increase the density of microvessels within the tumor microenvironment, thereby improving the tumor delivery efficiency of ZnPc@FOM-Pt and reducing HIF-1α expression.

In recent years, novel nanomedicines targeting the TME have been devised to reverse resistance to chemotherapy and immunotherapy because of the immunosuppressive nature of the TME. By utilizing tumor-specific midline nanobodies (Nbs) to target the tumor microenvironment (TME) of PDAC, researchers have developed novel light-responsive nanoplatforms capable of delivering semiconducting polymeric nanoparticles (NPs) to the TME of PDAC and generating abundant reactive oxygen species (ROS) locally for precise photoimmunotherapy.[54] Another TME-targeting nanomedicine called Combo-NPs, which include a biodegradable ROS-sensitive polymer together with DSPE-PEG2000 and lenvatinib, can effectively mitigate tumor hypoxia through the restoration of normal tumor vasculature.[57] This normalization process not only improved the effectiveness of PDT but also promoted greater infiltration of CTLs into the tumor microenvironment, enhancing the photodynamic and immunotherapeutic characteristics of the nanoparticles.

PDT in Combination with IDO Inhibitors

As the kynurenine (Kyn) pathway is involved in tumor-associated immunosuppression,[60] heme-containing enzymes, including indoleamine 2,3-dioxygenase 1 (IDO1), are pivotal immunotherapeutic targets. Kynurenine metabolites that result from IDO1 catalysis of the initial oxidation of L-tryptophan (L-Trp) accumulate,[61] ultimately inhibiting T-cell activity and enabling tumor cells to evade immune surveillance and clearance.[62] Hence, IDO functions as a substantial mediator, akin to PD-1/PD-L1 and CTLA-4, which aids in the suppression of peripheral immune responses. Combination therapies utilizing IDO inhibitors, such as NLG919, indoximod, INCB24360, and 1-MT, have been investigated as a means to regulate the immunosuppressive microenvironment.[43,44,46–49,51]

Owing to the appropriate size of the nanoparticle, a redox-activated liposome was developed, featuring prolonged blood circulation and enhanced tumor accumulation.[46] Through self-assembly of the porphyrin–phospholipid conjugate and coencapsulation of an indoleamine 2.3-dioxygenase (IDO) inhibitor (NLG919) into the interior lumen, these liposomes can induce immunogenic cell death (ICD) and reverse the suppressive effect on the tumor microenvironment. The use of another nanomedicine, ICy-NLG, has been found to be an effective strategy for addressing uncontrollable side effects caused by the uncontrolled distribution of normal tissue. This activatable photodynamic immunotherapeutic agent was created by linking the photosensitizer ICy-NH2 with NLG919 via a glutathione (GSH)-cleavable linker, which can only be activated at tumor sites.[49] The IDO inhibitor INCB24360 was also enclosed in nMOF channels to stimulate a widespread antitumor immune response, with effective local and distant tumor rejection in CT26 colorectal cancer models.[47] This synergistic combination confirmed that nMOF can also induce systemic antitumor immunity. Multishell-structured upconversion nanoparticles (MSUCNs) were created to have strong photoluminescence. These nanoparticles were designed for a therapy combining near-infrared light-induced photodynamic therapy with an IDO inhibitor (1MT), leading to cancer cell apoptosis and CD8(+) T-cell infiltration.[51]

In addition to targeting tumor cells, cell organelles such as the endoplasmic reticulum could also be specifically targeted to cause calreticulin exposure for the ICD effect. pH-responsive nanovesicles (pRNVs) formed by the self-assembly of the block copolymer polyethylene glycol-b-cationic polypeptide can act as nanocarriers and achieve endosomal escape to release cargos in the cytoplasm.[44] These findings indicate that the subcellular distribution of PSs should be investigated to optimize their efficiency. The TME is another target, with many studies contributing to the identification of precise and effective strategies. Among them, matrix metalloproteinase-2 (MMP-2) has been used to design a tumor microenvironment-sheddable prodrug vesicle by combining a PEGylated PS with a reduction-sensitive prodrug of an IDO-1 inhibitor (indoximod).[43] The prodrug vesicles remained inactive in the bloodstream but functioned in the TME, as MMP-2 could cleave the modified PEG corona. Notably, the PpIX-1MT peptide, which combines the photosensitizer PpIX with the IDO-1 inhibitor 1MT via a caspase-responsive peptide sequence, can also accumulate in tumor areas via enhanced penetration retention despite its weak targeting effect.[48]

PDT in Combination with Other Immunotherapeutic Agents

Immunologic adjuvants are chemicals that often increase the intensity and longevity of the immune response to certain

antigens when they are administered together. For immunotherapy, vaccine formulations, including TLR7 agonists, STING agonists, and M1 exosomes, usually use immunologic adjuvants to increase the immune response and effectiveness of immunizations. However, these immunotherapeutic agents could also drive cancer immunotherapy and promote a favorable TME for PDT treatment.[63]

First, a combination of Toll-like receptor 7 agonists, photodynamic therapy agents, and tumor antigens was created as a nanoplatform coated with cancer cell membranes, also called biomimetic nanoparticles (CCMVs/LTNPs).[50] After destroying tumor cells via PDT, the immune system can be stimulated to eradicate any remaining tumor cells with the assistance of immune adjuvants and tumor antigens from the cancer cell membrane. STING agonists for immunotherapy are highly promising and are now undergoing clinical studies. Two studies have used STING agonist-mediated (ADU-S100 and SR-717) immunotherapy with photodynamic therapy to treat breast cancer.[52,58] Despite the use of different delivery nanoplatforms, this rational combination was shown to activate the innate immune response and exhibit useful antitumor effects. Exosomes are extracellular vesicles that exist in the TME and are usually used as ideal drug delivery vectors. Notably, M1 exosomes derived from M1 macrophages may convert M2 macrophages into M1 macrophages, showing significant potential for cancer immunotherapy. Thus, synergistic therapy using M1 exosome-based nanoplatforms could not only achieve TNM-targeted accumulation but also reprogram immunosuppressive M2 macrophages into antitumor M1 macrophages for cancer immunotherapy.[56]

Multimodality Therapy Involving PDT for Enhancing Immunotherapy

To enhance the anticancer impact, multimodality treatment strategies have been created by integrating chemotherapy, PDT/PTT, and immunotherapy (Figure 1). Traditional chemotherapeutic medications do not have a specific method to target tumors, leading to increased toxicity and side effects in the body.[64] Like immunotherapy, resistance to chemotherapy also necessitates spatiotemporal precision and noninvasive properties, making PDT the most promising approach for

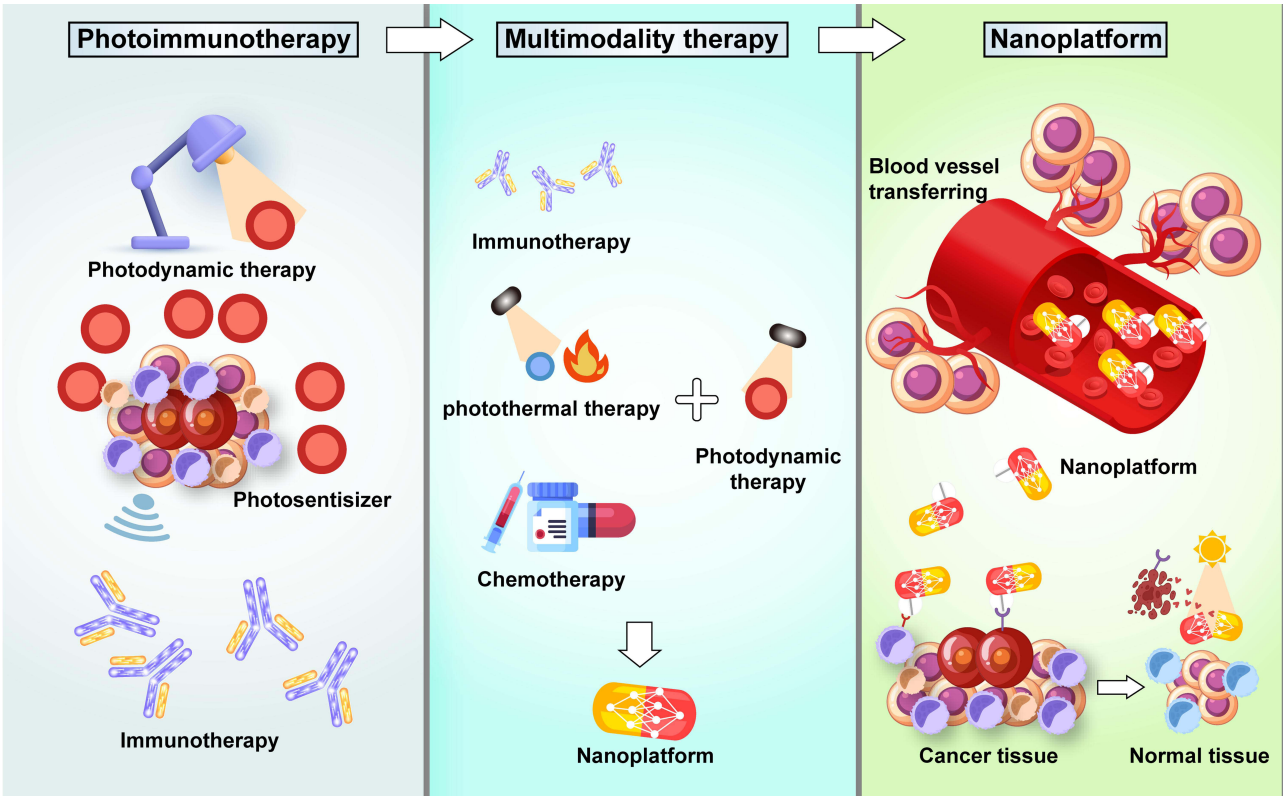

Figure 1 Multimodality therapy for photoimmunotherapy with nanoplatforms. Photodynamic therapy can also induce a native immune response via immunogenic cell death. In combination with nanoplatforms, multimodality treatment strategies can target cancer tissue with enhanced therapeutic effects by integrating chemotherapy, PDT/PTT, and immunotherapy.

addressing chemoresistant malignancies and enhancing therapeutic impact when combined with chemotherapy.[65] With immunogenic cancer cell death or other immunogenic effects, anticancer chemotherapy shares treatment aims with PDT so that the enhanced immune response can further eradicate other chemotherapy-resistant cancer cells.[66] For example, a biocompatible nanomedicine called PCL-NPs, which combines a chemiluminescence agent (luminol), a photosensitizer (Ce6), and a reactive oxygen species (ROS)-activatable thioketal-based paclitaxel (PTX) prodrug, was developed to simultaneously enhance chemotherapy and PDT in combination therapy.[67] To ensure a sufficient oxygen supply, this nanomedicine could produce excess hydrogen peroxide within the tumor, resulting in the oxidation of the luminol component and the production of light for photodynamic therapy via chemiluminescence resonance energy transfer (CRET). Moreover, the singlet oxygen ((1)O(2)) generated in this mechanism both directly eliminates tumor cells and enhances oxidative stress to accelerate the activation of the PTX prodrug. In combination with IDO inhibitors, an albumin-based nanoplatform was developed to further boost synergistic cancer treatment that simultaneously delivers IR780, the NLG919 dimer, and the hypoxia-activated prodrug tirapazamine (TPZ).[68] TPZ, a stimuli-activatable chemotherapeutic prodrug, can mediate chemotherapy to enhance PDT-induced tumor ICD and stimulate more potent antitumor immunity, which is activated only by the hypoxic TME. Although NLG919, an IDO inhibitor, reduces the immunosuppressive TME and increases the infiltration of CTLs, the presence of memory T cells also prevents tumor recurrence and metastasis almost completely, indicating that this is a successful strategy for treating hypoxic and immunosuppressive malignant tumors.

Photothermal therapy (PTT) destroys cancer cells by inducing high temperatures in tumor tissues via the conversion of light into heat in a minimally invasive manner. However, PTT compounds have not undergone significant clinical studies to determine their effectiveness in enhancing localized light-based heating and ablation of tumor tissues.[69] The PDT/PTT modality has usually been used in combination for skin cancer treatment. Similarly, PTT can use reactive oxygen species (ROS) and regulate local hyperthermia through mediators to disrupt the intracellular redox balance, causing DNA damage in the mitochondria and nucleus and ultimately triggering antitumor immune responses.[70] For example, a nanomedicine was designed to carry both IR780 and 2.2'-azobis[2-(2-imidazolin-2-yl)propane]-dihydrochloride (AIPH) to achieve combined treatment activated by photothermal therapy.[71] By targeting the MMP and modifying the anti-PD-L1-pep sequence on the surface of nanocarriers, this nanomedicine blocked immune checkpoints and the infiltration and activation of T cells (CTLs).

The Potential of PDT Nanoparticles to Target TAMs

Macrophages are specialized cells of the mononuclear phagocyte system that are crucial for maintaining balance in the body, healing wounds, regenerating tissues, and providing immunity. Derived from the myeloid cell lineage, they are distributed mainly on the first line of innate defense against invading pathogens through the phagocytosis of foreign substances or antigen presentation to T cells.[72] Following exposure to various signals, these primary macrophages undergo polarized activation and exhibit distinct characteristics. TAMs, which are representative polarized macrophages, can be divided into two subtypes: classically activated macrophages (M1) and alternatively activated macrophages (M2).[73] Specifically, M1 polarization is influenced by exposure to IFN-γ and lipopolysaccharide (LPS), and substantial amounts of IL-12 are released, which hinders tumor growth. In contrast, M2 polarization is influenced by exposure to IL-4 or IL-13, with IL-10 released to support tissue repair, wound healing, and tumor development. During tumorigenesis, TAMs switch from M1 to M2 polarization in response to alterations in the TME, such as hypoxia.[38] Moreover, TAMs, mainly M2 macrophages, also contribute to tumor advancement through mutual communication with malignant T cells. Therefore, reshaping TAM polarization is essential for successful TAM-directed cancer immunotherapy.[74] We describe the roles of TAMs and strategies for TAM reprogramming below. (Figure 2)

Role of TAMs in Promoting Tumorigenesis

As major components of the TME, TAMs play crucial roles in the cancer-related inflammatory milieu by secreting various cytokines, chemokines, and growth factors, leading to the maintenance of the activation status of various immune cells.[75] Although TAMs present mainly M1 macrophages in the first stages of tumor growth, most of the protumor inflammatory factors classified as "M1 cytokines" can also initiate tumorigenesis. For example, TNF-α produced by M1

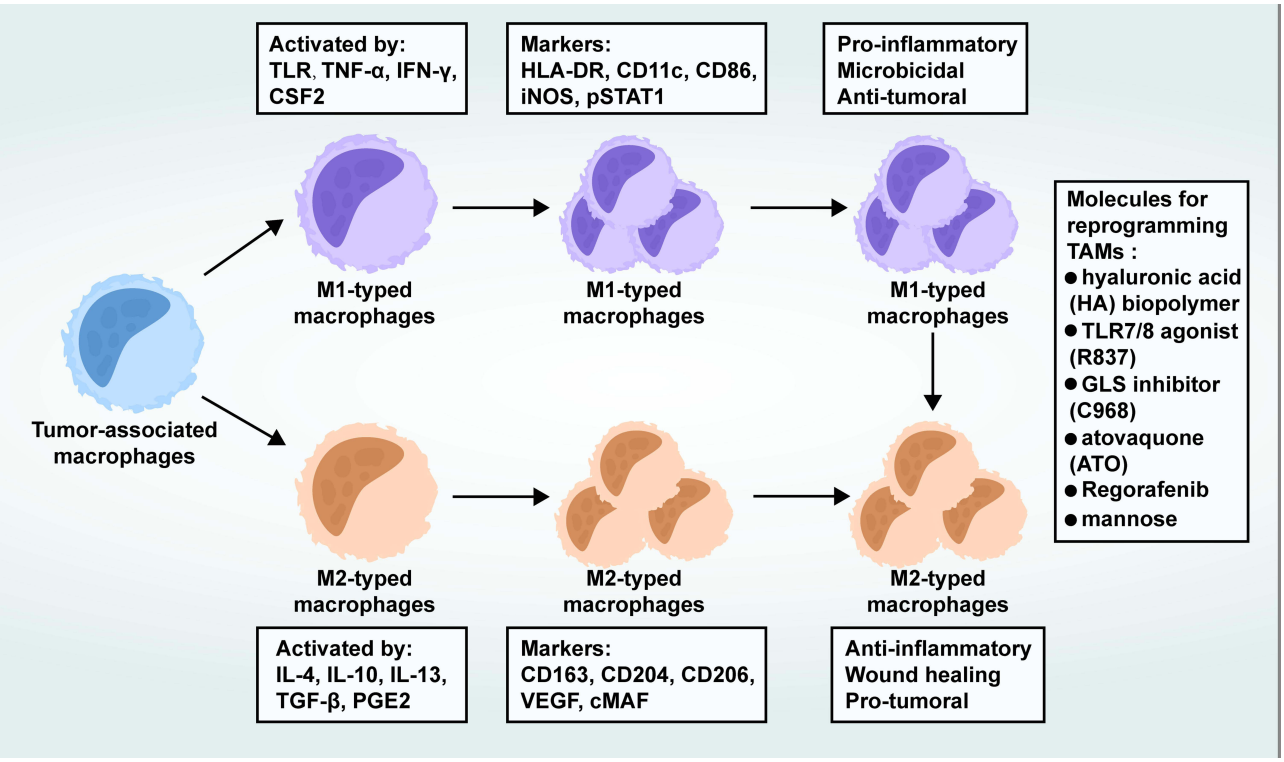

Figure 2 Polarization state characteristics of M1 and M2 macrophages and strategies for reprogramming.
Abbreviations: TLR, toll-like receptor; CSF2, colony stimulating factor 2; iNOS, inducible nitric oxide synthase; pSTAT1, phospho-signal transducer and activator of transcription 1; PGE2, prostaglandin E2; VEGF, vascular endothelial growth factor; cMAF, transcription factor; GLS, glutaminase.

macrophages or other immune cells can cause the accumulation of ROS in precancerous cells, resulting in changes due to oxidative damage to several oncogenes and tumor suppressor genes, such as p53.[76] It also activates NF-κB transcription factors, which stimulate the proliferation and survival of cancer cells.[77] These diverse cytokines tend to induce the accumulation of oncogenes and tumor suppressor genes, ultimately promoting tumor initiation.

Although DNA damage caused by M1 macrophages can promote tumorigenesis, M2 macrophages are involved after a tumor progresses and grows. M2 macrophages are characterized by the release of anti-inflammatory substances such as transforming growth factor b (TGF-β1) and IL-10, which are involved in tumor angiogenesis, malignant invasion, and immunosuppression.[78] In contrast, M1 macrophages can be relatively antitumorigenic since they help eradicate foreign substances such as precancerous cells. The presence of many TAMs and immunological checkpoints (ICs) has been reported to be a significant immunosuppressive feature in the TME. Proteins in ICs have been the primary focus of cancer immunotherapy, with current FDA-approved checkpoint inhibitors targeting CTLA4, PD-1, and PD-L1. However, multiple immune checkpoint molecules, such as SIRPa, Fcr, and Siglec-10, are commonly found on M2 macrophages to prevent their antitumorigenic effects.[79] Recent studies have shown that nanotechnology for drug delivery to target tumor-associated macrophages could enhance immunoadjuvant treatment for cancer.

Advantages of PDT Nanomedicines for TAM Reprogramming

There is growing evidence that targeting TAMs or inhibiting the tumorigenic function of TAMs with nanomedicines might increase the effectiveness of traditional cancer treatments. Nanomaterials have a variety of physical and chemical features that allow them to act as delivery vehicles and immunomodulators, showing potential for enhancing the immunosuppressive conditions within tumors.[80] Among these features, nanomedicine-based targeting, which is the determining factor, could achieve low toxicity, better pharmacokinetics, and increased bioavailability and therapeutic efficacy.[81] By targeting cancer cells or TME components, PDT nanomedicines can influence antitumor immune responses, in addition to destroying cancer cells directly.[82] Given that the immunosuppressive TME is mediated mainly by M2-type macrophages, reprogramming TAMs

to M1-type macrophages is important, as PDT nanomedicines enhance therapeutic effects via ICD. Some PDT nanomedicines have been designed in combination with specific molecules that reprogram TAMs, including hyaluronic acid (HA) biopolymer,[83,84] a Toll-like receptor 7 and 8 (TLR7/8) agonist (R837),[85,86] the glutaminase (GLS) inhibitor compound 968 (C968),[87] and atovaquone (ATO).[88]

As a natural glycosaminoglycan, HA can modulate the activation of protumor M2-type and antitumor M1-type macrophages by increasing IL4 and IL10 gene expression.[89] A novel photosensitizer-loaded nanoconjugate (PUN) was created by combining manganese dioxide (MnO(2)) nanosheets with an HA biopolymer to increase the effectiveness of NIR light-mediated PDT by reducing hypoxia and remodeling TAMs simultaneously.[83] After delivery into the acidic TME, MnO(2) nanosheets can be degraded to produce sufficient oxygen for PDT, while the bioinspired polymer HA can mediate TAM reprogramming, which effectively prevents tumor relapse after PDT treatment. A further advanced nanomedicine combining PDT and PTT was also modified with PEGylated HA. It not only achieves TAM reprogramming but also induces the maturation of dendritic cells (DCs) and activated effector cells to enhance antitumor immune responses.[84] Owing to their strong anticancer and immune-boosting effects, TLR7/8 agonists, such as resiquimod (R848), are usually used as immunological adjuvants. Notably, R848-loaded nanoparticles have also been shown to effectively reprogram TAMs from supporting tumors (M2-type) to fight against them (M1-type) via a chimeric peptide-engineered self-delivery system (ChiP-CeR) in a breast cancer model.[85] In addition to this nanoplatform modified by a tumor matrix-targeting peptide, a cell membrane-based delivery system based on cyclodextrin-based host–guest molecular interactions could repair errors caused by chemical and genetic alterations in cell membranes while providing R848 as a TAM-reprogramming agent.[86] GLS inhibitors have been found to convert M2-type TAMs into M1-type TAMs by inhibiting glutamine metabolism. With a carrier-free immunotherapeutic nanocarrier, the combination of C968 and the photosensitizer chlorin e6 could result in dual synergistic effects.[87] As tumor hypoxia is involved in the immunosuppressive TME, ATO could significantly improve the hypoxic microenvironment by inducing the maturation of DCs and the polarization of M2-type macrophages.[88] Like ATO, regorafenib (Reg), which is a vascular normalization agent that targets many kinases related to angiogenesis, can also improve the TME by normalizing the tumor vasculature. It was also reported to be used in a photodynamic polymer, showing the ability to reprogram TAM polarization.

Indirect reprogramming of TAMs is another strategy via the specialized property of novel nanoparticles loaded with only active PSs. First, the ROS generated by the type I photosensitizer can transform M2 macrophages into M1 macrophages and inhibit immunological checkpoints. This was confirmed by a photosensitizer-loaded lipidic nanosystem in which the immune checkpoint inhibitor Siglec-10 was modified to further boost the antitumor immune response of M1 macrophages.[90] In addition, oxidative damage to mitochondrial DNA reportedly modulates TAM polarization through PDT-induced ICD and impaired mitochondrial Ca(2+) overload.[91] Specialized nanoparticles, such as iron oxide nanoparticles (IONs), can decrease the level of M2-associated arginase-1 in macrophages, causing them to shift toward M1-type macrophages by increasing the activity of the interferon regulatory factor 5 signaling pathway.[92]

The Application of PDT Nanoparticles Targeting TAMs

Nanomedicine for tumor targeting is usually accomplished via passive and active targeting techniques. While passive targeting is based on the enhanced permeability and retention effect (EPR effect), active targeting involves attaching targeting ligands, such as antibodies or peptides, to nanoparticles. These ligands are designed to bind precisely to receptors that are overexpressed during disease, indicating that an appropriate targeting molecule is endowed with high efficiency and low toxicity.[82] For example, NP-PDT@Reg delivered by passive targeting was observed mainly in tumors as well as in the liver and kidney. Here, we have summarized the current strategies for nanoparticle targeting of TAMs and classified them as direct targeting, dual targeting, or TME targeting strategies according to their targeting mechanisms. (Table 2)

Direct targeting refers to specific receptors on TAMs, such as CD206 receptors, which are expressed on M2-like macrophages.[101] CD206, a mannose receptor, induces receptor internalization by endocytosis and phagocytosis of the attached ligands in macrophages upon binding mannose-rich glycoconjugates. One study described novel immunophotodynamic nanoparticles by combining TAM self-targeting acrylic acid-grafted mannan (a polysaccharide that is a highly branched polymer of mannose) with a photosensitizer (Ce6) and then incorporating a TLR7/8 agonist (R848).[99] Ultimately, it effectively targeted TAMs, modulated the immunosuppressive TME, and prevented tumor metastasis by

Table 2 The Strategies on Photodynamic Nanomedicine for Targeting TAMs

Photosensitizer and Targeting Molecule	Delivery System	Targeting Strategy	Characteristics	Model	Ref.
Photosensitizer chlorin e6 (Ce6) + PKγ inhibitor IPI-549	Liposome	TME (MDSCs, by PI3Kγ-AKT)	Facilitating the dendritic cell maturation and tumor infiltration of CD8(+) T cells while decreasing the tumor infiltration of immunosuppressive regulatory T cells, MDSCs, and M2-like TAMs.	CT26 (male balb/c mice)	[93]
Indocyanine green (ICG) + ALE/Man-g-HA conjugate	Mesoporous calcium silicate nanocomposites (MCNs)	Dual (tumor cell and TAMs, by CD44 and CD206 receptors)	Facilitating the delivery of chemotherapeutic agents to the tumor microenvironment	4T1 (female balb/c mice)	[94]
Red-emissive AIE photosensitizer +α-mannosides	A cost-effective theranostic probe (TPE-Man)	Direct (by CD206)	First small molecular theranostic probe for TAMs	Macrophages (in vitro)	[95]
NaYF4: Yb, Er@NaYF4 conjugated with Rose Bengal (NPR)	TAM membrane (TAMM)	Dual (tumor cell and TAMs, by CSF1 −CSF1R)		4T1 (balb/c mice)	[96]
Hydrophobic photosensitizer (IR780) + zoledronic acid (Zol)	Lipo Zol/IR NPs	Dual (tumor cell and TAMs, by microcalcifications)	Enable precise spatiotemporal targeting of different types of cells in the TME	4T1 (female balb/c mice)	[97]
Aggregation-induced emission luminogens (AIEgens)+ CRV (amino acid sequence, CRVLRSGSC)	NPs	Dual (tumor cell and TAMs, by retinoid X receptor beta)	Eliminating both lung cancer cells and TAMs and remodeling the TME	LLC (male C57BL/6 male mice)	[98]
Photosensitizer chlorin e6 (Ce6) + mannan	NPs	Direct (by CD206)	Repolarizing anti-inflammatory M2-like cells to pro-inflammatory M1-like cells	CT26 (male balb/c mice)	[99]
Photosensitizer chlorin e6 (Ce6) + mannose	A mannosylated macrophage-membrane coated upconverting nanoparticles	Direct (by CD206)	Targeting by macrophage cell membrane–coating and surface mannose modification	4T1 (female balb/c mice)	[96]

reprogramming TAMs and increasing the infiltration of T immune cells. In addition, the first small-molecule theranostic probe for TAMs based on a targeting strategy was constructed with a red-emissive aggregation-induced emission (AIE) photosensitizer core and two flanking TAM-targeting α-mannosides. This method has demonstrated benefits such as cost-effectiveness, precise targeting, fluorescent light-up imaging, and effective photodynamic ablation.[95] In addition, TAM-like upconversion nano-PSs were designed for binding specific immunoregulatory molecules related to TAMs on the surface. For example, the combination of TAM-like upconversion nano-PSs and mannose was used to strongly target TAMs via two approaches, (i) a macrophage membrane coating and (ii) surface mannose modification, to generate our UCNPs@mSiO2-PFC/Ce6.[100]

Dual-targeting nanomedicines that target both TAMs and tumor cells should use at least two different targeting ligands. By targeting CSF1−CSF1R, NPR@TAMM was constructed with a tumor-associated macrophage membrane derived from the primary tumor, modified by macrophage colony-stimulating factor 1 receptor (CSF1R), although it was found to be tumor-targeted by binding to CSF1 secreted by tumor cells.[96] To prepare the TAM-coated NPR@TAMMs, the TAM membrane (TAMM) was derived from purified primary TAMs sorted by anti-F4/80 and CD206 beads and coated onto NPR (NPR@TAMM), implying that the ability of NPR@TAMMs to bind CSF1 was conferred by their TAM membrane coating due to the high CSF1R content of the TAM membrane. Notably, HA and mannose, which are known to target different types of tumor cells and TAMs, were used in combination with PDT to promote cell apoptosis both in vitro and in vivo via precise localization to tumor cells and TAMs.[94] In addition, a zwitterion-type near-infrared (NIR) AIE luminogen (AIEgen) compound was used for lung cancer treatment after undergoing biomimetic alteration.[98] The dual-targeting potential of the CRV peptide for both LLC cells and M2 macrophages was mediated through CRV peptide binding with retinoid X receptor beta and CRV-engineered exosomes targeting LLC cells. Nitrogen-containing bisphosphonates (N-BPs), such as zoledronic acid (Zol), are also hydrophilic compounds utilized to reverse the immunosuppressive properties of TAMs.[102] However, it is a potential molecule for only breast cancer treatment because of its distinct ability to attach to microcalcifications present in breast tumors. Thus, one study designed a dual-targeting nanomedicine in a 4T1 breast cancer model. Once Zol is loaded on a nanomedicine arriving at a breast tumor, it achieves precise spatiotemporal TAM targeting and causes the death or repolarization of TAMs through the pinocytosis or phagocytosis of TAMs in combination with a hydrophobic photosensitizer (IR780).[97]

TME targeting involves a broad spectrum of signaling pathways, such as the PI3K-γ-AKT pathway. PI3Kγ, a member of the PI3K family, is prominent in myeloid cells and has a specific role in controlling their immunosuppressive actions. With immunotherapy targeting MDSCs to effectively suppress tumor growth, a liposome-based nanomedicine could induce the maturation of DCs and the infiltration of CD8(+) T cells into tumors while reducing the infiltration of regulatory T cells, MDSCs, and M2-type TAMs.[93]

Factors Influencing the Therapeutic Efficacy of PDT Nanomedicines

Various variables greatly restrict the effectiveness of PDT, hence diminishing its potential to stimulate an immunological response. Although advanced nanomedicines have created new opportunities to increase and optimize the effectiveness of PDT, resulting in a stronger immunological response, some influencing factors need to be focused on, such as the size and shape of nanomedicines, precise targeting, the aggregation-caused quenching (ACQ) effect, and biocompatibility with low toxicity.

Size, shape, and surface chemistry will be crucial factors when researchers begin to build multifunctional nanostructures, which endow photodynamic nanomedicines to be able to use the enhanced permeability and retention effect (EPR).[103] A study demonstrated the significance of nanoparticle size and shape, as well as the non-specific adsorption of proteins, in achieving optimal intracellular absorption.[104] It indicated that the size and shape of nanometer-scale structures can be manipulated to control the administration of proteins, medicines, and oligonucleotides utilizing nanoparticles for diagnostic and therapeutic purposes. Recently, some studies have explored different photodynamic nanoparticles with optimal size and shape in combination with checkpoint blockade for cascade synergetic treatment of cancer.[105,106] However, there are still many areas that can be improved, such as reducing the size of the construct, strengthening the efficiency of upconversion, improving stability in photosensitizer loading, optimizing settings for photodynamic therapy (PDT), and ultimately increasing the effectiveness of PDT.[107]

With respect to targeting strategies, active targeting with targeting ligands has the potential for precise targeting, but there are many disadvantages to be debated and addressed, such as overall targeting efficiency, particular cell delivery, formulation complexity, and translational potential.[108] The ACQ effect is a phenomenon in which a fluorophore exhibits strong luminescence in solution but loses its luminescence when aggregated, leading to a reduction in the amount of PSs. To avoid the ACQ effect, AIEgens are a promising choice for developing versatile phototheranostic agents. Owing to their unique aggregation-induced emission and aggregation-induced production of ROS, these specific PDT nanomedicines exhibit strong aggregation-enhanced theranostics (AET) properties, which are different from those of their counterparts with aggregation-induced quenching (ACQ) characteristics.[109] When nanomedicines function as targets, the degree of absorption by the body effectively increases with bioavailability, which challenges the solubility and permeability of pharmaceuticals. Recent studies have shown that drug nanocrystals have increased solubility, particle dissolution and a greater affinity for biological mucosa than drug nanocarrier systems do, leading to an improved EPR effect and bioavailability.[110] In addition to enhancing the effectiveness of PDT, the safety of nanomedicines is so important that we need to be seriously concerned about the biocompatibility and toxicity of nanomaterials.[111]

Conclusions and Future Perspectives

As previous findings have demonstrated, TAMs are critical in many pathophysiological processes of cancers, such as tumorigenesis and the immunosuppressive TME, leading to tumor initiation and metastasis. However, there are several limits to PDT and PTT.[112] Local therapy with an optical fiber in PDT or PTT has difficulty destroying tumor cells outside the focus region or affecting therapeutic results in patients with advanced-stage cancer. Light irradiation has limited penetration effectiveness into deep tissue because endogenous biomolecules absorb light. It is difficult to efficiently stimulate photosensitizers located more than 1 cm below the tumor surface.[113] Second, most anticancer nanomedicines accumulate heterogeneously in tumors, resulting in limited therapeutic results because of a failure to overcome realistic physiological transport obstacles and interpatient variability.[114] Despite breakthroughs in technology for directing therapeutic nanoparticles to tumor tissue, less than 1% of nanoparticles administered intravenously reach the tumor. Nanomedicines that target particular chemicals that are overexpressed on the surface of cancer cells or in the TME have yet to reach the market owing to the complexity and heterogeneity of malignancies in the body.[115] As a result, it is becoming clear that current nanomedicines for PDT must overcome the constraints of old nanomedicines, such as limited delivery effectiveness and poor clinical results, via creative methodologies. Finally, the immunotherapeutic effect of PDT should be verified by its extensive use in clinical trials.

In recent years, an increasing number of new strategies have been developed, suggesting that nanomedicines that target TAMs have effects similar to those of nanomedicines that target tumor cells. Through targeting TAMs, nanomedicine can directly reprogram immunosuppressive M2 macrophages into antitumor M1 macrophages for cancer immunotherapy, resulting in the modulation of the immunosuppressive TME and prevention of tumor metastasis. Although there is a lack of clinical trials evaluating mature nanomedicines, the development of more nanomedicines with direct-targeting or dual-targeting TAMs for cancer photoimmunotherapy is promising.

Data Sharing Statement

All the data generated or analyzed during this study are included in this published article.

Ethics Approval

Ethical approval does not apply to this article.

Author Contributions

YW participated in the literature searches and data collection and wrote the manuscript in consultation with XM. XM was responsible for the study conception and manuscript revision. All the authors discussed the results and contributed to the final manuscript.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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