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REVIEW

Self-assembled nanoplatforms for cancer immunotherapy: Principles, progress and perspectives

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Combination therapy

Abstract Cancer immunotherapy is an innovative treatment approach that leverages the immune system's ability to identify and attack tumor cells. Its goal is to initiate or re-establish the tumor−immune cycle. However, challenges such as limited response rates and adverse immune responses have hindered the further application and advancement of this therapy. Recent progress in nanomedicine, particularly in self-assembled nanomaterials, has attracted significant attention due to their excellent physical and chemical properties. Self-assembled nanoplatforms can be designed to selectively deliver immunoadjuvants, therapeutic drugs, photosensitizers, and sonosensitizers, overcoming the limitations of traditional monotherapies. By utilizing these self-assembled nanoplatforms to synergistically combine cancer immunotherapy with photodynamic therapy (PDT), photothermal therapy (PTT), radiotherapy (RT), and sonodynamic therapy (SDT), it becomes possible to amplify and enhance the immune responses elicited by these localized treatments, thus offering new strategies for cancer therapy. In this review, we discussed various immunotherapy platforms based on the self-assembly of nucleic acids, peptides and proteins, metals, and supramolecules. We also highlight the significant research advancements over the past three years in the use of self-assembled nanomaterials for combination therapies centered on immunotherapy, aiming to provide valuable insights and references for ongoing tumor therapy research.

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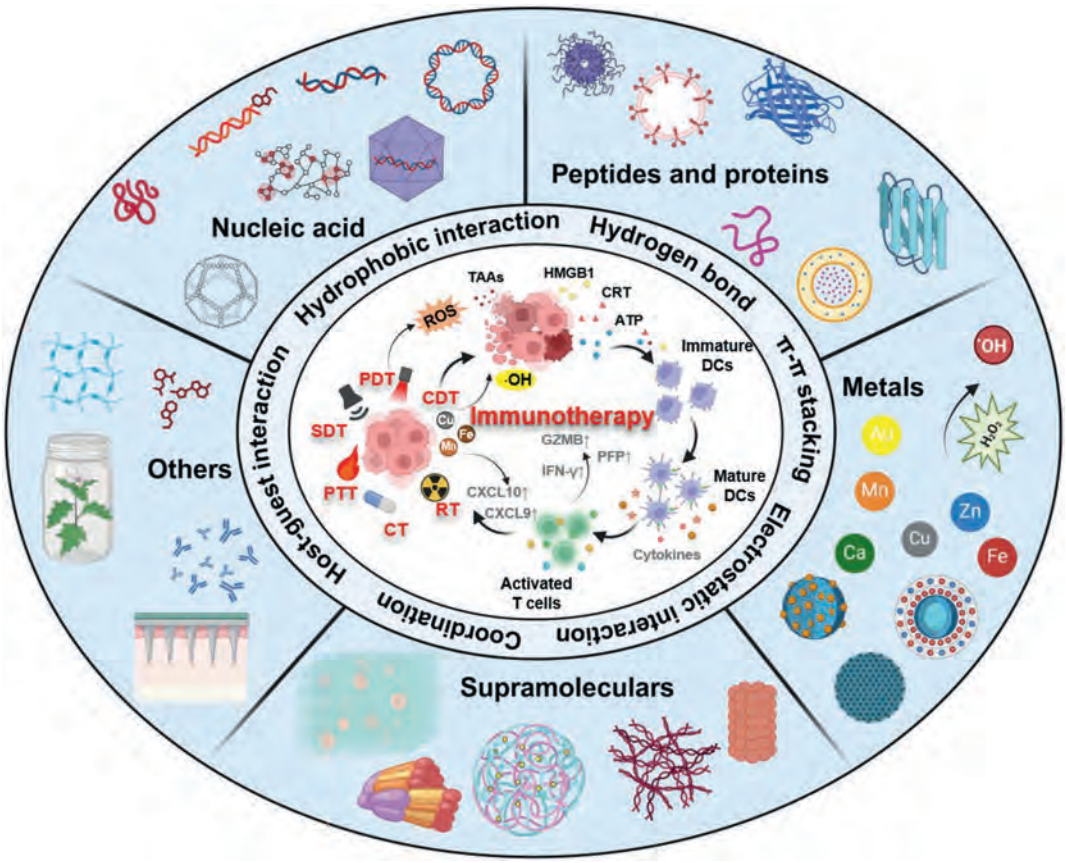
1. Introduction

Malignant tumors possess the ability to evade the body's defense and immune systems, allowing them to proliferate and become challenging to treat, and have become a leading cause of death worldwide[1]. Common cancer treatments include surgery, chemotherapy (CT), and radiotherapy (RT), which can inhibit tumor growth to some extent but often come with serious side effects and negative impacts surrounding healthy tissues[2,3]. Moreover, tumors present a complex interplay of tumor cells, host cells, various regulatory factors, and peripheral tissues. This intricate tumor microenvironment (TME) often leads to recurrence and metastasis in patients following traditional treatment, highlighting the urgent need for new therapeutic approaches[4–6]. In this context, cancer immunotherapy has emerged as a promising treatment method. It harnesses the immune response and memory generated by both the innate and adaptive immune systems to restart and maintain the tumor−immune cycle, providing specific tumor cell killing and preventing recurrence. This may be the fundamental strategy for overcoming tumors[3,7]. Currently, cancer immunotherapy has made significant strides and has become the fourth cornerstone of cancer treatment, alongside surgery, RT and CT. Numerous immunotherapy drugs are either being developed or already in clinical use, including ipilimumab (a monoclonal antibody) and immune checkpoint inhibitors (ICIs). These therapies activate the immune system by targeting proteins such as cytotoxic T lymphocyte-associated protein-4 (CTLA-4) or programmed cell death protein-1 (PD-1), further enhancing the destruction of tumor cells[8]. Although these results are encouraging, challenges such as limited response rates and adverse immune reactions continue to hamper the further application and development of cancer immunotherapy[9].

Fortunately, with the rapid development of nanotechnology, strategies based on nanomaterials have garnered widespread attention due to their tumor-targeting ability, stability, low toxicity, ease of modification, and prolonged blood circulation[10]. An



Scheme 1 Self-assembled nanoplatforms for cancer immunotherapy. The outermost circle illustrates the material sources of the self-assembled nanoplatforms for cancer immunotherapy. The middle circle shows the driving force behind the self-assembly of these nanomaterials into nanoplatforms. The innermost circle highlights the mechanism of self-assembled nanoplatforms driven by different interactions for cancer immunotherapy and the mechanism of how CT, CDT, PDT, PTT, RT, and SDT enhance the efficacy of cancer immunotherapy. This image is created with BioRender.

increasing number of nanomaterials are being utilized in the diagnosis and treatment of cancer. Many researchers have combined immunotherapy with nanomaterials to effectively destroy tumors, demonstrating great potential in reshaping the TME and delivering clinical drugs[11,12]. For example, nanoparticles (NPs) can act as immune adjuvants or agonists to enhance the immune response to antigens[13]. Typically ranging in size from 1 to 300 nm, NPs can be engineered to prolong the circulation time of drugs in the bloodstream and increase their accumulation at tumor sites, thereby improving the efficacy of anticancer drugs[14]. Additionally, NPs can actively target the spleen, lymph nodes, antigen-presenting cells and tumor cells through surface modification and functionalization, activating robust immune response while minimizing damage to healthy tissue[15].

An increasing amount of research in recent years has shown that, compared with traditional nano drug systems, self-assembled nanoplatforms have the advantages of lower toxicity, simpler preparation, and higher drug-loading capacity[16,17]. Self-assembly refers to the process by which disordered molecules self-assemble into an entropy-favored ordered phase through some non-covalent interactions among the molecules[18]. Self-assembled nanoplatforms are a class of nanosystems that self-assemble into structures with controllable size, shape and surface properties and precise biofunctionalization, relying on some relatively weak non-covalent interactions such as hydrogen bonds, van der Waals forces, electrostatic interactions, hydrophobic interactions, $\pi-\pi$ stacking and host−guest interactions. In addition to common biomaterials such as polymers and liposomes, a new generation of self-assembled nanomaterials, like metal−organic frameworks (MOFs) composed of adjustable metal nodes and multi-site organic ligand bridges, is emerging as a standout choice for constructing self-assembly nanoplatforms. They can self-assemble into multifunctional platforms that integrate MOFs, functional NPs, clinical drugs, and other components through the interaction among the units. The inherent fluorescence properties of the porous coordination network (PCN) material combined with photodynamic therapy (PDT) treatment further enhance the therapeutic efficacy of these NPs[19−21]. Moreover, many special nanomaterials are designed to respond to specific signals in the TME or external conditions, such as environmental pH, light and temperature, facilitating targeted delivery and drug release[22−25]. Beyond their intrinsic properties, the responsiveness and controllable drug loading of self-assembled nanoplatforms allow for the selective assembly of necessary components, addressing the limitations of traditional monotherapies and enabling synergistic treatments or enhancing the efficiency of specific therapies[26]. Combining cancer treatment modalities such as chemodynamic therapy (CDT), PDT, and photothermal therapy (PTT) with immunotherapy drugs or immune adjuvants through self-assembled nanomaterials holds promise for achieving long-lasting immunotherapy and effective cancer management.

In this review, we systematically summarize the research progress of self-assembled nanoplatforms in tumor immunotherapy and their strategies for combining with other treatment modalities. First, we briefly summarize and outline the concepts, principles and various treatment methods of cancer immunotherapy. Next, we delve into self-assembled nanoplatforms, discussing the materials that can self-assemble and the underlying mechanisms of their interactions. We categorize these nano self-assembled materials based on their types, with a focus on the application of self-assembled platforms based on nucleic acids, peptides and proteins, metal materials and supramolecules in cancer immunotherapy over the past three years. Additionally, we explore the application strategies of self-assembled nanomaterials in combination with immunotherapy, including CDT, CT, PDT, PTT, sonodynamic therapy (SDT) and RT (see Scheme 1). Finally, we summarize and project the future development prospects, design considerations, and optimization strategies for nano self-assembled platforms in cancer immunotherapy, aiming to provide valuable insights and references for ongoing research in this field.

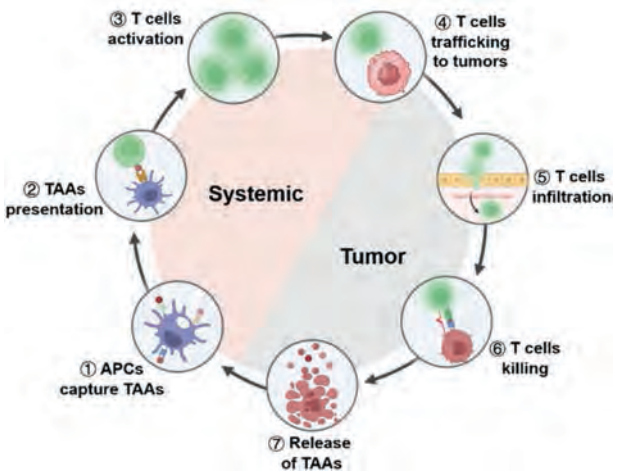


Figure 1 Schematic illustration of cancer−immunity cycle. Modified from Ref. 3. This image is created with BioRender.

2. Cancer immunotherapy

Immunotherapy is a treatment method that activates or inhibits the immune function to treat certain diseases; cancer immunotherapy is a treatment method based on the immune system's ability to recognize and attack tumor cells. Unlike traditional surgery, CT and RT that directly act on tumor tissue, cancer immunotherapy kills or even eradicates tumors by stimulating and enhancing the host's immunity and has the advantages of stronger targeting, better efficacy and higher specificity[27]. This immunotherapy, based on the antitumor activity of cytotoxic T lymphocyte cells (CTLs), shows high specificity and immune memory against tumor cells. Therefore, a deeper understanding of the tumor−immune cycle pathway is crucial for developing personalized cancer immunotherapy strategies[28]. The tumor−immune cycle specifically includes the following seven key steps (Fig. 1). 1) New antigens generated by tumors are captured by antigen-presenting cells (APCs) and bind to the major histocompatibility complex (MHC) on their surface to form antigen peptide-MHC complexes. 2) APCs carrying tumor antigens travel through the lymphatic system to the lymph nodes, where they present tumor-associated antigens (TAAs) to T cells *via* MHC molecules. 3)The activation of T cells depends on multiple interactions, including the T cell receptor (TCR) recognizing the antigen-MHC complex on the surface of APCs, the binding of CD28 on the surface of T cells to B7 molecules on the surface of APCs, and the stimulation of multiple cytokines. 4) After entering the blood circulation, activated T cells are transported to the tumor under the action of selectins. 5) Activated T cells further infiltrate into the TME through blood vessels. 6, 7) Activated T cells

recognize and kill tumor cells, and new tumor antigens are released in tumor cells, allowing the tumor−immune cycle to continue.

Immunotherapy that develops multiple strategies targeting the above steps is expected to fully mobilize the immune system to play its role. Cancer immunotherapy can be roughly divided into "active" immunotherapy and "passive" immunotherapy[29]. Active immunotherapy mainly refers to the treatment process in which the host's immune system responds after the administration of tumor vaccines, ICIs or cytokines, aiming to induce endogenous and persistent tumor antigen-specific immune responses[30]. Vaccines were initially designed to prevent the occurrence of infectious diseases. However, their ability to induce immune responses has gradually been recognized and has become one of the promising treatments for cancer. Cancer vaccines are a treatment method based on systemic immunity and can be divided into multiple types, such as protein or peptide vaccines, whole cell vaccines, DNA and mRNA vaccines, viral vector vaccines, and dendritic cells (DCs)-based vaccines. Cancer vaccines typically consist of tumor antigens and immune adjuvants. Immune adjuvants can stimulate APCs, especially DCs, to mature and uptake, process and present antigens to MHC-I and MHC-II molecules. These DCs migrate to lymphoid organs and present TAAs or tumor-specific antigens (TSAs) in the vaccine to the initial T cells through the interaction of MHC molecules with T cell receptors, leading to their activation. Activated T cells migrate to the tumor and control tumor growth by direct killing or secretion of factors[31]. The emergence of ICIs, anti-CTLA-4, anti-PD-1, and ligand for PD-1 (anti-PD-L1) antibodies, etc., blocks the transmission of immunosuppressive signals, effectively improves the response rate of immunotherapy and is widely used in the research of T cell-induced tumor death[32]. Cytokines are low-molecular-weight soluble proteins secreted by a variety of cells, including immune cells, and play a crucial role in regulating immune responses and cell behavior[33]. These molecules can be classified into interleukins (ILs), tumor necrosis factor (TNF) superfamily, interferons (IFNs), chemokines, growth factors etc. They typically mediate intercellular interactions by binding to corresponding receptors and have the functions of promoting cell growth and differentiation, regulating innate immunity and adaptive immunity, and participating in inflammatory responses, wound healing, and tumor growth[34].

Passive immunotherapy includes adoptive cell therapy (ACT) and tumor-targeted monoclonal antibodies because they are endowed with antitumor activity. This treatment method relies on the repeated application of tumor-specific antibodies[29,35]. ACT refers to a treatment method that separates autologous or allogeneic immune cells from the patient, activates, genetically modifies and expands them *in vitro*, and then returns them to the patient. The antitumor activity of this therapy is highly dependent on the activity, number, and maintenance of adoptively transferred cells[36]. The most researched are tumor-infiltrating lymphocytes (TILs), TCR-modified T (TCR-T) cells, and chimeric antigen receptor-modified T (CAR-T) cells. The rapid development of ACT technology has revolutionized the status quo of cancer immunotherapy, especially for the treatment of hematologic malignancies[37]. Oncolytic immunotherapy is an immunotherapy method that kills tumor cells by direct oncolysis and inducing specific immune responses. In short, oncolytic viruses (OVs) selectively replicate in tumor cells, triggering immunogenic cell death (ICD). The subsequent release of TAAs and damage-associated molecular patterns (DAMPs) can activate the immune system and reshape the immunosuppressive TME. Subsequent viral replication and infection further eliminate surviving tumor cells[38]. Compared with active immunotherapy, passive immunotherapy has a short survival period and is prone to antibody−threat reactions[39].

Overall, these cancer immunotherapy methods have significantly improved the therapeutic effect of a variety of solid tumors and hematologic malignancies and prolonged the survival of patients. Different from traditional therapies, cancer immunotherapy has the advantages of higher specificity, fewer side effects and better efficacy, especially with rapid developments in recent years, providing new directions for tumor treatment. Currently, cancer immunotherapy still faces the following challenges: 1) Immunosuppression in the TME. Suppressive immune cells such as myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and tumor-associated macrophages (TAMs) inhibit T cell activation, weakening the effectiveness of immunotherapy. Immunosuppressive factors like IL-10, TGF-β, and IDO directly suppress T cell function and proliferation while promoting Tregs differentiation. Additionally, factors such as hypoxia and acidic metabolic byproducts further impair immune cell function. 2) Tumor heterogeneity and escape mechanisms. Different tumor cells within the same patient may exhibit varying antigens and resistance mechanisms, allowing certain tumor clones to evade immune attacks, ultimately leading to treatment failure or recurrence. Additionally, tumor cells can release exosomes and cytokines to reshape the immunosuppressive TME, further weakening the effectiveness of immunotherapy. 3) Immune-related adverse events (irAEs). As ICIs can relieve T cell inhibition, they may lead to T cells attacking normal tissues, triggering autoimmune inflammation. Overactivation of the immune system can cause a large release of cytokines such as IL-6, leading to a systemic inflammatory response. 4) Individual differences lead to inconsistent efficacy. Immunotherapy depends on the patient's immune system status, but the degree of T cell infiltration and immune tolerance varies among different patients, resulting in a lack of response to immunotherapy in some individuals. Additionally, tumors with low tumor mutational burden (TMB), such as pancreatic cancer and some breast cancers, often lack sufficient neoantigens, making it difficult for T cells to recognize and attack the tumor. 5) Development of resistance. Some patients are inherently non-responsive to immunotherapy, such as tumors with low PD-L1 expression or MHC-I loss, which are difficult for T cells to recognize. As treatment progresses, tumors may gradually adapt and evade immune attack by regulating PD-L1 expression, altering antigen presentation pathways, and upregulating metabolic pathways. In summary, due to tumor heterogeneity, complex TME, and tumor immune evasion mechanisms, single immunotherapy approaches face numerous challenges, including low bioavailability, limited immune effects, and the development of resistance. It typically cannot achieve optimal antitumor effects, and its clinical application is still limited to a small number of cancers. Combination therapy strategies are of great significance in reducing side effects and improving treatment results. Whether immunotherapy is combined with conventional treatment or a variety of immunotherapy drugs and methods are used in combination, they have shown better efficacy in preclinical studies[40,41]. In recent years, the widespread application of nanomaterials, especially self-assembled nanomaterials, has provided new avenues for cancer immunotherapy. For example, antigen-capturing nanoparticles (AC-NPs) and self-assembled nanovaccines (PCL-OVA nanovaccine) have shown good efficacy in promoting antigen presentation and enhancing

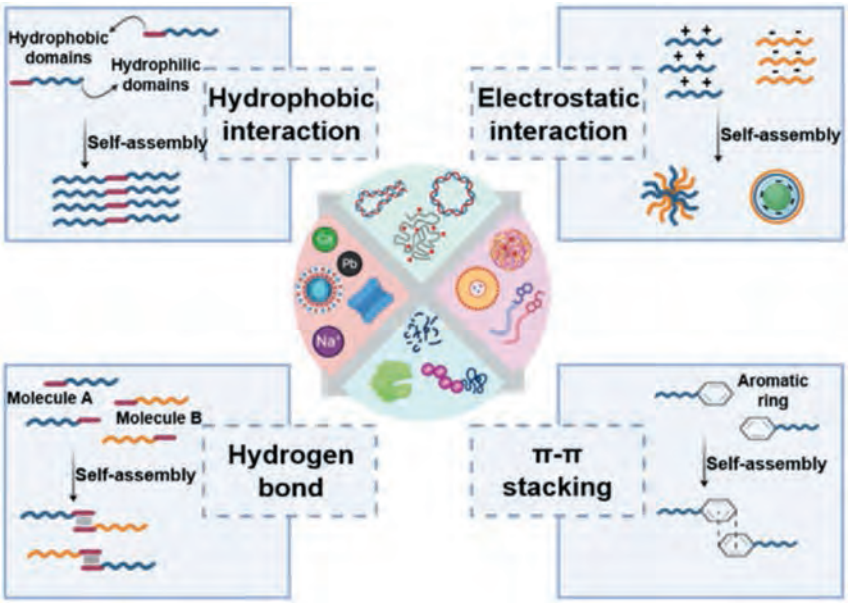


Figure 2 Schematic diagram of the four main driving forces of self-assemble nanomaterials for immunotherapy. Pink indicates self-assembly motif, orange and blue indicate different molecules. This image is created with BioRender.

immunogenicity[42,43]. Self-assembled Au nanoparticles (GNPs) and oxygen self-supply nanomaterials (mTi_3C_2—Pt) are capable of reversing the immunosuppressive TME and enhancing antitumor effects[44,45]. They are able to undergo transformation and self-assembly at the tumor under internal and external stimulation, achieving improved cancer treatment[46,47].

3. Introduction to self-assembly

Self-assembly is ubiquitous in biology. For example, DNA uses self-assembly to wind into a helical structure, and peptides use self-assembly to fold into functional three-dimensional structures. Many drug delivery vehicles have been designed in recent years using the principle of self-assembly. The construction of self-assembled nanoplatforms is a cutting-edge technology in immunotherapy. Its design and application aim to enhance the efficiency and targeting of immunotherapy by assembling multiple functional components onto one platform in a controllable and targeted manner[48,49]. Different from traditional biomaterials, self-assembled nanomaterials are small molecule materials that spontaneously assemble into nanomaterials with specific structures and functions by utilizing intermolecular interactions, such as

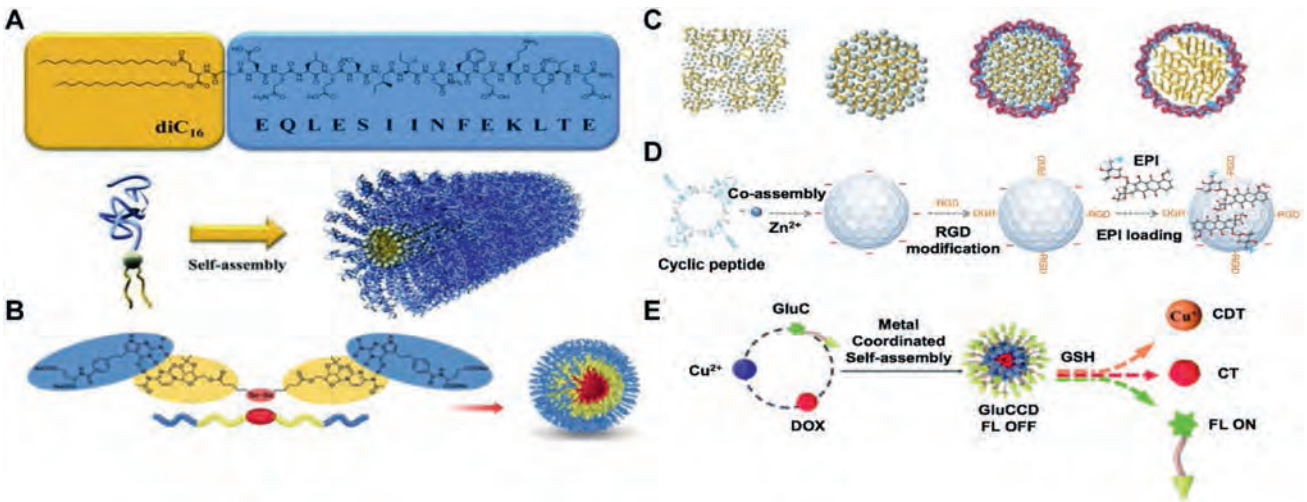


Figure 3 Schematic illustration of self-assembled nanoplatforms driven by different forces for immunotherapy. (A) DiC_{16}-OVA micelles self-assembled *via* hydrophobic interaction. Reprinted with the permission from Ref. 51. Copyright © 2012, WILEY. (B) Pem/Se self-assembled *via* hydrogen bond. Reprinted with the permission from Ref. 52. Copyright © 2020, WILEY. (C) Polyelectrolyte microcapsule self-assembled *via* electrostatic interaction. Reprinted with the permission from Ref. 53. Copyright © 2009, WILEY. (D) RGD-f-PNPs/EPI self-assembled *via* $\pi-\pi$ stacking and electrostatic interaction. Reprinted with the permission from Ref. 55. Copyright © 2018, Springer Nature. (E) GluCCD self-assembled *via* coordination. Reprinted with the permission from Ref. 56. Copyright © 2022, Royal Society of Chemistry.

hydrophobic interactions, hydrogen bonding, electrostatic forces, van der Waals forces, metal coordination, and $\pi-\pi$ stacking. This process requires almost no additional energy and overcomes the limitations of complex formulations[50]. We show the action modes of four common driving forces in Fig. 2, hoping to gain a deeper understanding of the assembly mechanism of self-assembled nanomaterials.

Amphiphilic molecules (comprising both hydrophobic and hydrophilic components) can self-assemble into entropy-favored ordered phases through hydrophobic interactions. For example, Black et al.[51] designed a self-assembled amphiphilic peptide micelle (PAs) containing a cytotoxic T-cell epitope. The PAs are conjugated with a diallyl tail with two palmitic acids (C16) chains and a peptide containing a known CTL epitope from the model tumor antigen ovalbumin (OVA) (Fig. 3A). In the aqueous phase, the hydrophobic, lipid tail is embedded in the core, and the hydrophilic, bifunctional peptide head is displayed on the outside, which further self-assembles into 50−300 nm cylindrical micelles through hydrophobic interactions. An increasing number of studies have utilized hydrogen bonds to create complex self-assembled nanomaterials. Li et al.[52] designed self-assembled nanoplatforms that integrate cancer immunotherapy, RT, and CDT using hydrogen bonds between pemetrexed and cytosine-containing diselenides (Fig. 3B). Under γ-radiation, the hydrogen bonds break, resulting in the release of pemetrexed, which inhibits a variety of folate-related enzymes and exerts an antitumor effect. Simultaneously, the diselenide bonds are cleaved by reactive oxygen species (ROS) generated under radiation irradiation and oxidized to selenosulfinic acid, which can inhibit the expression of human leukocyte antigen E (HLA-E) in cancer cells, thereby activating natural killer cell (NK)-based cancer immune responses. Electrostatic interaction is also a powerful driving force that drives oppositely charged components to self-assemble into complexes. This strategy is also widely applied in the development of therapeutic drugs, such as using electrostatic self-assembly to adsorb antigens and/or adjuvants to carriers. De Koker et al.[53] demonstrated an efficient *in vitro* antigen delivery system for DCs using polyelectrolyte capsules as microcarriers. The system was prepared by a layer-by-layer coating of calcium carbonate microparticles with OVA, followed by coprecipitation and then the deposition of two layers of dextran sulphate/poly-arginine. The core template can be removed by ethylenediaminetetraacetic acid (EDTA) aqueous solution. The study evaluated in detail the uptake and processing of antigens encapsulated in polyelectrolyte capsules by DCs. *In vitro* and *in vivo* experiments found that the efficiency of cross-presentation of antigens was increased, activating more $CD4^+$ and $CD8^+$ T cells (Fig. 3C). $\pi-\pi$ stacking is a weak interaction specific to aromatic ring compounds, and it has broad application prospects in the biomedical field[54]. A variety of NPs driven by $\pi-\pi$ stacking for self-assembly have been reported. For example, Fan et al.[55] proposed a fluorescent nanoparticle (RGD-f-PNPs/EPI) assembled by cyclic peptides. First, the fluorescent cyclic peptide NPs (f-PNPs) were coupled with RGD peptides to provide tumor targeting function. The coupled RGD-f-PNPs were further encapsulated by $\pi-\pi$ stacking and electrostatic interaction between epirubicin (EPI) and peptides (Fig. 3D). The peptide nanoparticle is composed of natural amino acids offering better biocompatibility and biosafety. *In vitro* and *in vivo* experiments have shown that the peptide nanoparticle has enhanced tumor targeting and permeability, achieving efficient delivery of EPI. Metal-based coordination interaction is the process of metal ions binding to ligand molecules through coordination bonds, in which metal ions provide vacant orbitals and ligand molecules provide lone pairs of electrons. Li et al.[56] constructed a Cu^{2+}-based ethylene glycol nano drug (GluCCD), which utilized the coordination effect between Cu^{2+} and doxorubicin (DOX) as well as GluC to achieve tumor targeting and combined therapeutic efficacy (Fig. 3E). Van der Waals force is a weak electrical attraction that often works together with other forces to construct self-assembled nanoparticle[57].

4. Self-assembled nanoplatforms for immunotherapy

Most drugs used in clinical cancer treatment are hydrophobic and often exist in their free form, resulting in low bioavailability and poor therapeutic effect. Based on this, a variety of nano-delivery systems, including liposomes, biological membranes, vesicles, and inorganic NPs, have been developed to enhance antitumor efficacy[15,58,59]. Among them, organic nanomaterials such as biological membranes and lipids have become classic biomaterials for drug delivery due to their excellent biocompatibility and biodegradability. The emergence of self-assembled nanoplatforms with higher precision and environmental sensitivity provides an innovative opportunity for cancer immunotherapy. Increasingly, researchers are exploring new nanomaterials based on nucleic acids, proteins, metals and supramolecules, which can be used to co-assemble with clinical therapeutic drugs to construct multifunctional nanomedicines and have achieved encouraging results in disease treatment[60].

In this section, we aim to introduce the self-assembled cancer immunotherapy platforms based on nucleic acids, peptides and proteins, metals, supramoleculars and other materials, and classify them according to the driving forces of their self-assembly, including hydrophobic interaction, hydrogen bond, $\pi-\pi$ stacking, electrostatic interaction, coordination, host−guest interaction, and Van der Waals force (Table 1[61−397]). This may help to develop more nanomedicines for clinical cancer treatment in the future[16].

4.1. Self-assembled nucleic acid-based nanoplatforms

DNA is a natural biopolymer that is considered a good carrier for drug delivery due to its inherent programmability and excellent hydrophilicity[398,399]. Currently, nucleic acid-based functional nanomaterial, including DNA tetrahedrons, DNA nanoflowers, DNA aptamers, DNA hydrogels, DNA origami and so on, can achieve drug loading through self-assembly and have been widely designed for precision treatment of cancer. Zhang et al.[400] reported a synthesis strategy for DNA tetrahedron-based self-assembled nanomedicines. The DNA tetrahedron framework modified with phosphorothioate (PS) was used as the structural model and reacted with carbon bromide-modified camptothecin (CPT) to form a self-assembled nanomedicine with responsive disulphide bonds. Notably, the hydrophilicity of the DNA drug conjugate can be controlled by adjusting the number and position of PS on the DNA backbone. *In vitro* experiments have shown that CPT-containing DNA tetrahedra (CPT-TET) exhibits effective cellular uptake and cytotoxicity to tumor cells. Enhanced tumor accumulation and antitumor efficacy were shown in tumor-bearing mouse models (Fig. 4A). DNA aptamers have unique advantages in engineering and stabilizing self-assembled drugs, including easy synthesis, easy modification, low immunogenicity and low toxicity and have been widely used in tumor targeted

Table 1 Various types of self-assembled nanoplatforms based on nucleic acids, peptides and proteins, metals, and supramoleculars.

Nanoplatform	Self-assembled mechanism	Nanomaterials
Nucleic acids	Hydrophobic interaction	MCMD NPs[61]; GA-LNPs[62]; USNA[63]; NaVs[64]; MiR@PCPmP NPs[65]; RGD-DMA/pCCL19-BMS-1[66]; T7-C/siRNA[67]; hNPs[68]; NVs[69]; MCO NVs[70]; CLSV[71]
	Hydrogen bond	siRNA/PPA-NG[72]; DNDA[73]; UBLE[74]; PEG-Q11T3R4@CDN[75]; DP7-C/siRNA/CpG ODNs[76]; EaCpG[77]; DNAnc[78]; Mn-CpG MS[79]; LC-aAPCs[80]; 2′F-CpG/Obsl1 NPs[81]
	$\pi-\pi$ stacking	PDA-B@SD[82]; MCN-NPs[83]
	Electrostatic interaction	MiR@PCPmP NPs[65]; PEG-Q11T3R4@CDN[75]; polyplexe[84]; NVs[69]; Trp2/CpG[85]; 2′F-CpG/Obsl1 NPs[81]; CNPs[86]; MCN-NPs[83]
	Coordination	iDP-NS[87]
	Others	Cy5-CPG/DOX[88]; F-PEI/mRNA^{Ag}NP[89]; FNC@NF[90]; DNA nanogel vaccine[91]; PEEPlipo@OxPt[92]; RNA-OG-pOVA[93]; LND-CDNs[94]
Peptides and proteins	Hydrophobic interaction	NVs[69]; MCO NVs[70]; CLSV[71]; antiCD3-G7-RGD[95]; TAPP-GCP@TCPP@BSA[96]; LND (F)-SS-PEG NP[97]; Comp. 1[98]; PSNAs[99]; PCL-OVA nanovaccine[42]; TMCB[100]; DA-L-DSA[101]; FE^{R}@MN[102]; CAT-Ce6@OMV-aPDL1[103]; UR@M NPs[104]; KFM[105]; PAP[106]; IBs[107]; DOX@DCS NPs[108]; PEI NPs[109]; PAP NPs[110]; aP/IR@FMKB[111]; PT-NPs[112]; NLG@PF[113]; Nap-CTP-HCQ-Yp[114]; PVA-CD40[115]; BMN/PAZA[116]; BSA-MHI148@SRF[117]; PNpC[118]; TLR7/8a-Sur[119]; DOX/IpYR[120]; LT-NPs[121]; DT/Pep1[122]; REPNs[123]; CAP-NPs[124]; PMMEBOx-R/B-IMDQ-OVA[125]; cRGD-NPDJ[126]; HBCiF-NPs[127]; PPC nanospheres[128]; PAC-SABIs[129]; SIV[130]; PAIs[131]; Ato/siP@SLNP[132]; c-di-GMP-PNT[133]; αS-AuNP[134]; Ag_2S@P@M-A[135]; BANSs[136]; FFPG[137]; AuHQ[138]
	Hydrogen bond	DP7-C/siRNA/CpG ODNs[76]; LC-aAPCs[80]; 2′F-CpG/Obsl1 NPs[81]; antiCD3-G7-RGD[95]; TAPP-GCP@TCPP@BSA[96]; TMCB[100]; ArgNPs[139]; PAP[106]; PCS[140]; Comp.4[141]; TPM1[142]; FEGCG@MPI NPs[143]; BMN/PAZA[116]; TAP[144]; pre-GP1[145]; I-OVA NE[146]; MCL[147]; BANSs[136]; FFPG[137]
	$\pi-\pi$ stacking	MCN-NPs[83]; TAPP-GCP@TCPP@BSA[96]; LCCS[148]; ArgNPs[139]; KFM[105]; aP/IR@FMKB[111]; TPM1[142]; LPNs[149]; BMN/PAZA[116]; AmpF-E7[150]; LT-NPs[121]; CAP-NPs[124]; cRGD-NPDJ[126]; HBCiF-NPs[127]; FFPG[137]
	Electrostatic interaction	NVs[69]; Trp2/CpG[85]; 2′F-CpG/Obsl1 NPs[81]; CNPs[86]; MCN-NPs[83]; PSNAs[99]; KFM[105]; M@AP[151]; HSA/CAT-PEPA@Ce6[152]; C8[153]; TfR/TATH7/PTX/R837 NMs[154]; PDL1-NP-FEXO[155]; HMIC[156]; DNPs[157]; *N*-Ac-PamCS-M-6[158]; Exos-PH20-FA[159]; PLRS[160]; FCS-OVA NPs[161]; c-di-GMP-PNT[133]; APP-Fe-NCs[162]; CIC-Gal[163]; FFPG[137]; AuHQ[138]
	Coordination	APP-Fe-NCs[162]; FCM@4RM[164]; Nery-PMIV[165]; CIC-Gal[163]; EMS-PDBP[166]; FFPG[137]; MMCC[167]
	Others	F-pY-T[168]; Biotin-Cip-CPT-Nap[169]; FRS[170]; F-ΔF-M3[171]; MHI-TMX@ALB[172]; EISA[173]; AmpFY9[174]; LND-Pep + FA-Pep[175]; TR3-M-NP-5k[176]; ZNPs/I@CML[177]; P17[178]; NM-7/OVA[179]; ^{D}TBP-3NP-siANRIL[180]; SAP[181]; MA-NPs[182]; GSC[183]; IR-LND@Alb[184]; SR717@RGE-HFnNP[185]; ^{D}PAM@OA[186]; cGAMP-SIINFEKL-STINGΔTM[187]; ZnS@BSA[188]
Metals	Hydrophobic interaction	αS-AuNP[134]; Ag_2S@P@M-A[135]; BANSs[136]; FFPG[137]; AuHQ[138]; SMTA[189]; PIMS NPs[190]; CCNAs[191]; CE-Fc-Gel[192]; MPN NPs[193]; IPC[194]; FMMC[195]; PRNs^{MT}[196]; ONc-Mn-A-malF127[197]; Pt-In-NP[198]; NP$^{Pt/Azo/PTT}$[199]; CF@NDOX[200]; FeCORM-NPs[201]; C/I-Mil[202]; NPs[203]; TCPP@Hf-TK-PEG-PAMAM-FA@siHIF-1α[204]
	Hydrogen bond	BANSs[136]; FFPG[137]; IPC[194]; KEEM[205]; CACG[206]; Cel hydrogel[207]; iRGD-R7-LAHP-M[208] MPN/CpG[209]; D-A-DA/TPP[210]
	$\pi-\pi$ stacking	FFPG[137]; SMTA[189]; Cu-DON[211]; FMMC[195]; ECNM[212]; ROCA[213]
	Electrostatic interaction	APP-Fe-NCs[162]; CIC-Gal[163]; FFPG[137]; AuHQ[138]; SMTA[189]; IPC[194]; C/I-Mil[202]; D-A-DA/TPP[210]; TC@Ch-MS[214]; Mn-MTO@PAA[215]; TCPP@Hf-TK-PEG-PAMAM-FA@siHIF-1α[204]
	Coordination	APP-Fe-NCs[162]; FCM@4RM[164]; Nery-PMIV[165] CIC-Gal[163]; EMS-PDBP[166]; FFPG[137]; MMCC[167]; PtR/CPG[216]; KS Ru[217]; PIMS NPs[190]; MPNs@OVA + CHA[218]; CCNAs[191]; 2DG@FS-Nb[219]; CpG-NPs[220]; MOICP[221]; PCD@CM[222]; PMR NAs[223]; F-MGC[224]; C820@Cu/LOD-ALG[225]; MPN NPs[193]; Fe-Ace-O3[226]; Cu-DON[211]; IPC[194]; FMMC[195]; GdOFBAu[227]; ONc-Mn-A-malF127[197]; FerH[228]; BMR[229]; Fe@nGOx[230]; MDP NPs[231]; ZGd-NRs[232]; ECNM[212]; CaCuZC[233]; KEEM[205]; CACG[206]; Cel hydrogel[207]; iRGD-R7-LAHP-M[208]; CDDP-PMs[234]; TC@Ch-MS[214]; MOF-CpG-DMXAA[235]; AmGd-NPs[236]; MFe-NCPs[237] ; Mn-MTO@PAA[215]; TZR-NSs[238]; PFZF-Dox NPs[239]; AZ-NPs[240]; ROCA[213]
	Others	ZnS@BSA[188]; Ru1 NPs[241]; ZPM@OVA-CpG[242]; GF/CuES[243]; FA-M[244]; nPDA-cis[245]
Supramoleculars	Hydrophobic interaction	DA6C1[246]; SA[247]; TEP-FG-CRAY[248]; MSDNc[249]; AB-Flu[250]; SA@VitC[251]; 4RDP(F5)-OVA[252]; NCSNPs[253]; ABCA[254]; TAP[255]; aCD47/PF[256]; RCPATpl-Tcc[257]; DR3C1/OVA/CpG[258]; PolyMN-TO-8[259]
	Hydrogen bond	SA[247]; LS-Al-ICG NPs[260]; SA@VitC[251]; TAP[255]; sBBI&PDP[261]; CUH-cGAMP[262]; TP5-ICG NFs[263]

Table 1 (*continued*)

Nanoplatform	Self-assembled mechanism	Nanomaterials
	$\pi-\pi$ stacking	DA6C1[246]; PSAs[264]; DR3C1/OVA/CpG[258]
	Electrostatic interaction	DA6C1[246]; CHTR/siRNA[265]; DR3C1/OVA/CpG[258]
	Coordination	LS-Al-ICG NPs[260]; MSDNc[249]; CA-NBF[266]
	Host–guest interaction	GNP[44]; CHTR/siRNA[265]; CD3-PPP/pCAR@α-CD[267]; Pt-Tu@NPs[268]; NCSNPs[253]; IMD@Ada-GMNPs[269]; PolyMN-TO-8[259]
	Others	NanoPcM[270]; DBT-2FFGYSA[271]; IND-G^{D}F^{D}F^{D}Y-^{D}PPA-1[272]; Y−K(Ag)-ERGD[273]; PcN4[274]; Supra-BiCE[275]
Others	Hydrophobic interaction	ApMDC[276]; CeBLZ[277]; dBTR-NPs[278]; HBI NDs[279]; TerBio[280]; HB-NLG8189@MPCM[281]; CM-NAs[282]; SC-MSN@D/B[283]; PROTAC[284]; CCXB[285]; CNS[286]; PEM-PPFs[287]; G-SNAT[288]; Smac-TLR7/8 hydrogel[289]; cN@SS-IMQ[290]; PCR780-APP-NMs[291]; PPor NPs[292]; CsBPNs[293]; PyroR[294]; DMP@NPs[295]; CpG EXO/TGM[296]; BDP-I-N-anti-PD-L1 NPs[297]; CpG@NRT[298]; Lipo-MT-SNAP[299]; SeP/DOX[300]; CASN[301]; CPDS[302]; C9SN[303]; GC@ICG[304]; PSMA-ICG NPs[305]; DOX@FA-RHPs-SA[306]; TS-PP@FU[307]; CeSe[308]; C-Moc[309]; S-NP-CPT[310]; sg*Pik3cg*-DHP/DGA-NVs[311]; CCFG[312]; PPCNs[313]; COS-BA/Ce6 NPs[314]; TPPC[315]; C-BTA NPs[316]; SA@PDA-FA NPs[317]; PLA-*b*-PItEG[318]; SPNM[319]; TMNPs[320]; DR-SIP[321]; NP@Poly^{FBODIPY}[322]; Nanoglycocluster[323]; PSeLYAb NPs[324]; IQS[325]; GA-Ce6-FA NPs[326]; SVMAV[327]; i-NP$_{BTZ}$[328]; R848@dSeNPs[329]; CMA-R848[330]; MB-R837-PEG(MRP)[331]; PPD[332]; AZD@BGSSP[333]; CDK4/6 PROTAC[334]; ISDN[335]; PDPCA@ATRA[336]; GEM-CXB NPs[337]; ImmSt[338]; MR NPs[339]; PTX@PoxMTP NPs[340]; VB12-Sericin-PBLG-IR780[341]
	Hydrogen bond	FDU-IOX1-FF-Nb[342]; CM-NAs[282]; NP5[343]; Smac-TLR7/8 hydrogel[289]; DMP@NPs[295]; CpG EXO/TGM[296]; CS-PEG-NPs[344]; CASN[301]; QU@FU-TS[345]; CPDS[302]; C9SN[303]; UEA NPs[346]; MS NPs[347]; BNB[348]; ISDN[335]
	$\pi-\pi$ stacking	FDU-IOX1-FF-Nb[342]; (*p*shPD-L1+*p*Spam1)/CRA[349]; HBI NDs[279]; HB-NLG8189@MPCM[281]; CM-NAs[282]; PROTAC[284]; Ce6-IMDQ NPs[350]; CCXB[285]; NP5[343]; G-SNAT[288]; PPor NPs[292]; CS-PEG-NPs[344]; CASN[301]; QU@FU-TS[345]; CPDS[302]; C9SN[303]; CCFG[312]; COS-BA/Ce6 NPs[314]; C-BTA NPs[316]; SA@PDA-FA NPs[317]; GA-Ce6-FA NPs[326]; DCC@M2[351]; CDK4/6 PROTAC[334]; PTX@PoxMTP NPs[340]; DSe-NP[352]
	Electrostatic interaction	CeBLZ[277]; (*p*shPD-L1+*p*Spam1)/CRA[349]; HB-NLG8189@MPCM[281]; F-PPD/pCKb11[353]; GH-PID[354]; PROTAC[284]; Ce6-IMDQ NPs[350]; CNS[286]; Smac-TLR7/8 hydrogel[289]; CpG@NRT[298]; CASN[301]; MEAO-Z[355]; TPE-Py-Pyk(TPP)Py[356]; C9SN[303]; GC@ICG[304]; LVAI[357]; MS NPs[347]; TS-PP@FU[307]; C-Moc[309]; TNP@CS-A/pDNA[358]; $CaCO_3$@(OVA/HPAA-CpG)$_3$[359]; P/LNV@IDO/AE/CpG[360]; aPD-L1-PolyMet/BPN[361]; SA@PDA-FA NPs[317]; GA-Ce6-FA NPs[326]; Gel@M/CuO_2/DOX/STING[362]; PPD[332]; PLNR840[363]; ISDN[335]; NLM/DMG[364]; DEX-ALA/DTX NPs[365]
	Coordination	PFCE/hCe6@CaF-PEG[366]
	Van der Waals force	DEX-ALA/DTX NPs[365]
	Others	iMade[367]; mtDSN-2[368]; LTB-6 NPs[369]; DMAM/psIL-15[370]; AMDR[371]; sc NPs[372]; R837/ICG@Lip[373]; BioPEGDMA@RM[374]; SPN-R848[375]; SPNI[376]; CSTD[377]; NP-DBD[378]; Rg3-PNPs@PPP[379]; M-G1-TBPNa@DOX[380]; DHCRJ NPs[381]; P−I/II micelles[382]; FCS/poly(I:C) NPs[383]; FA-Hemesome-ART NPs[384]; iPDPA-ICG NPs[385]; SP3 NPs-^{D}F^{D}FG^{D}PPA[386]; DMC@P−Cs[387]; T22-PE24[388]; DSe@POC[389]; SPN@Pro-Gem[390]; HVMN[391]; αM-Exos[392]; BDPd NPs[393]; DMP/mIL-22BP[394]; IL10-E7-BBVs[395]; PNBJQ[396]; CSAN[397]

therapy[401,402]. Zhang et al.[403] proposed a DNA aptamer-based self-assembled active pharmaceutical ingredient (API) nanodrug for enhancing synergistic cancer immunotherapy, PDT and CT therapy. The CT drug (irinotecan), photosensitizer chlorin e6 (Ce6) and Scgc8 aptamer self-assembled into aptamer-empowered full-API nano drugs (ICS AFANDs) driven by hydrophobic interaction, hydrogen bonding and $\pi-\pi$ stacking. Studies have shown that the nanodrug has good tumor targeting and tumor cell permeability. Under near-infrared (NIR) irradiation, tumor cells generate a large amount of ROS and singlet oxygen, which ultimately induces the ICD of tumor cells. Injectable hydrogels are also widely used in combination with drugs to enhance tumor therapy and can effectively deliver various drugs to tumors[404,405]. Under favorable environmental conditions, DNA polymers can spontaneously self-assemble into hydrogels with unique chemical properties and porous structures, providing many binding sites for therapeutic drugs[406]. For example, Fan et al.[407] designed a programmable ultrasoft DNA hydrogel system based on aptamers, forming a synergistic treatment system integrating CT and immune checkpoint blockade (ICB). First, the complementary sequences of CpG ODN and adenosine triphosphate (ATP) aptamer were used to design the DNA template and synthesize DNA Gel. αPD-L1 was encapsulated in the gel matrix through electrostatic interactions and coordination between nucleic acids and proteins to form αPD-L1@DNA Gel. Finally, DOX is embedded in the ATP aptamer binding sites. After intratumoral injection, the DNA Gel undergoes conformational changes after binding to the target, releasing DOX, CpG ODN, and αPD-L1, resulting in a strong systemic immune response and immune memory effects, which has a good inhibitory effect on subcutaneous tumors and lung metastases tumors (Fig. 4B). In summary, the DNA-based self-assembled nanomaterials combine the advantages of strong tumor targeting, excellent biosafety, low immunogenicity, long blood circulation time, good biocompatibility and structural stability.

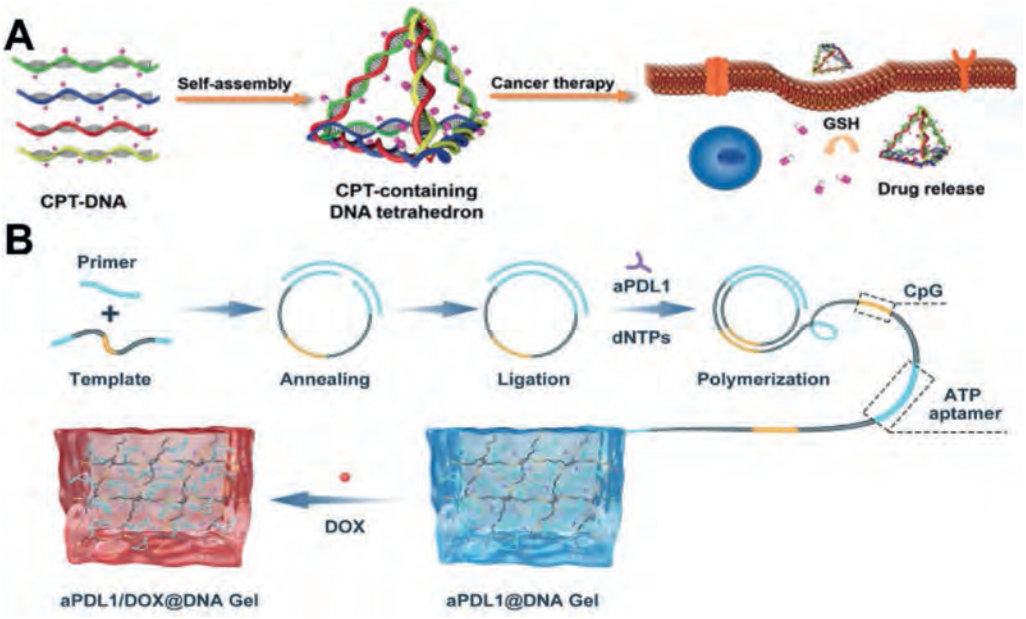


Figure 4 Schematic diagram of different technical routes of self-assembled nucleic acid-based nanoplatforms for immunotherapy. (A) The synthesis process of CPT-TET. Reprinted with the permission from Ref. 400. Copyright © 2019, WILEY. (B) The synthesis process of aPDL1/DOX@DNA Gel. Reprinted with the permission from Ref. 407. Copyright © 2023, WILEY.

These features provide great potential for targeted delivery, and there is an urgent need to design and optimize DNA nanostructures to achieve more efficient cancer immunotherapy.

4.2. Self-assembled peptide and protein-based nanoplatforms

As we all know, peptides and proteins are the fundamental components of cells and have high biocompatibility, biorecognition ability and cell membrane transport ability. However, free peptides are unstable and easy to clear. Self-assembly can be used to manipulate peptides to synthesize stable and multifunctional nanomaterials[408]. At present, the self-assembly of peptides and proteins has been widely applied in the biomedical field. The self-assembly process is mainly affected by thermodynamics and occurs spontaneously under conditions close to thermodynamic equilibrium. By strictly controlling the amino acid sequence and physicochemical parameters (pH, temperature, metal ion concentration and salt concentration), it can form a stable structure through non-covalent interactions[409−411]. In addition to their inherent advantages, such as biocompatibility, degradability and assembly flexibility, peptides also have immunomodulatory activity. Some peptide sequences contain abundant enzyme cleavage sites, and some peptides themselves are immune-related drugs or immunomodulators[412]. Therefore, the introduction of peptide and protein self-assembled particles for cancer immunotherapy may exert a powerful antitumor effect. In recent years, many self-assembled NPs based on structures such as α-helix, β-sheets peptides, triple helix, and ELP-like, etc., have been designed for cancer immunotherapy. Common structural forms include helical ribbons, nanofibers, hydrogels, collagen-like peptides, nanotubes, spherical micelles, lamellar sheets and vesicle structures. These peptide NPs have clear and stable structures under physiological conditions, high drug-loading capacity, and excellent killing effects. He et al.[413] designed a cluster of nanohybrids (pCluster) assembled from an anticancer peptide (β-catenin/Bcl9 inhibitors, BBIs) and gold ions. A series of *in vitro* and *in vivo* experiments demonstrated that pCluster disrupted the Wnt/β-catenin signaling pathway, inhibited the proliferation of Hep3B, HCT116, and B16F10 tumor cells, and showed a synergistic effect with PD-1/PD-L1. This peptide delivery strategy has a wide range of implications for the design of peptide drugs for intracellular protein−protein interactions (Fig. 5A). Song et al.[57] constructed a highly personalized and safe biomimetic nanofiber trivalent peptide hydrogel vaccine using three antigen epitope-coupled peptides. The self-assembled F peptide was conjugated with three melanoma-specific and MHC I-restricted epitopes. By adjusting the peptide concentration in aqueous solution, F-peptide and the epitope-coupled F-MART1 and F-Tyr peptides spontaneously formed nanofibers driven by hydrogen bonding, hydrophobic interactions, and van der Waals forces, and F-gp100 formed NPs. Upon further increasing the peptide concentration in the aqueous solution, trivalent peptide-hydrogel vaccines formed spontaneously. This nanomaterial acted as an antigen reservoir, co-delivering the antigen epitopes, promoting antigen presentation by DCs, enhancing $CD8^+$ T cell response and increasing IFN-γ secretion. Notably, this system exerted a broad-spectrum antitumor $CD8^+$ T cell response and significantly inhibited the growth of B16 tumors without additional adjuvants (Fig. 5B). In addition, protein nanocages represented by E2 NPs were shown to have good DCs uptake properties[414]. For example, Neek et al.[415] used the pyruvate dehydrogenase E2 subunit assembly (E2 nanoparticle) as the basis and connected CpG and peptide (cancer-testis (CT) peptide) in its cavity and surface, respectively. After immunizing mice, the CpG-peptide-E2 NPs enhanced the secretion of antigen-specific IFN-γ, which was attributed to higher DCs activation and more effective cross-presentation of CT-related antigen epitopes, thereby enhancing antigen-specific T cell responses and lysing tumor cells.

Proteins or peptides contain essential amino required by the human body, thus exhibiting good biocompatibility without issues

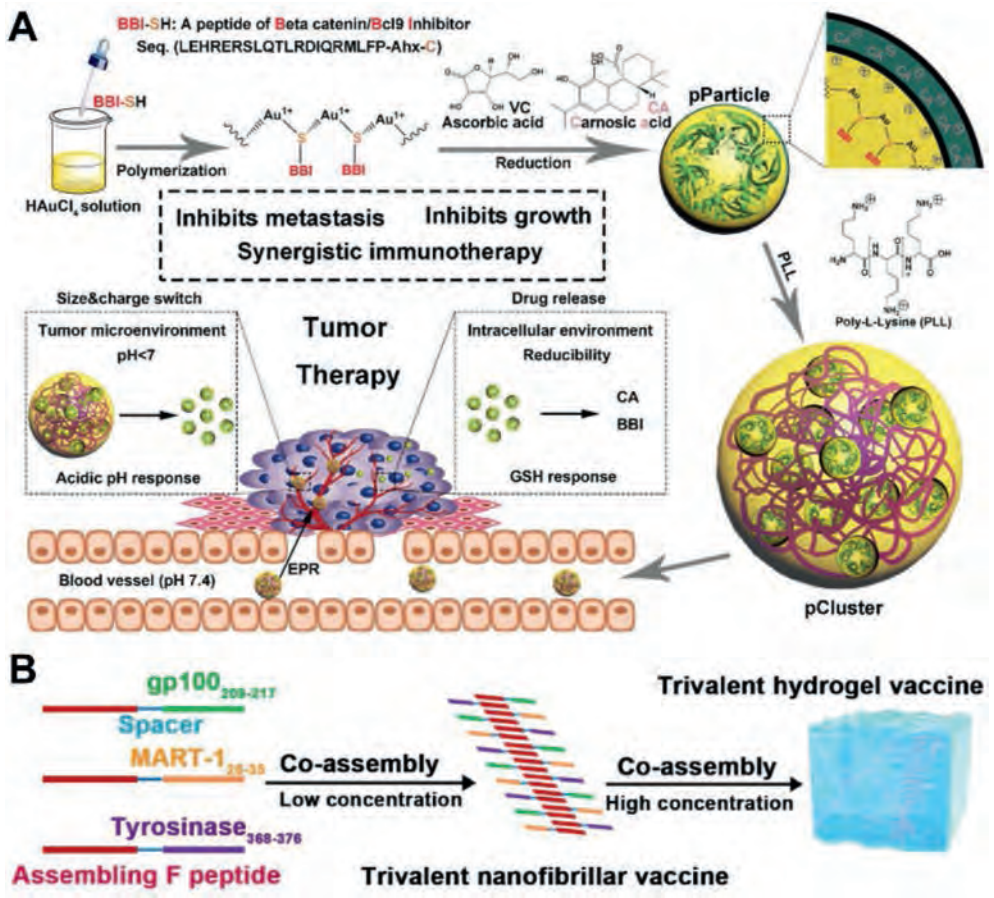


Figure 5 Schematic diagram of different technical routes of self-assembled peptides and proteins-based nanoplatforms for immunotherapy. (A) The synthesis process of pCluster. Reprinted with the permission from Ref. 413. Copyright © 2019, WILEY. (B) The synthesis process of peptide-hydrogel vaccine. Reprinted with the permission from Ref. 57. Copyright © 2023, Elsevier.

such as toxicity or resistance to degradation, making them highly suitable for clinical applications. Self-assembled peptides and proteins are excellent precursors for the synthesis of self-assembled nanoplatforms due to their unique biological, chemical and physical functions, as well as targeting ability, selectivity, low toxicity, ease of synthesis, and scalability. They have broad application prospects in cancer diagnosis and immunotherapy.

4.3. Self-assembled metal-based nanoplatforms

Metals are an essential component for the function of many enzymes involved in biological processes and play an important role in various physiological activities. Some metals, such as zinc (Zn), manganese (Mn), copper (Cu) and iron (Fe), are also important trace nutrients. Increasing research has shown that there is a close connection between metal ions and various immune responses, such as Ca^{2+} and NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation[416], Mn^{2+} and the cyclic GMP−AMP synthase-stimulator of interferon genes (cGAS−STING) signaling pathway[417], Zn^{2+} and toll-like receptors (TLR) adaptor proteins(MyD88 and TRIF)[418], Fe^{2+} and nuclear transcription factor-κB (NF-κB) activity and hypoxia-inducible factor 1α (HIF-1α) stability[419], and K^+ and TCR induced Akt-mTOR signaling[420]. Deng et al.[417] leveraged the property of Mn^{2+} in activating the STING pathway to design an αPDL1@MnO_2 therapeutic nanoplatform. Under the acidic conditions of TME, the Mn^{2+} released by αPDL1@MnO_2 activates the cGAS−STING signalling pathway and promotes the maturation of DCs. Meanwhile, RT-triggered ICD releases TAAs and the two processes synergistically activate specific immune responses. The release of αPD-L1 further promotes CTLs infiltration intratumorally and exerts antitumor effects (Fig. 6A).

Various metal-based nanomaterials have been widely developed for cancer treatment in recent years. Based on their physicochemical properties, they are roughly divided into nMOFs, metal-polyphenol coordination nanosystems, inorganic metal NPs and metal-based hydrogels. Inorganic-organic hybrid nanomaterials composed of nanometals and organic frameworks have been widely used as effective immunomodulators and catalysts. Calcium, Zn, aluminum (Al), Fe, gold (Au), Mn, magnesium (Mg), and Cu have been reported to be highly attractive materials[421]. MOFs have the advantages of inherent porosity, structural adjustability, molecular modularity and good biocompatibility. Shao et al.[20] designed an upconversion nanoparticle@porphyrinic MOFs (UCSs) for cancer immunotherapy. In brief, the previously synthesized UCNPs were modified with citric acid (CA) or polyvinylpyrrolidone (PVP) to grow into a UCNP@MOF core−shell structure. Tirapazamine (TPZ) was further encapsulated into the voids of the MOF shell to form the final nanoplatform TPZ/UCSs. The results showed that under hypoxic conditions, the hypoxic response of TPZ and NIR light-induced PDT activated a higher cytotoxic killing effect. This phenomenon was further

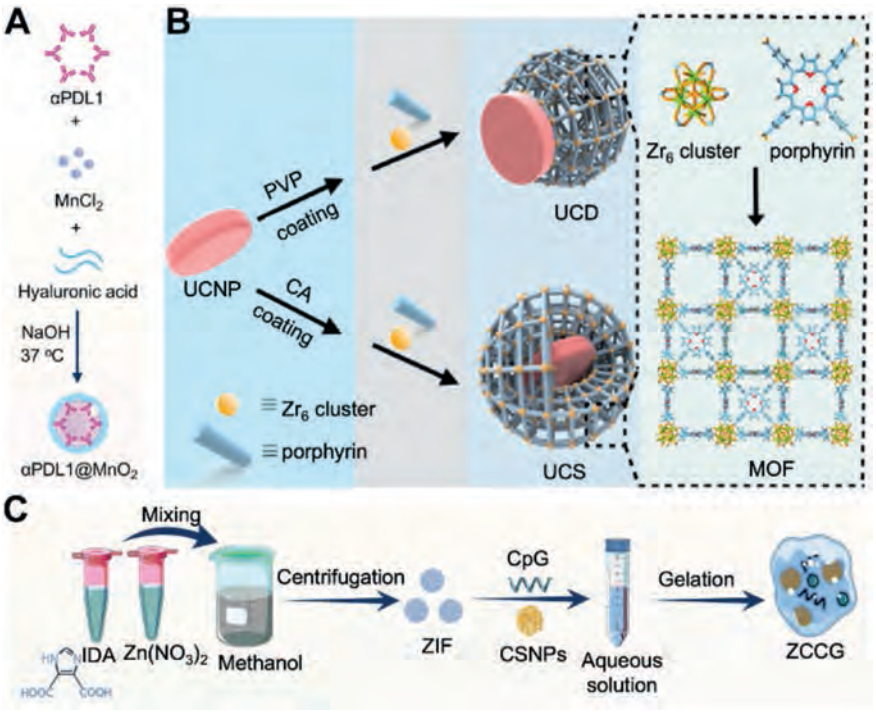


Figure 6 Schematic diagram of different technical routes of self-assembled metal-based nanoplatforms for immunotherapy. (A) The synthesis process of αPDL1@MnO_2. Reprinted with the permission from Ref. 417. Copyright © 2023, American Chemical Society. (B) The synthesis process of TPZ/UCSs. Reprinted with the permission from Ref. 20. Copyright © 2020, American Chemical Society. (C) The synthesis process of ZCCG. Reprinted with the permission from Ref. 424. Copyright © 2023, American Chemical Society.

demonstrated in *in vivo* experiments. NIR light-triggered TPZ/UCSs exert a powerful antitumor effect and synergize with PD-L1 to increase the proportion of $CD4^+$T, $CD8^+$T and NK cells, which can effectively inhibit the growth of primary tumors and distant tumors (Fig. 6B). Polyphenols are natural organic compounds containing phenolic hydroxyl groups and benzene rings, which can assemble with different molecules and metal ions through covalent and non-covalent interaction[422]. Metal-polyphenol coordination nanosystems are also considered to be an ideal platform for cancer immunotherapy. For example, natural polyphenol tannins react with oxaliplatin (OXA) precursor (1,2-diaminocyclohexane-Pt (II)) to form well-defined NPs, which are then formed into stable PTI NPs through Fe (III)-polyphenol complexation reactions. Once internalized by tumor cells, PTI NPs undergo a transformation under acidic conditions and high levels of ROS, showing enhanced tumor accumulation and rapid drug release. The cascaded ICD event stimulates tumor immunogenicity and has a good anti-tumor effect when combined with ICB therapy. The above shows that polyphenol-based Pt delivery is a promising strategy[423]. Hydrogels have a three-dimensional network structure and are widely used for drug encapsulation; Jin et al.[424] coordinated Zn^{2+} with 4,5-imidazole dicarboxylic acid and integrated Chitosan (CS) and CpG to design a metal-based hydrogel nanosystem with dual-pathway activation of cGAS−STING and TLR9. Intratumoral administration activated the systemic immune response, especially the infiltration of immune cells and the expression of cytokines at the tumor, ultimately promoting the formation of tertiary lymphoid structures (TLSs) and enhancing the therapeutic effect of αPD-1. In addition, ZCCG induced long-term immune memory, thereby preventing tumor recurrence and metastasis (Fig. 6C).

4.4. Self-assembled supramolecular-based nanoplatforms

The rapid development of nanomedicine and materials science has provided a favorable weapon for cancer immunotherapy. Among them, supramolecular materials with flexible and multi-module hierarchical structures have the advantages of high loading efficiency, good biocompatibility and diversified functions, making them widely used to explore excellent delivery platforms for cancer immunotherapy drugs. Compared with other nanomaterials, supramolecular materials have emerging properties. They can interact with key molecules in tumor immunotherapy in a precise and controllable manner through intelligent design, providing a multifunctional platform[425]. Supramolecular chemistry connects a variety of complex molecules with non-covalent interactions to produce a range of specific and tunable self-assembled nanosystems, including supramolecular peptide assembly (SPA), supramolecular DNA assembly (SDA), lipid hydrophobic assembly (LHA), host−guest assembly (HGA) and biomolecular recognition assembly (BRA) and so on[426].

Peptide-based materials are biodegradable and generally have good biocompatibility. Their well-defined structure and reasonable sequence design mean that they have a wide range of functions and are a promising choice for supramolecular nanomaterials in cancer immunotherapy. For example, Cheng et al.[427] synthesized an amphiphilic peptide composed of functional 3-diethylaminopropyl isothiocyanate (DEAP) molecule, a peptide substrate of matrix metalloproteinase-2 (MMP-2), and ^{D}PPA-1, which was co-assembled with indoleamine 2,3-dioxygenase (IDO) inhibitor (NLG919). Upon reaching the tumor, the acidic environment causes the DEAP molecule to swell, and the MMP-2 overexpressed at the tumor cleaves the substrate, resulting in the

disintegration of the NPs. The released ^{D}PPA-1 and NLG919 target PD-L1 and IDO, respectively. This dual-responsive multifunctional peptide assembly nanoplatform promoted the recruitment and proliferation of CTLs, slowed the growth of melanoma, and prolonged survival (Fig. 7A). Using supramolecular DNA assembly interactions is another approach to constructing supramolecular nanomaterials. For example, Huang et al.[428] designed an artificial immune cell engager (AICE) platform based on supramolecular interactions between DNA base pairs. First, the synthetic short DNA chains were fixed on the surface of poly (lactic-*co*-glycolic acid) (PLGA), forming a stable scaffold. Then, the biomolecules were loaded onto the DNA surface through a bifunctional linker strategy or a complementary DNA-biomolecule direct hybridization strategy. Experiments have shown that local injection of the particles promoted the activation of T cells and tumor clearance.

Huang et al.[429] designed a dual TME-sensitive nano drug (P-αPD-L1/C) to intelligently turn on SDT for precision immunotherapy of melanoma. Ce6 was loaded into a pre-synthesized lipid micelle nanocarrier through hydrophobic interaction, and then the αPD-L1 antibody was connected to the surface of the lipid carrier through an MMP-2-cleavable peptide. Finally, the polyethylene glycol (PEG) chain formed a PEG coating through an amide bond. After reaching the tumor site, the acidic pH condition triggered the release of PEG coating, exposing the NPs. The MMP-2 overexpressed in the tumor cut the linker, resulting in the release of αPD-L1 and the dispersion of Ce6 in cancer cells. Upon ultrasound irradiation, Ce6-mediated SDT generated enough ROS to kill tumor cells and induce ICD. Studies have shown that this P-αPD-L1/C, which combines αPD-L1 immunotherapy and SDT, effectively promoted the infiltration of T cells and effectively inhibited the growth, recurrence and metastasis of melanoma (Fig. 7B). Among various non-covalent interactions, supramolecular host−guest systems exhibit unparalleled advantages, as they can encapsulate small molecule drugs and ensure the drugs are released at the desired target site[430]. Macrocyclic molecules act as host molecules to bind guest molecules into the cavity through non-covalent forces while interacting with the external environment. The most commonly used host molecule is β-cyclodextrin (β-CD), a conical

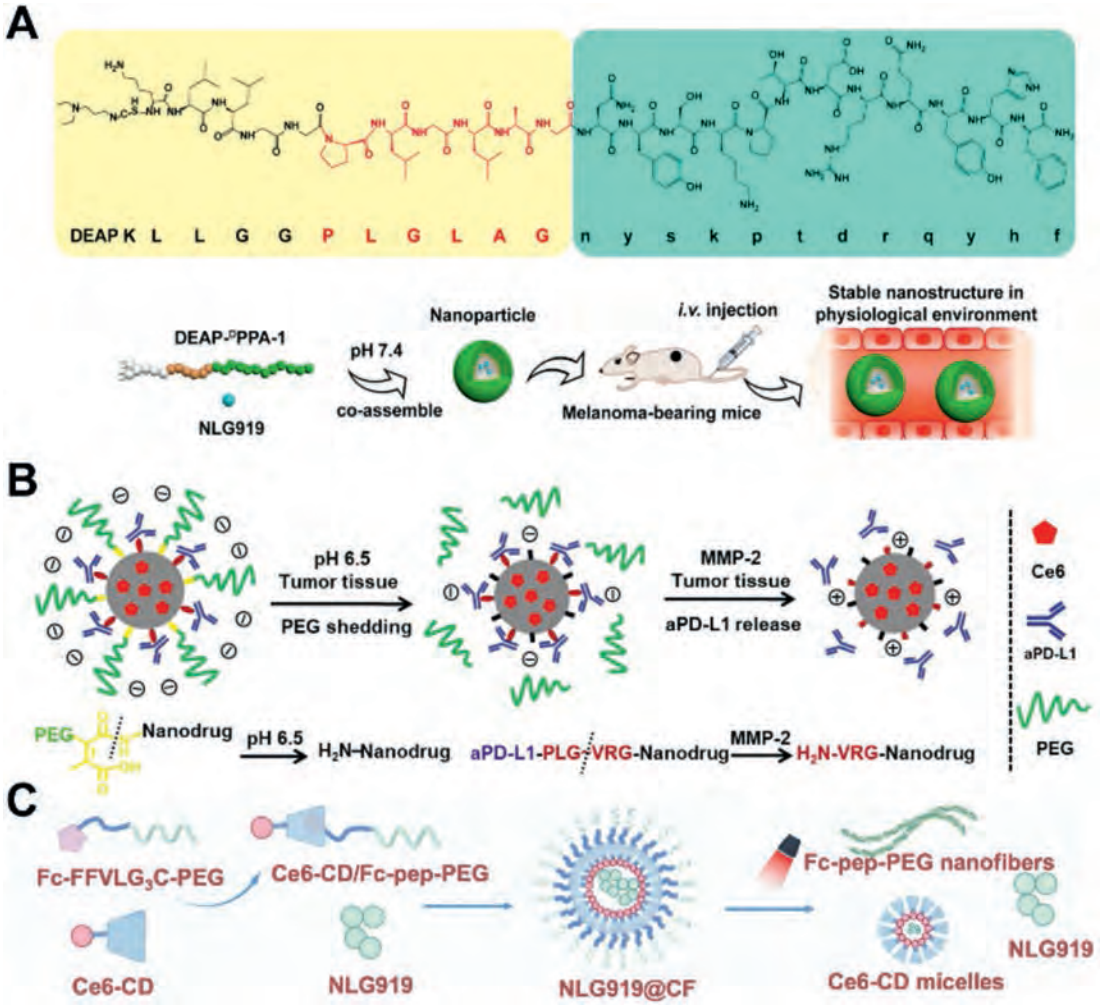


Figure 7 Schematic diagram of different technical routes of self-assembled supramolecular-based nanoplatforms for immunotherapy. (A) The synthesis process of NLG919@DEAP-^{D}PPA-1. Reprinted with the permission from Ref. 427. Copyright © 2018, American Chemical Society. (B) Schematic illustration of *in vivo* performance of P-αPD-L1/C. Reprinted with the permission from Ref. 429. Copyright © 2021, Elsevier. (C) The synthesis process of NLG919@CF. Reprinted with the permission from Ref. 432. Copyright © 2024, Springer Nature.

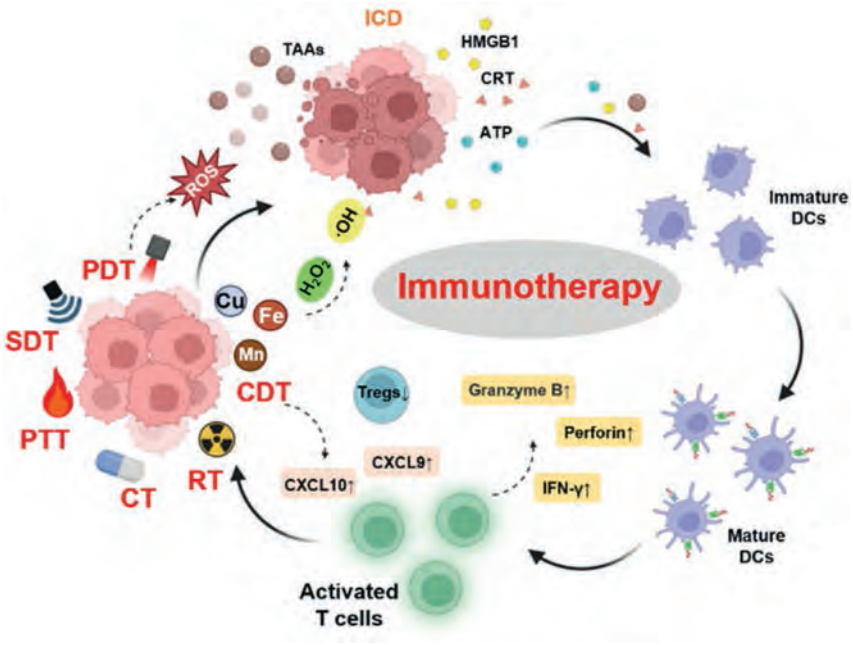


Figure 8 A mechanism diagram of how CT, CDT, PDT, PTT, RT, and SDT enhance the efficacy of cancer immunotherapy. This image is created with BioRender.

macrocycle with a hydrophobic cavity, which can encapsulate drugs within its interior through host−guest interactions[431]. Liu et al.[432] designed a convertible self-delivery supramolecular nanosystem through the host−guest interaction between β-CD and ferrocene (Fc). Ce6 was coupled to β-CD to form Ce6-CD, while ferrocene was combined with FFVLG3C peptide and PEG chain to form Fc-pep-PEG. NLG919 was loaded with Ce6-CD and Fc-pep-PEG to construct supramolecular NPs (NLG919@CF). This study proved that NLG919@CF NPs could effectively target the tumor, and PDT combined with immunotherapy significantly improved the tumor immunosuppressive microenvironment, that is, reduced the proportion of Tregs and restored the function of CTLs (Fig. 7C). In addition to the supramolecular assembly systems mentioned above, the mutual recognition and binding between biomolecules can also be applied to drive the construction of supramolecular assembly systems, such as the interaction between receptor-ligand, antigen−antibody, and avidin-biotin[433].

In addition to the self-assembled nanoplatforms based on nucleic acids, peptides and proteins, metals and supramolecular structures mentioned above, nanomicelle polymers, carrier-free nanosystems, biomimetic self-delivery nanosystems, and self-assembled nanoplatforms based on inorganic nanomaterials, liposomes, nanoglycocluster and natural products have wide applications in cancer immunotherapy. For example, the multivalent aptamer drug conjugate (ApMDC) reported by Geng et al.[276] is an amphiphilic nanomicelles polymer self-assembled from hydrophilic aptamers and hydrophobic monomers (anticancer drugs), paving the way for the delivery of multiple anticancer drugs to tumor sites. Carrier-free self-assembled nanomedicines are prepared from active pharmaceutical ingredients without complicated synthesis steps, offering advantages such as simple preparation and high drug-loading capacity. For example, Zhao et al.[280] designed a carrier-free nano drug (TerBio), self-assembled from Ce6, SB505124 (SB), and lonidamine (Lon), and Kong et al.[285] developed a self-delivering carrier-free nano drug (CCXB), through the self-assembly of Ce6 and celecoxib (CXB), both of which effectively inhibit tumor growth. The design principles of biomimetic nanosystems are primarily based on structural types such as cell membranes, exosomes[296], and vesicles[311]. The most notable advantages include evading immune recognition and prolonging blood circulation time. For example, Xie et al.[281] constructed a biomimetic nanosystem by combining HB (a photosensitizer) and NLG8189 to form HB-NLG8189 and then injected it into macrophage membranes, which showed the advantages of preferential accumulation in tumors and inducing strong immune responses. In addition, the nano-confinement effect of inorganic mesoporous silica nanoparticles plays an outstanding role in co-loading therapeutic drugs and controlling drug release[283]; nanoglycoclusters (such as mannose) can bind to mannose receptors on the surface of TAMs to achieve antitumor phenotype conversion[323]; and nano-self-assembly systems based on natural products (such as ursolic acid and polyphenol) have advantages such as good anticancer activity and low toxicity[346].In summary, an increasing number of self-assembled nanoplatforms have been developed for tumor immunotherapy and achieved remarkable results.

5. Immunotherapy-based self-assembled nanoplatforms for combination therapy

Cancer is an extremely complex disease with a high mortality rate, and traditional surgical intervention, CT, and RT are often ineffective, especially for patients with advanced cancer. Immunotherapy, as a novel treatment method, has shown promising results in tumor treatment by restarting the immune system[434]. However, single therapy usually leads to poor tumor treatment effects and is difficult to achieve anticancer effects. Combination therapies can target different aspects of tumor cells and inhibit tumor growth in

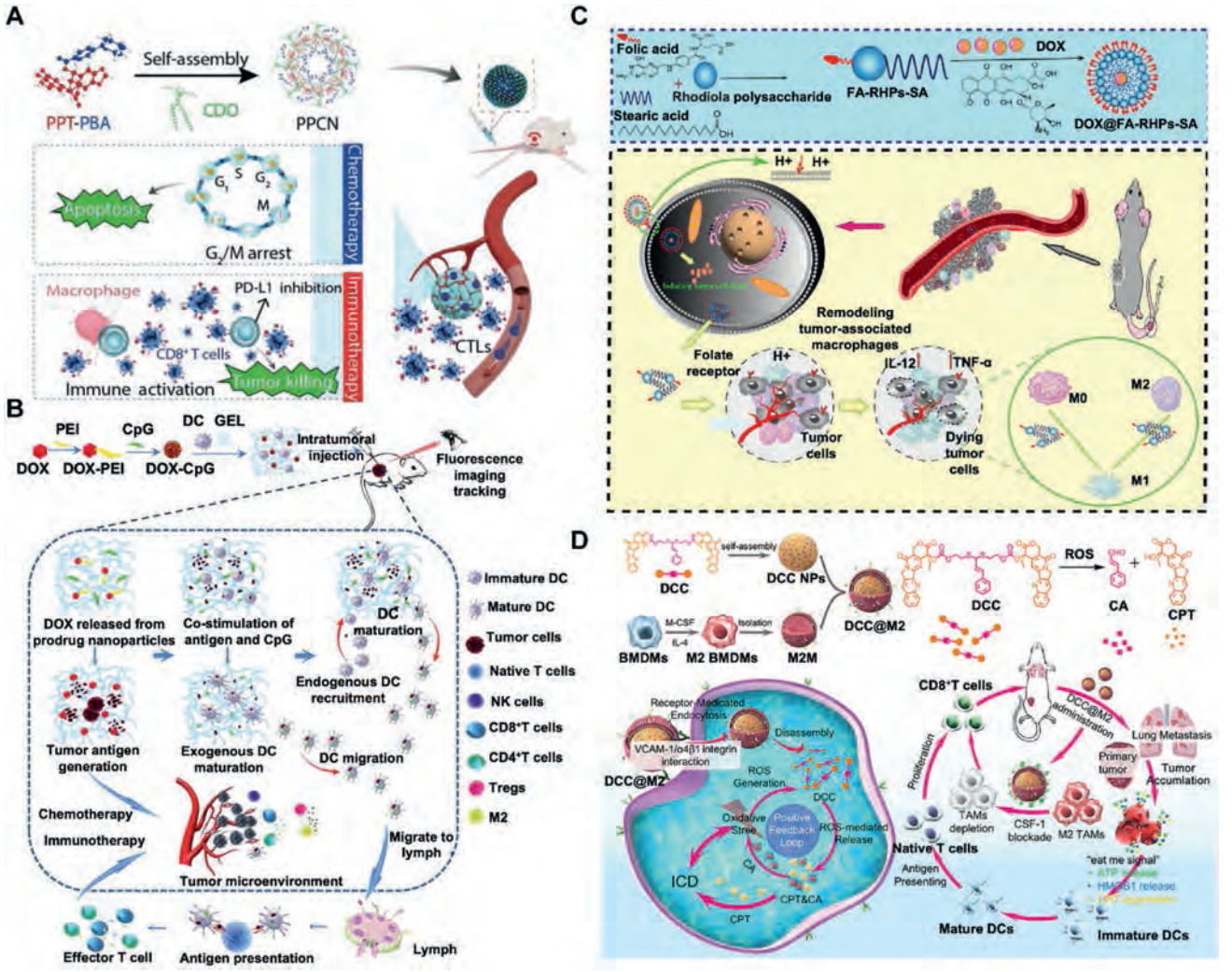


Figure 9 (A) Schematic representation of the principle of the PPCN nanoplatform for ICB/CT combined therapy. PPCN nanoplatform promotes tumor-specific immune responses by inhibiting PD-1 production in lung cancer cells, demonstrating a certain therapeutic effect on this highly heterogeneous and aggressive tumor. However, in the complex physiological environment, the targeted delivery efficiency and stability of PPT may still be affected. The release of PPT in non-targeted sites (such as the liver and spleen) may lead to normal tissue damage and systemic toxicity. Reprinted with the permission from Ref. 313. Copyright © 2022, American Chemical Society. (B) Schematic representation of the principle of the multifunctional hydrogel system nanoplatform for DCs-based immunotherapy/CT combined therapy. This nanoplatform induces a strong CTL-killing effect and increases CTL infiltration. However, the degradation rate of the hydrogel and the drug release rate are influenced by the *in vivo* microenvironment, which may lead to individual variability and affect therapeutic efficacy. Additionally, the survival rate and activity of DCs *in vivo* may be impacted by the immunosuppressive TME, potentially resulting in an insufficient immune response. Reprinted with the permission from Ref. 442. Copyright © 2021, Elsevier. (C) Schematic representation of the principle of the DOX@FA-RHPs-SA nanoplatform for TAMs-based immunotherapy/CT combined therapy. DOX@FA-RHPs-SA nanoplatform exerts a synergistic anti-tumor effect by inducing tumor cell apoptosis and regulating immune cell function. However, nanoparticles still have some shortcomings, such as delivery efficiency issues and non-specific immune activation, and further complex modification strategies are needed. Reprinted with the permission from Ref. 306. Copyright © 2023, Elsevier. (D) Schematic representation of the principle of the DCC@M2 nanoplatform for immunotherapy/CT combined therapy. The DCC@M2 nanoplatform exerts its anti-tumor effects by establishing a positive feedback loop of "ROS-triggered CA/CPT release and CA/CPT-mediated ROS generation," along with the multifunctionality of the M2-TAM membrane. However, M2 macrophage membrane-coated nanoparticles may adsorb immunosuppressive molecules and deplete TAMs in non-tumor sites, thereby affecting normal immune function. Reprinted with the permission from Ref. 351. Copyright © 2022, Elsevier.

multiple ways, including inducing ICD, anti-angiogenesis, immunosuppressive cell depletion and activating T cell responses. With the in-depth research on cancer, cancer-type-specific biomarkers are continuously being discovered, and cancer treatment strategies are also developing rapidly. Cancer nanomedicine engineering has provided new approaches for drug delivery and reducing toxic side effects. Self-assembly methods have shown enormous potential in nanoengineering drugs, and an increasing number of self-assembled nanosystems are being explored for novel tumor treatments due to their excellent physical and chemical properties. These systems can effectively encapsulate and deliver drugs to tumors through non-covalent driving

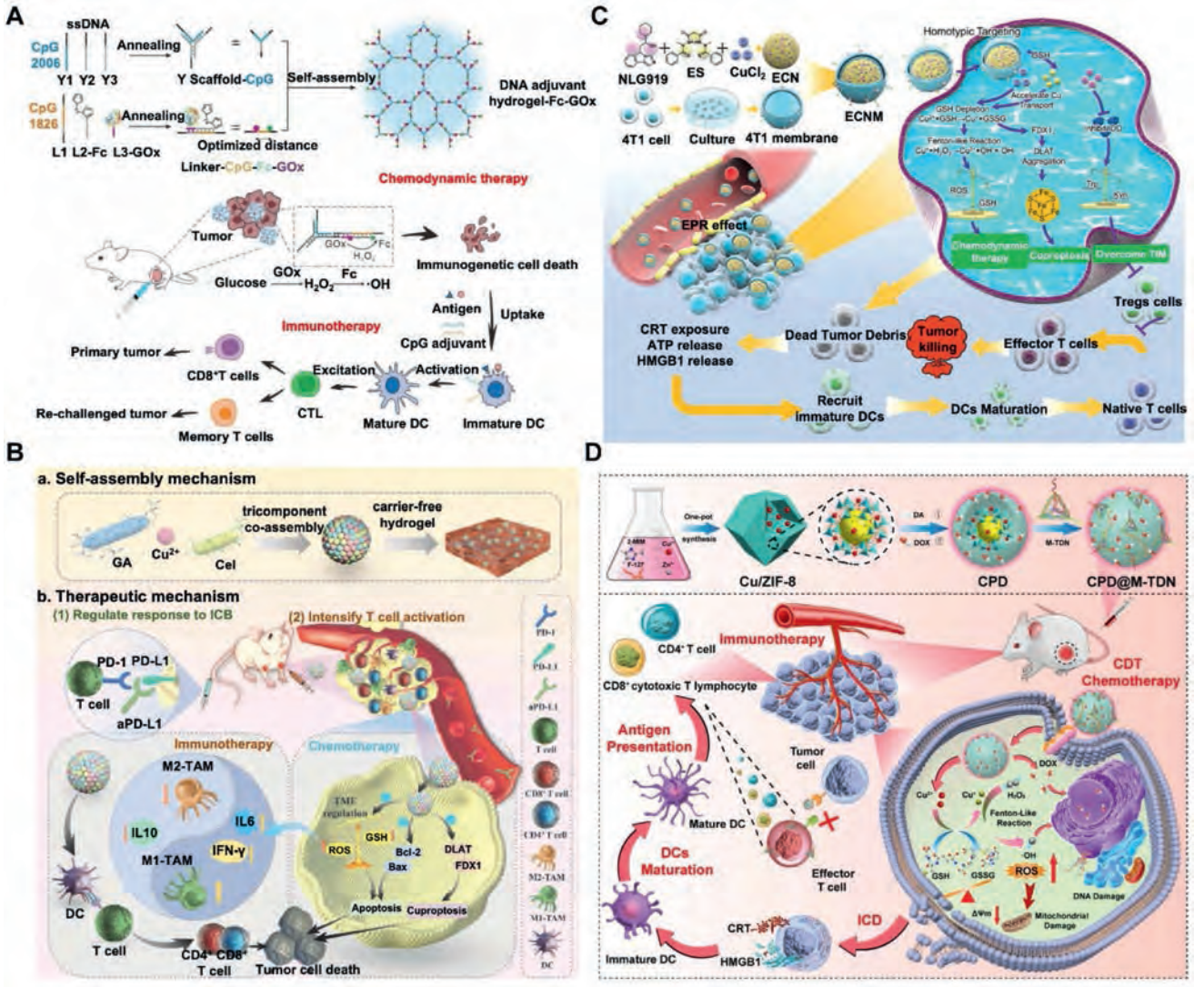


Figure 10 (A) Schematic representation of the principle of the DNA adjuvant hydrogel-Fc-GOx nanoplatform for immunotherapy/CDT combined therapy. This DNA adjuvant hydrogel, after intratumoral injection, can effectively inhibit the growth of local tumors; however, its application is limited in non-solid tumors. Reprinted with the permission from Ref. 444. Copyright © 2024, WILEY. (B) Schematic representation of the principle of the hydrogel system nanoplatform for ICB-based immunotherapy/CDT combined therapy. Cel hydrogel exerts a strong anti-tumor effect through the synergy of immunotherapy, CDT, and cuproptosis. It is worth noting that metal ion coordination may pose a toxicity risk, as excessive metal ion release and metal ion release at non-tumor sites could lead to metal toxicity, affecting the function of normal cells. Reprinted with the permission from Ref. 207. Copyright © 2025, Elsevier. (C) Schematic representation of the principle of the ECNM nanoplatform for immunotherapy/CDT/cuproptosis combined therapy. ECNM can be used for cancer therapy through the synergistic effects of cuproptosis, CDT process, and reversal of TIM. Similarly, excessive release of Cu may cause toxicity to normal tissues, especially as Cu affects cell metabolism and protein function, potentially leading to nonspecific damage. Reprinted with the permission from Ref. 212. Copyright © 2024, WILEY. (D) Schematic representation of the principle of the CDP@M-TDN nanoplatform for immunotherapy/CDT combined therapy. CDP@M-TDN can effectively promote T cell activation and proliferation in multiple ways; however, the stability of the tetrahedral DNA nanostructure needs further validation in the *in vivo* environment to ensure its stability and sustained release in different physiological conditions. Reprinted with the permission from Ref. 445. Copyright © 2024, Elsevier.

forces such as hydrogen bonds, hydrophobic interactions and electrostatic interactions, thereby improving the therapeutic efficacy[435,436]. Local treatments such as CT, PDT, SDT, PTT, and RT can achieve precise treatment for the tumor without damaging normal cells. However, these therapeutic strategies can only temporarily control tumor growth. After treatment cessation, residual tumor cells in the body may proliferate and metastasize, leading to tumor recurrence[437]. In short, CT and RT directly induce ICD, releasing TAAs and DAMPs (such as ATP, endoplasmic reticulum calcium-binding protein (CRT), and high mobility group protein (HMGB1)), thereby activating DCs. PDT and SDT rely on light-activated photosensitizers and ultrasound-activated sonosensitizers, respectively, to generate ROS, inducing ICD. PTT directly kills tumor cells, leading to the release of TAAs. CDT utilizes transition metal ions (such as Fe, Cu, and Mn) to catalyze H_2O_2 through the Fenton reaction or Fenton-like

reactions, generating ·OH, which induce tumor cell death and release DAMPs (Fig. 8). Therefore, cancer immunotherapy combined with CT, PDT, PTT, and SDT is expected to exert more effective and potent antitumor effects. This chapter aims to discuss the important research progress in the past three years regarding the combination of cancer immunotherapy with other local minimally invasive treatment methods based on self-assembly, including immunotherapy combined with CT, immunotherapy combined with CDT, immunotherapy combined with PDT, immunotherapy combined with PTT, immunotherapy combined with PTT, and immunotherapy combined with RT, in order to provide new insights into cancer treatment[437,438].

5.1. Immunotherapy combined with CT

CT is currently one of the most effective and commonly used methods for treating invasive and metastatic tumors. Commonly used CT drugs include antimetabolites, alkylating agents, antibiotics and botanicals, which promote tumor cell apoptosis by blocking metabolism, damaging DNA, activating signal transduction and other mechanisms. However, contrary to expectations, CT usually cannot completely eliminate tumor cells and can easily cause serious damage to healthy cells and tissues, such as nephrotoxicity, cardiotoxicity, hepatotoxicity, and neurotoxicity[439–441]. Therefore, it is urgent to explore effective methods to enhance the efficacy of CT.

Immunotherapy combined with CT based on a self-assembled nanoplatform is a promising treatment method. The self-assembled system can effectively deliver higher doses of CT drugs to tumor tissues through targeting ability and enhanced permeability and retention (EPR), thereby reducing the adverse reactions associated with traditional CT drugs. Podophyllotoxin (PPT) is a lignin antitumor component that has been widely used as a lead molecule for designing anticancer drugs and is widely used in CT. Wang et al.[313] designed a self-assembled nanoparticle based on PPT, which maximized the therapeutic efficacy of PPT while reducing systemic toxicity. In brief, PPT was connected to 4-(4-methyl-1-piperazinylmethyl) benzoic acid through amido linkage and further co-assembled with tripeptide cationic lipid to form self-assembled NPs (PPCNs). After intravenous administration, PPCNs accumulated at the tumor through the EPR effect. Under the acidic conditions of TME, tripeptide cationic lipid (CDO) became unstable, and PPT was released by further enzymolysis. PPT caused tumor cells to be arrested in G0/G1 or S phase, eventually resulting in cell apoptosis. Excitingly, PPCNs are able to inhibit the expression of PD-L1. This innovative self-assembled nanoplatform combining ICB and CT has enhanced anticancer therapeutic efficacy and safety and is far superior to PTT alone (Fig. 9A). As we all know, DCs play a key role in cancer immunotherapy, and the maturation and antigen presentation ability of DCs determine the activation of T cells and the tumor-killing efficacy. Yang et al.[442] designed a multifunctional hydrogel system for the combined treatment of CT and DCs-based immunotherapy. The immune adjuvant CpG was conjugated with PEI-DOX to construct a pH-sensitive prodrug, and DCs and DOX-CpG were further combined by a hydrogel (GEL) scaffold. GEL not only provides a platform for the co-assembly of DOX, CpG, and DCs but also provides an environment that supports the growth of DCs. After reaching the tumor, DOX-induced ICD and released TAAs, while CpG acted as an immune adjuvant to promote the maturation of DCs. Different from the traditional strategy of promoting the maturation of DCs, this nanosystem directly transplants exogenous DCs, effectively making up for the lack of endogenous DCs. Another highlight is that this nanosystem provides a platform for the interaction between antigens, adjuvants and DCs. The results also showed that the system increased the infiltration of effector T cells, improved the immunosuppressive TME, and thus enhanced the antitumor efficacy (Fig. 9B). In addition to the key role of DCs in cancer immunotherapy, different phenotypes of TAMs play distinct roles in the occurrence and development of tumors, promoting the transformation of TAMs from the immunosuppressive M2 phenotype to the antitumor M1 phenotype is a promising strategy for cancer treatment. Xiong et al.[306] modulated TAMs by introducing *Rhodiola rosea* polysaccharides (RHPs), a heteropolysaccharide that can modulate phenotypic changes in TAMs. RHPs were modified with folic acid (FA) and stearic acid (SA) to obtain tumor cell targeting and self-assembled capabilities. Hydrophobic DOX is then loaded into FA-RHPs-SA to form DOX@FA-RHPs-SA. After actively targeting and reaching the tumor site, polysaccharide carrier RHPs induce macrophage polarization and achieve the transformation of M0 and M2 to M1. The released DOX causes the direct killing of tumor cells. This synergistic effect of immunotherapy based on regulating TAMs and DOX-based CT significantly enhances the antitumor efficacy (Fig. 9C). Even more ingenious is that Zhang et al.[351] designed a multifunctional nanomaterial wrapped in an M2-type TAM membrane, realizing a virtuous cycle of "ROS-triggered cinnamaldehyde (CA)/camptothecin (CPT) release and CA/CPT-mediated ROS generation." In brief, a ROS-responsive CA derivative was first synthesized and then combined with CPT to form this ROS-cleavable CPT/CA prodrug (DCC). These were self-assembled into spherical NPs. Finally, the M2-type TAM membrane was coated to prepare DCC@M2. DCC@M2 achieved tumor targeting through VCAM-1/$\alpha 4\beta 1$ integrin, CA stimulated intracellular ROS generation, triggering the release of CA and CPT, and then induced ICD. The TAM membrane acts as a bait to bind to CSF-1, resulting in the depletion of CSF-1 secreted by tumor cells, which in turn leads to the depletion of TAMs. The final result is the interference with the interaction between TAMs based on the M2 phenotype and tumor cells, increasing T-cell infiltration and enhancing the antitumor efficacy (Fig. 9D).

By forming CT drugs into nanoparticle prodrugs, selecting the required ingredients with specific modifications to form multifunctional self-assembled nanomaterials, and combining them with immunotherapy, it is expected to achieve effective tumor targeting and controlled drug release. When NPs target tumors, they prevent premature drug release, enhance drug accumulation at the tumor, and reduce the toxic side effects of the drugs. Influenced by stimuli such as pH in the TME, the self-assembled nanoplatform undergoes structural changes, releasing the CT drugs to exert their therapeutic effects. Notably, some CT drugs, such as DOX, can induce ICD and release TAAs, providing an antigen source for cancer immunotherapy and enabling personalized antigen-specific immune responses at the tumor. In summary, cancer immunotherapy based on self-assembled nanosystems brings new hope to CT and is very promising in terms of safety and effectiveness.

5.2. Immunotherapy combined with CDT

CDT is a novel type of therapy and has become a potential cancer treatment strategy. It is based on the use of metal ion-based nanomaterials as catalysts to produce hydroxyl radicals (·OH) by catalyzing H_2O_2[443]. Almost all studies have proven the

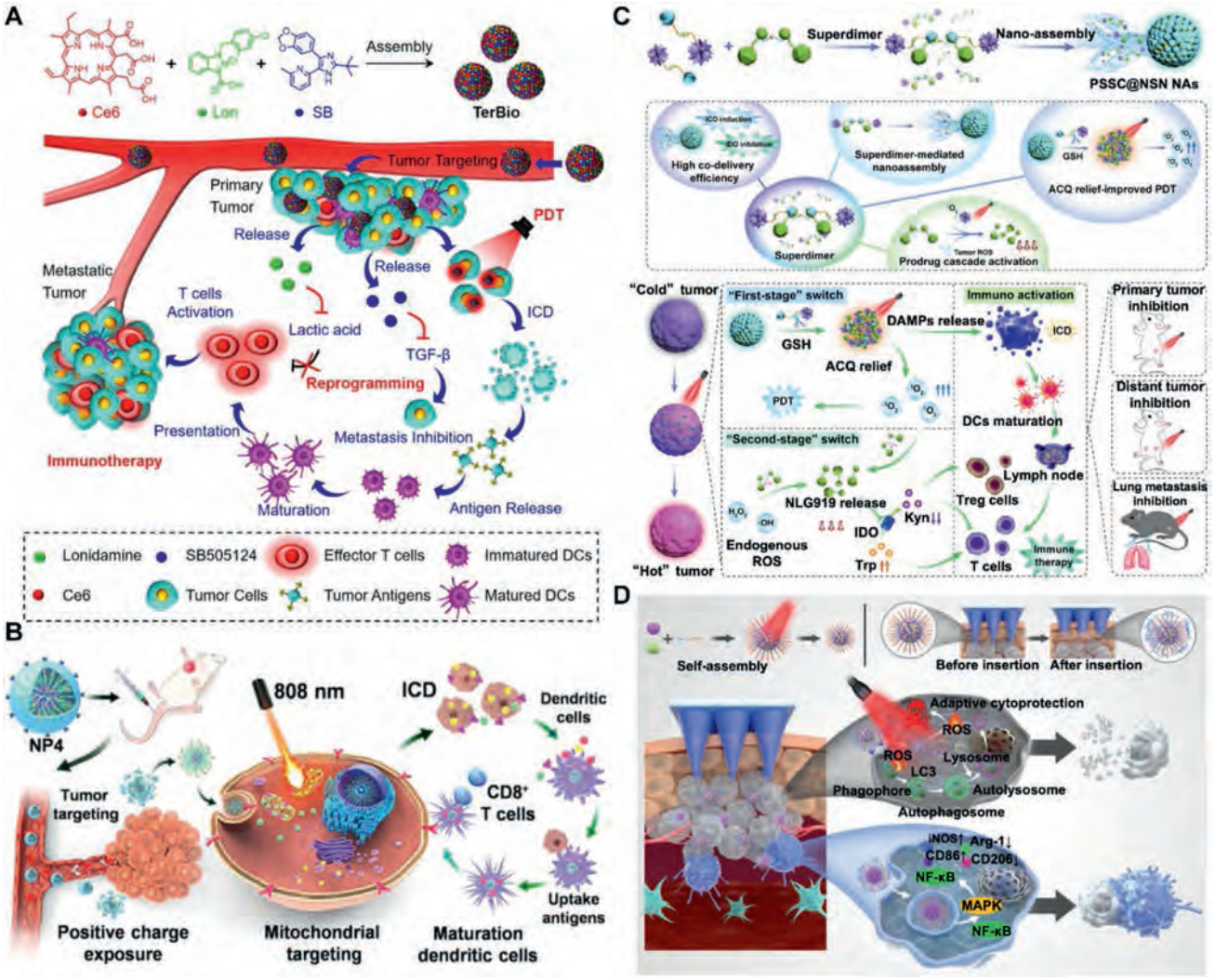


Figure 11 (A) Schematic representation of the principle of the TerBio nanoplatform for immunotherapy/PDT combined therapy. The carrier-free TerBio significantly inhibited the growth of distal and metastatic tumors by amplifying immunotherapy through PDT. However, the stability and biodegradability of the bioregulators *in vivo* need further evaluation to optimize the long-term efficacy of TerBio. Reprinted with the permission from Ref. 280. Copyright © 2022, American Chemical Society. (B) Schematic representation of the principle of the NP4 nanoplatform for immunotherapy/PDT combined therapy. NP4 targets tumor cells and mitochondria in a cascade manner, further killing tumor cells through the PDT process. Whether the nanodrug is activated sequentially *in vivo* still requires further evaluation. Reprinted with the permission from Ref. 447. Copyright © 2021, Elsevier. (C) Schematic representation of the principle of the PSSC@NSN NAs nanoplatform for ICB-based immunotherapy/PDT combined therapy. The superdimeric PSSC@NSN NAs can selectively activate the photosensitizer and NLG919 as needed, promoting PDT-induced ICD responses and amplifying immunotherapy effect. However, PSSC@NSN NAs are constructed using supramolecular dimer engineering, which involves multi-step chemical synthesis, nano-assembly, and optimization processes, greatly limiting their clinical application. Reprinted with the permission from Ref. 448. Copyright © 2024, Elsevier. (D) Schematic representation of the principle of the DMNs nanoplatform for immunotherapy/PDT combined therapy. The DMNs patch delivers photosensitizers and autophagy inhibitors directly into the lesion, significantly enhancing the phototoxicity of the photosensitizer and effectively supporting anti-tumor therapy. However, DMNs are only suitable for skin cancer or superficial tumors, with limited effectiveness in treating deep-seated tumors such as pancreatic and liver cancer. Additionally, the biodegradability of microneedle residues and the long-term immunological effects still require clinical validation to ensure long-term safety. Reprinted with the permission from Ref. 202. Copyright © 2021, American Chemical Society.

existence of ICD and immune response; thus, combining CDT with immunotherapy is also a promising cancer treatment strategy. Zhao et al.[444] developed a DNA adjuvant hydrogel formulation for synergistic treatment of CDT and immunotherapy. They first synthesized DNA hydrogels with a well-defined structure and then further integrated CpG ODN, glucose oxidase (GOx) and ferrocene molecules. After intratumoral injection, GOx catalyzed glucose to produce H_2O_2, while Fc catalyzed H_2O_2 into highly toxic ·OH. CpG, as a DNA molecule to form a hydrogel, also serves as an immune adjuvant. Together with the TAAs released by CDT-induced ICD, it forms an *in situ* tumor vaccine. This combined strategy of CDT and immunotherapy significantly inhibited tumor growth, recurrence and metastasis (Fig. 10A). Similarly, Wu et al.[207] also proposed a

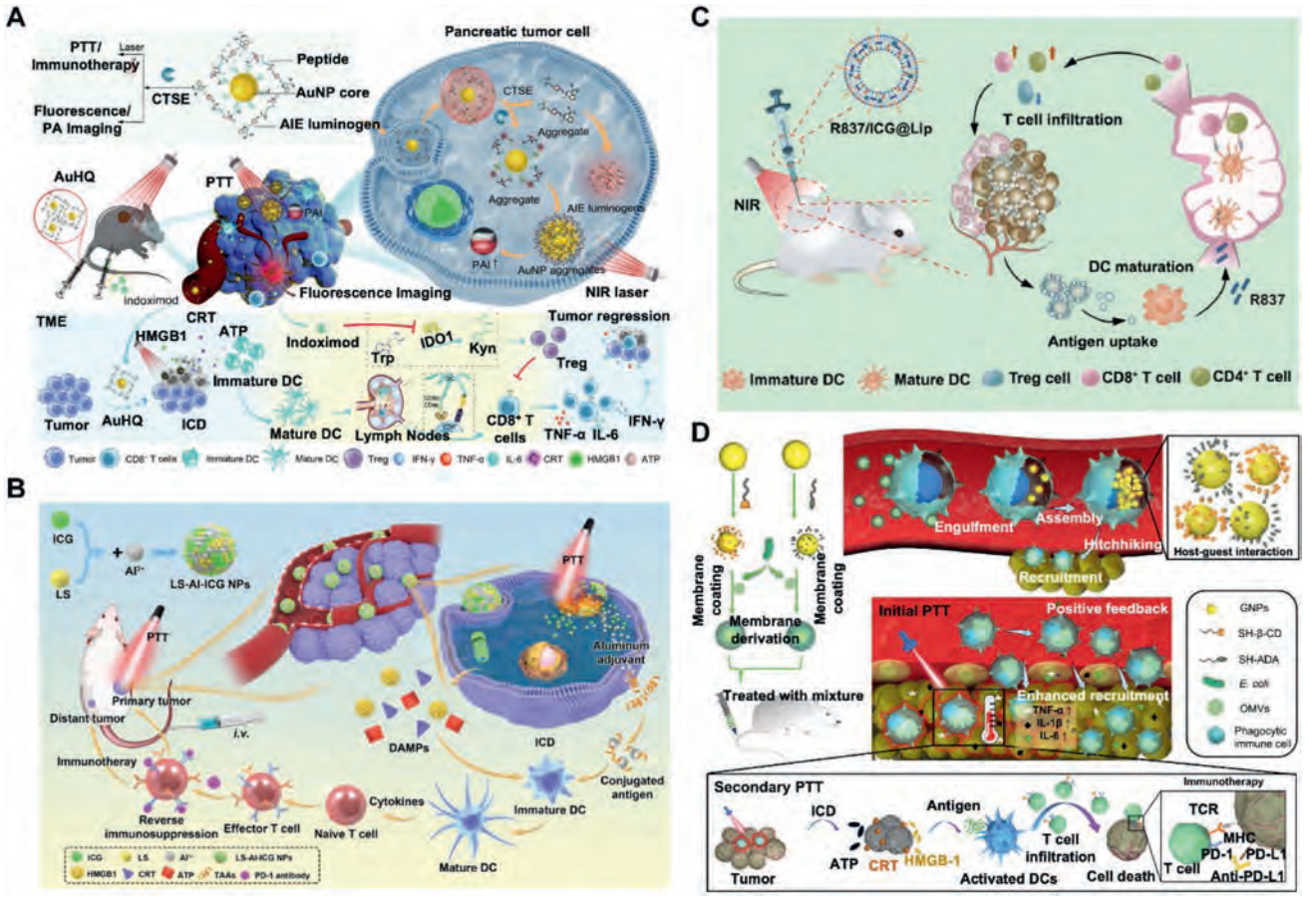


Figure 12 (A) Schematic representation of the principle of the AuHQ nanoplatform for fluorescence imaging and immunotherapy/PTT combined therapy. This nanoplatform undergoes dual self-assembly triggered by cancer cell-specific enzymes, demonstrating promising efficacy in photothermal therapy and photoacoustic imaging for pancreatic cancer. However, this enzyme-triggered self-assembly approach is only suitable for tumors with high expression of specific TME enzymes, and its stability requires further investigation. The long-term retention of Au nanoparticles in the body may lead to bioaccumulation, and their long-term toxicity and excretion pathways still need further study. Reprinted with the permission from Ref. 138. Copyright © 2024, American Chemical Society. (B) Schematic representation of the principle of the LS-Al-ICG NPs nanoplatform for immunotherapy/PTT combined therapy. LS-Al-ICG can induce amplified ICD, effectively triggering an immune response by activating DCs and initiating a CTL response to kill tumor cells. Although LS has good biocompatibility, its long-term effects in the TME and potential immune regulatory functions still require further investigation. Additionally, the ultra-small size of NPs may lead to rapid clearance in the circulatory system, necessitating further optimization of their stability and targeting ability. Reprinted with the permission from Ref. 260. Copyright © 2022, Elsevier. (C) Schematic representation of the principle of the R837/ICG@Lip nanoplatform for immunotherapy/PTT combined therapy. R837/ICG@Lip-mediated mild PTT can simultaneously promote TAAs release, DCs activation, and $CD8^+$ T cell infiltration, demonstrating excellent antitumor efficacy. The use of mild PTT avoids the damage to normal tissues caused by traditional high-temperature PTT. However, the stability of thermosensitive liposomes is influenced by temperature and the microenvironment, and their long circulation ability and precise controlled release *in vivo* still need to be determined and optimized to ensure that the drug is released under appropriate temperature conditions without premature leakage. Reprinted with the permission from Ref. 373. Copyright © 2023, Elsevier. (D) Schematic representation of the principle of the GNPs nanoplatform for immunotherapy/PTT combined therapy. GNPs form stable nanostructures through intracellular self-assembly and utilize immune cells as "carriers" for targeted transport, demonstrating high antitumor efficacy. However, the loading capacity of immune cells is limited, and the self-assembly of GNPs inside the cells may affect their normal functions, reducing their survival rate or migration ability, which could ultimately impact delivery efficiency. Reprinted with the permission from Ref. 44. Copyright © 2022, The American Association for the Advancement of Science.

hydrogel system constructed by glycyrrhizic acid (GA), Cu^{2+} and celastrol (Cel) through coordination and hydrogen bond interactions. This system highlights the broad-spectrum antitumor advantages of natural bioactive products. GA and Cel could induce ROS production, prompting the polarization of TAMs to the M1 phenotype. Cu^{2+}-mediated CDT further regulates TME, enhancing antigen presentation of DCs and infiltration of T cells. Combined with αPD-L1 administration, this strategy synergistically exerts antitumor effects, inhibiting both primary and metastatic tumors (Fig. 10B). In addition to Cu-mediated CDT, the Cu-dependent "cuproptosis" has also attracted attention as a novel form of cell death. Wu et al.[212] developed a biomimetic nanomedicine (ECNM). Elesclomol (ES), Cu^{2+} and NLG919 are self-assembled together through coordination and $\pi-\pi$ stacking and finally coated in the 4T1 cell membrane. The presence of tumor cell membranes prompted ECNM to

homotypic target tumor cells. After internalization, Cu^{2+} reacted with glutathione (GSH), and the reduced Cu^{+} further reacted with H_2O_2 to generate ·OH, exerting the CDT effect. On the other hand, ES could transfer extracellular Cu to the cell, resulting in intracellular Cu overload and triggering cuproptosis, which ultimately disrupts tumor cell function. The dual action increased the release of CRT and HMGB1, activating the cascade immune response of DCs and CTLs. In addition, the addition of NLG919 inhibited the activity of IDO1 and further enhanced the activation of CTLs. ECNM has been shown to have strong antitumor effects and had great potential in cancer treatment (Fig. 10C). Among various immunotherapy methods, ICB therapy, has made significant progress in clinical transformation and has been successfully applied to the treatment of various solid tumors, but it still faces the challenge of limited efficacy. Li et al.[445] developed a core−shell structured nanoparticle (CDP@M-TDN) with Cu/ZIF-8 as the core and DOX-loaded polydopamine as the shell. CpG oligodeoxynucleotides and PD-L1 aptamer-based M TDN were connected to the shell through biotin-avidin interaction. Under low pH conditions, the NPs dissociated, and Cu^{2+}-mediated CDT and DOX-mediated CT induced strong ICD levels, increasing the activation levels of DCs and the infiltration levels of CTLs. CpG could induce T helper cell 1 (Th1) cell differentiation and the secretion of proinflammatory factors. A series of studies have shown that CDP@M-TDN enhances the response rate of immunotherapy and has excellent potential in tumor treatment (Fig. 10D).

The emergence of a variety of functional self-assembled nanomaterials has significantly improved the response rate of the Fenton reaction while also making great progress in the combination of CDT and immunotherapy. CDT-induced ICD enhances immune response, and CDT improves the immunosuppressive TME, thereby increasing the response rate of immunotherapies such as PD-L1. Therefore, combining CDT with immunotherapy will be an effective means to improve the therapeutic efficacy.

5.3. *Immunotherapy combined with PDT*

PDT is a light-based tumor ablation method with the advantages of minimally invasive, low side effects, and light controllability[446]. Oxygen, photosensitizer, and light are the three essential conditions for PDT. Laser irradiation of a specific wavelength activates the photosensitizer, and the excited photosensitizer transfers energy to oxygen to generate singlet oxygen. Singlet oxygen reacts with various biomacromolecules in cells to produce cytotoxic effects, resulting in tumor damage or death. PDT could induce ICD, establish a pool of TAAs, promote DCs maturation, and activate tumor antigen-specific immune responses. However, due to the presence of immunosuppressive TME, the effectiveness of PDT is often limited. Therefore, combining immunotherapy to improve TME with PDT may be a promising option for cancer treatment. Zhao et al.[280] developed a self-delivery nanoplatform (TerBio) targeting immunosuppressive TME for the treatment of colorectal cancer. TerBio was assembled through hydrophobic interactions between three parts: Ce6, SB, and Lon. Ce6 is a photosensitizer, SB is a TGF-β receptor-I inhibitor, and Lon is a lactate (LA) inhibitor. TerBio accumulates at the tumor after intravenous injection through the EPR effect. Ce6-mediated PDT treatment-induced ICD promoted the release of TAAs, SB blocked the TGF-β pathway, and Lon inhibited the efflux of LA secreted by tumor cells. Both effectively reverse immunosuppressive TME. The pure active drug self-assembled TerBio has been shown to effectively inhibit the growth of primary, distant and metastatic tumors through PDT amplified immunotherapy (Fig. 11A). As a local treatment, the effectiveness of PDT depends on the tumor delivery efficiency of the drug, especially for intravenous injection, which involves

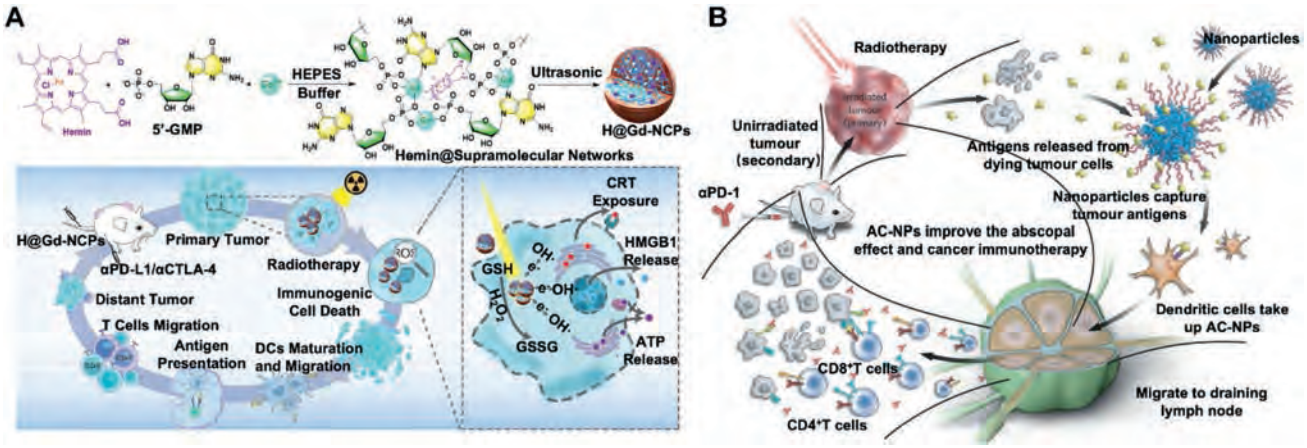


Figure 13 (A) Schematic representation of H@Gd-NCPs nanoplatform enhancing immunotherapy/RT combined therapy by depositing X-ray absorption. H@Gd-NCPs combine RT with ICD-induced immunotherapy, not only directly killing tumor cells but also activating the body's immune system to provide long-term antitumor protection. Since Gd is a heavy metal, its long-term bioaccumulation in the body over extended treatment cycles may pose potential toxicity risks, particularly concerning its effects on kidney function, which require further evaluation. Reprinted with the permission from Ref. 455. Copyright © 2021, Springer Nature. (B) Schematic representation of the principle of the AC-NPs nanoplatform for immunotherapy/RT combined therapy. AC-NPs capture tumor antigens and efficiently deliver them to immune cells such as DCs, activating T cells and promoting antitumor immune responses, enabling the immune system to recognize and attack tumor cells. This process exposes the immune system to various tumor-derived protein antigens in a patient-specific manner, offering personalized treatment characteristics. However, the targeting delivery efficiency of AC-NPs may be affected by factors such as the TME and vascular permeability, which could influence the final therapeutic outcome. Reprinted with the permission from Ref. 43. Copyright © 2017, Springer Nature.

multiple processes such as blood circulation, tumor accumulation, tumor cell internalization, and drug release. Therefore, improving targeting and delivery efficiency is a promising strategy for improving PDT. Wei et al.[447] developed a core−shell nanomaterial targeting both tumor and mitochondria to optimize the combination therapy of PDT and immunotherapy. Polymer P1 is self-assembled to form NP1, which is further assembled with P2 to form NP2 with a positively charged surface. Negatively charged PEG is introduced through electrostatic interaction to form NP3. Subsequently, SH-RGD is modified on the surface of NP3 to obtain the final nanoparticle NP4. Notably, they selected a photosensitizer with a 3D molecular structure that is superior to a planar molecular structure and synthesized an aggregation-induced emission (AIE) monomer with two hydroxyl groups to promote the generation of ROS. After intravenous injection, NP4 can effectively target tumors due to the presence of RGD peptide. Under continuous NIR light irradiation, NP4 produced ROS, PEG detached, and the thioketal bond in P3 is broken, resulting in the exposure of positively charged NP2 for mitochondrial targeting. NP2 generated a large amount of ROS in the mitochondria to kill tumor cells. The released DAMPs promote DC maturation and activate T cell response. In conclusion, a series of studies have shown that NP4 can cascade target tumor cells and mitochondria, maximizing the combined effects of PDT and immunotherapy in the treatment of triple-negative breast cancer (Fig. 11B). Wang et al.[448] focused on designing drug delivery systems to enhance the therapeutic effect of PDT. They reported a unique super-dimer self-assembled nanosystem for drug delivery. Magnesium pheophorbide a (PPa) was conjugated with β-CD to form a photodynamic cyclodextrin conjugate (PSSC), which was further assembled with an NLG919 dimer through host−guest interactions to form a super-dimer (PSSC@NSN NAs). GSH overexpressed in the tumor triggered the breakage of disulphide bonds in PSSC. Under laser irradiation, endogenous and exogenous ROS generated by PPa triggered the release of NLG919 and inhibited the production of IDO. Combination therapy with αPD-L1-driven immunotherapy effectively enhanced cancer immunotherapy, improved TME and inhibited tumor metastasis. Notably, this system not only allows the co-delivery of PPa and NLG919 to consume GSH and inhibit the production of IDO but also alleviates the aggregation concentration quenching problem common to photosensitizers, providing new insights into PDT-based immunotherapy (Fig. 11C). The nanomaterials in the above three studies were all administered by intravenous injection, while dissolving microneedles (DMNs) as an innovative transdermal drug delivery strategy has the advantages of drug accumulation in tumor, overcoming the stratum corneum barrier and avoiding circulation metabolism. Chen et al.[202] designed a self-assembled nano micelle DMNs (C/I-Mil), which encapsulated the photosensitizer (IR780) and the autophagy inhibitor chloroquine (CQ) and was coated with hyaluronic acid (HA). which is assembled by DMNs encapsulating photosensitizer (IR780) and autophagy inhibitor chloroquine (CQ) and coating HA. Upon tumor-site administration, HA-CD44 receptor interaction achieved tumor cell targeting. After NIR light irradiation, the tumor site heated up, causing the DMNs to dissolve and releasing IR780 and CQ. Continuous light-induced ICD, while CQ inhibited autophagy by interfering with lysosomal degradation, leading to the accumulation of damaged lysosomes and the release of more hydrolases to induce tumor cell death. This strategy precisely mobilized immunotherapy at the tumor, has been shown to effectively inhibit the growth of primary and distant tumors, and has great potential in reshaping the tumor immunosuppressive microenvironment and prolonging survival (Fig. 11D).

In summary, photosensitizer-based PDT induces tumor cell ICD by generating ROS, releasing TAAs, and ultimately promoting DCs maturation and T cell infiltration, thereby exerting antitumor efficacy[449]. However, standalone PDT is limited by the immunosuppressive TME. In order to improve the therapeutic efficacy of PDT, increasing research efforts are devoted to combining immunotherapy with PDT. Particularly in recent years, with the development of nanotechnology, more and more nano-delivery systems have been designed to deliver immune adjuvants, immunotherapeutic drugs and photosensitizers, such as nano-micelles and MOFs, which have shown great prospects in cancer treatment.

5.4. Immunotherapy combined with PTT

PTT is also a non-invasive local treatment method that induces tumor cell death through heat generated by photothermal agents under near-infrared light irradiation, which is also an attractive cancer treatment method[450]. Similar to PDT, PTT also triggers an immune response by inducing tumor cell ICD and releasing TAAs, so it is also a promising option to combine with immunotherapy. The key to PTT in tumor ablation lies in the selection and design of photothermal agents. Currently, various organic and inorganic photothermal agents have been used in PTT, among which AuNPs stand out due to their low toxicity, easy surface modification, active targeting ability, surface plasmon absorption, and excellent photothermal conversion performance. They have broad application prospects in PTT treatment[451,452]. Bian et al.[138] reported a photothermal modulator based on AuNPs and AIE self-assembly for the diagnosis and treatment of pancreatic cancer. They utilized Ala-Gly-Phe-Ser-Leu-Pro-Ala-Gly-Cys (AGFSLPAGC) to connect AuNPs and AIE luminogens (quinoline-malononitrile-COOH) to form AuHQ. After administration, when AuHQ reaches the tumor, AGFSLPAGC is cleaved by cathepsin E (CTSE), which is highly expressed in pancreatic cancer. The exposed positive charge and the negative charge on the surface of AuNPs were assembled through electrostatic interaction to form an amphoteric gold aggregate complex, which enhanced the photothermal effect. In addition, the released AIE luminogens are also aggregated through hydrophobic interaction. After NIR laser irradiation, the PTT effect activated by AuNPs induces ICD in tumor cells, further stimulating DC maturation and $CD8^+$T infiltration. Real-time and specific fluorescence imaging and PTT are effectively achieved. Furthermore, AuHQ combined with IDO1 inhibitors alleviated immunosuppressive TME in pancreatic cancer (Fig. 12A). PTT has a short action time and limited penetration depth, making it difficult to activate a strong and effective immune response. To address these challenges, Fan et al.[260] designed metal-coordinated supramolecular self-assembled nanomaterials by introducing immune adjuvants to construct an *in situ* vaccine strategy to amplify the ICD response and solve the problem of limited immune stimulation by PTT. Lignosulfonate (LS), photosensitizer indocyanine green (ICG) and aluminum adjuvant (Al) were co-assembled into LS-Al-ICG NPs through hydrogen and coordination bonds, where LS serves as a complexing agent, stabilizer and surfactant to co-deliver ICG and Al. The LS-Al-ICG NPs accumulated in the tumor are degraded under acidic pH conditions, and ICG acts as a photothermal agent to induce photothermal reactions. The presence of Al significantly promoted the maturation of DCs, enhanced the processing and presentation. of antigens, and thereby promoted the proliferation and differentiation of lymphocytes (Fig. 12B). In addition to introducing immune adjuvants to directly promote DCs

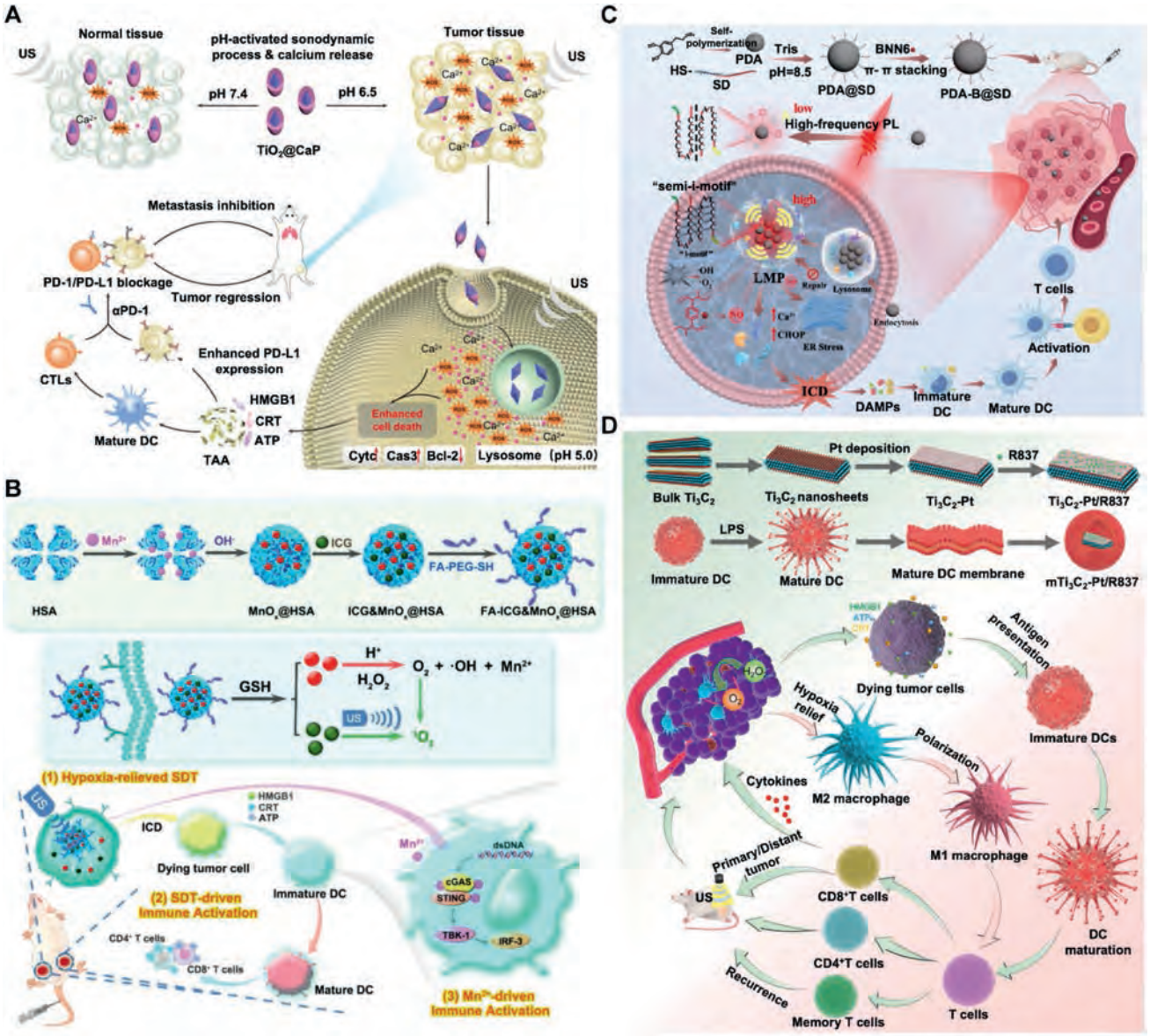


Figure 14 (A) Schematic representation of the principle of the TiO_2@CaP nanoplatform for ICB-based immunotherapy/SDT combined therapy. TiO_2@CaP induces mitochondrial dysfunction by overloading intracellular Ca^{2+}, which synergistically works with the SDT process in the TME, specifically killing tumor cells while also modulating immune responses. However, the targeting delivery efficiency of this nanoparticle and the controllability of Ca^{2+} release warrant further attention and optimization. Reprinted with the permission from Ref. 459. Copyright © 2021, WILEY. (B) Schematic representation of the principle of the FA-ICG&MnOx@HAS nanoplatform for immunotherapy/SDT combined therapy. FA-ICG&MnOx@HAS nanoplatform enhances tumor cell killing through the synergistic effect of SDT and STING agonist immunotherapy, while simultaneously activating anti-tumor immune responses, achieving dual therapeutic effects. Although the HSA carrier has good biocompatibility, its long-term stability and degradability *in vivo* need further evaluation. Long-term bioaccumulation and potential immune responses still require further research. Reprinted with the permission from Ref. 460. Copyright © 2024, Elsevier. (C) Schematic representation of the principle of the PDA-B@SD nanoplatform for immunotherapy/SDT combined therapy by promoting lysosomal membrane permeabilization (LMP) and inhibiting its repair. PDA-B@SD promotes LMP and immunotherapy of triple-negative breast cancer (TNBC) through the synergistic effects of spatially confined photoacoustic effects and NO release. Reprinted with the permission from Ref. 82. Copyright © 2024, Elsevier. (D) Schematic representation of the principle of the mTi_3C_2−Pt/R837 nanoplatform for immunotherapy/SDT combined therapy. mTi_3C_2−Pt/R837 achieves oxygen self-supply, effectively enhancing the CDT-SDT combined immunotherapy and improving tumor cell-killing efficacy. Ti_3C_2, as an MXene nanomaterial, requires further evaluation of its long-term biocompatibility and metabolic pathway of degradation products to avoid potential long-term accumulation and toxicity issues. Reprinted with the permission from Ref. 45. Copyright © 2023, Elsevier.

maturation, Sun et al.[373] introduced TLR-7 agonists and successfully constructed a cascade synergistic nanosystem (R837/ICG@Lip) for colorectal cancer treatment. ICG and Imiquimod (R837) were self-assembled into PEGylated liposomes. After NIR light irradiation, tumor cells were ablated, and TAAs were released. R837 could promote DCs maturation, enhance antigen-

specific T cell responses, and have good therapeutic efficacy on colorectal cancer (Fig. 12C). The above three studies all prepared NPs *in vitro* and relied on active targeting to reach the tumor. This process may have certain effects on the body and undergo varying degrees of immune clearance. Gao et al.[44] designed an intracellular self-assembled supramolecular system, where β-CD-modified gold NPs (GNPs) and adamantane (ADA)-modified GNPs were separately coated with *Escherichia coli* outer membrane vesicles (OMVs). The mixture of the two NPs was then injected into the mice. Components such as lipopolysaccharide, lipoprotein and peptidoglycan on the surface of OMVs induced immune cells to phagocytose them, and the exposed β-CD and ADA drive the self-assembly of GNPs into aggregates with photothermal effects through host−guest interactions. Immune cells further carried GNPs aggregates to the tumor. After the initial PTT, the released DAMPs and other signals induced autoimmune responses, recruited more immune cells to the tumor, and then delivered more GNPs for continued enhanced PTT efficacy. Studies have demonstrated that this system had a positive feedback effect on immune response and significantly improved the effect of PTT-based immunotherapy (Fig. 12D).

Overall, PTT based on self-assembled nanomaterials induces the ICD of tumor cells through thermal ablation, and the released TAAs and DAMPs actively trigger immune responses. Multiple studies have proven that PTT significantly promotes DC maturation and CTL infiltration when combined with immune adjuvants, has great potential in antitumor.

5.5. *Immunotherapy combined with RT*

RT is also one of the traditional local treatment methods, which mainly uses the free radicals generated by high-energy radiation to damage DNA and induce tumor cell death. The ICD induced by RT also promotes DC maturation and enhances the tumor-killing activity of $CD8^+$T cells[453]. However, the immune response induced by RT faces great challenges in clinical treatment, such as weak radiation absorption and endogenous problems like overexpression of GSH and H_2O_2, resulting in RT being insufficient to meet clinical needs[454]. Huang et al.[455] designed a dual amplification strategy for RT by self-assembling gadolinium (Gd^{3+}) and 5′-guanosine monophosphate (5′-GMP) into Gd-NCPs and then integrating Hemin (PANHEMATIN®) to form H@Gd-NCPs. The presence of the metal element Gd promotes the generation of hydroxyl ·OH, while Hemin exerts peroxidase activity to consume GSH and decompose H_2O_2. This dual sensitization mechanism enhances the efficacy of RT by depositing X-ray absorption. The final result induced stronger ICD, increased DCs activation and $CD8^+$ T cell infiltration, thereby boosting the effectiveness of ICB therapy (Fig. 13A). Their research aims to enhance the efficacy of immunotherapy by amplifying the effects of RT, while Min et al.[43] designed various antigen-capturing NPs (AC-NPs) for actively capturing TAAs released during RT and transporting them to APCs to enhance the efficacy of RT-based immunotherapy. NPs were prepared from the polymer poly (lactic-*co*-glycolic acid) (PLGA) and their surfaces are modified to produce NPs that can bind to TAAs through various mechanisms, including PLGA AC-NPs, amine polyethylene glycol (NH_2 AC-NPs), 1,2-dioleoyloxy-3-(trimethylammonium)propane (DOTAP AC-NPs), maleimide polyethylene glycol (Mal AC-NPs), and methoxy polyethylene glycol (mPEG AC-NPs). Mass spectrometry was used to separate and identify the specific antigens captured by AC-NPs, and it was demonstrated in multiple tumor models that these AC-NPs can improve the efficacy of immunotherapy and promote distant effects, mainly through the presentation of antigens by DCs and activating of $CD8^+$T cells (Fig. 13B).

RT combined with immunotherapy has been shown to enhance immune response, mainly through immune stimulation induced by radiation and the release of TAAs and DAMPs from tumor cell death[456]. However, several studies also suggested that RT can promote the proliferation of immunosuppressive cells and the expression of immunosuppressive factors, thereby affecting the efficacy of immunotherapy[453]. Therefore, strategies aimed at amplifying RT-based immunotherapy and reversing immunosuppressive TME to enhance the therapeutic effects of RT are expected to provide new approaches for radioimmunotherapy of tumors.

5.6. *Immunotherapy combined with SDT*

SDT is a therapeutic approach that utilizes ultrasound to activate sonosensitizers, generate ROS and trigger ICD to induce tumor cell death. Unlike PDT, PTT and RT, SDT has better tissue penetration and can reach deeper, harder-to-target tumor sites[457]. However, it is not very effective in tumor treatment, limited by immunosuppressive TME, hypoxia at the tumor site, the low delivery efficiency of sonosensitizers and short action time. PDT alone can only limit tumor growth but cannot completely eliminate tumor cells and prevent recurrence and metastasis, which greatly limits its clinical translation[458]. Immunotherapy can mobilize the innate and adaptive immune systems to exert powerful antitumor effects. Therefore, SDT-assisted immunotherapy can offer a promising therapeutic option for solid tumors. Tan et al.[459] designed a pH-responsive core−shell nanomaterial activated by the acidic TME, which can controllably generate ROS and selectively kill tumor cells at the tumor site. TiO_2 was first prepared by thermal decomposition and then coated with CaP to form a core−shell TiO_2@CaP structure. After reaching the tumor, the acidic pH condition triggered the decomposition of CaP, releasing TiO_2 and Ca^{2+}. Excessive Ca^{2+} interfered with mitochondrial function and ROS homeostasis, leading to excessive ROS production and tumor cell death. TiO_2-mediated SDT further induced more ROS production and ICD in tumor cells, and more TAAs were released. In general, the synergistic effect of TiO_2@CaP caused more mitochondrial damage and tumor cell death, ultimately promoting DC maturation and CTL tumor infiltration. Combined with ICB therapy, it enhanced the effect of immunotherapy, effectively inhibited the growth of primary tumors, promoted the regression of distant tumors and inhibited the formation of lung metastases (Fig. 14A). Immune adjuvants can be combined with antigens to form *in situ* tumor vaccines to regulate the function of DCs and improve the effect of immunotherapy. Therefore, combining immune adjuvants with SDT is a promising strategy for enhancing antitumor responses. Huang et al.[460] constructed a nanosystem that co-delivered sonosensitizers and STING agonists to enhance the antitumor immunotherapy effect based on SDT. IFN-β produced by the cGAS−STING signaling pathway can bind to IFNAR on the surface of DCs, promoting DCs maturation and T cell activation, while Mn^{2+} can act as an agonist to activate the cGAS−STING signaling pathway[417]. $MnCl_2$ and ICG aqueous solution were gradually added to the human serum albumin (HSA) solution, and ICG&MnOx@HSA NPs were formed through disulphide cross-linking between HSA NPs. The thiol groups on the surface of HAS were then linked to the thiol groups on FA-PEG-SH, forming the final system (FA-ICG&MnOx@HAS). After injection, the

presence of folic acid (FA) achieved targeted delivery to the tumor, and the high level of GSH in the tumor dissociates the disulphide bonds and Mn^{2+} and ICG are released. On the one hand, Mn^{2+} catalyzed H_2O_2 to generate oxygen to alleviate the hypoxic environment of the tumor, further enhancing the tumor-killing efficacy of ICG-mediated SDT. On the other hand, Mn^{2+} plays an immunomodulatory role as an activator of the cGAS−STING signaling pathway, gradually activating the cGAS−STING signalling pathway, promoting DCs maturation, CTL tumor infiltration and triggering systemic antitumor response, providing a novel idea for immunotherapy strategies based on SDT (Fig. 14B). ICD-induced TAAs are often not effectively released but degraded in lysosomes, which greatly affects ICD-based immunotherapy methods such as PDT, PTT and SDT[461]. Therefore, targeting disruption of lysosomal function in tumor cells to interrupt autophagy and prevent the self-digestion of tumor antigens holds great potential for achieving more effective immune activation. Li et al.[82] developed a photothermal conversion agent that promoted lysosomal membrane permeabilization (LMP) and inhibited its repair. Polydopamine (PDA) was first synthesized, and then thiolated pH-responsive DNA linkers (SD) were modified on the PDA surface. Finally, the NO release precursor (BNN6) was loaded into PDA@SD to obtain PDA-B@SD. Under low pH conditions, SD was stacked into an i-motif structure, which promoted the specific assembly of PDA-B@SD in lysosomes. After pulsed laser irradiation, the degradation of BNN6 induced by the photoacoustic effect accelerated NO release, which inhibited the repair of lysosomes by the endoplasmic reticulum, aggravated LMP, and enhanced the ICD-based immune activation response (Fig. 14C). In addition to the aforementioned strategies, such as responding to TME, introducing immune adjuvants and inhibiting lysosomal function, improving the hypoxic microenvironment is also a powerful approach. Zhang et al.[45] designed an intelligent bionic nanomaterial with a self-sufficient oxygen generation function for combined CDT/SDT/immunotherapy. First, Ti_3C_2 was synthesized, followed by Pt layer deposition on one side. TLR7 agonist (R837) was further loaded on the Ti_3C_2−Pt surface. Finally, the DCs membrane was wrapped around the Ti_3C_2−Pt/R837 to construct tumor-targeting mTi_3C_2−Pt/R837. The introduction of mature DC membranes had a complete antigen-presentation function, which gave Ti_3C_2−Pt/R837 the ability to activate DCs. The immune activation ability was further enhanced by R837, effectively presenting the antigens produced by Ti_3C_2−Pt/R837-mediated SDT-induced ICD and promoting the activation of T cells. The Pt could catalyze H_2O_2 to produce O_2 to create a good environment for SDT. In addition, the darkening of the Pt surface enhanced electron capture prolonged the separation time of electron−hole pairs, and further enhanced the SDT efficacy. Ti_3C_2 itself also served as a CT agent to catalyze H_2O_2 to produce ·OH. The combined strategy effectively inhibited the growth of primary, distant and metastatic tumor (Fig. 14D). In conclusion, PDT has the advantages of non-invasiveness, excellent tissue penetration, and biosafety. In the presence of sonosensitizers and oxygen, ROS are generated to induce tumor cell death, and tumor-related immune responses can be triggered in various ways, such as inducing ICD. Therefore, SDT combined with immunotherapy is an innovative method worthy of attention.

Different from traditional surgical treatment and CT, therapies such as PDT, PTT, SDT and RT can quickly shrink the tumor volume and promote the infiltration of inflammatory cells. However, due to the limited penetration depth and short stimulation duration, it is difficult to eliminate the tumor alone. Tumor immunotherapy activates the innate and adaptive immune system to exert systemic and long-term antitumor effects. Combining the fast-acting properties of CT, PDT, PTT, SDT, and RT with the sustained effects of immunotherapy using self-assembled nanomaterials is expected to stimulate a lasting immune response and provide new insights into cancer treatment.

6. Conclusions and perspectives

In this review, we systematically summarize the research progress in the past three years on self-assembled nanoplatforms based on various material types to evaluate immunotherapy and innovative strategies combined with other treatment methods, which will provide valuable insights for future research on cancer treatment. Cancer immunotherapy can fully regulate the immune system to attack tumor cells without damaging normal cells and has tremendous potential in eradicating or inhibiting tumors. With advancements in science and technology in recent years, cancer immunotherapy has become one of the important research directions in the field of treatment. Self-assembled nanomaterials have become a promising technology to promote the advancement of traditional immunotherapy, offering the following advantages: 1) Self-assembled nanomedicines can achieve accurate recognition and efficient internalization of tumor cells through their unique structure and surface modification. They can be enriched in tumor tissues while minimizing interactions with normal tissues, thereby reducing systemic toxicity and adverse side effects. 2) Self-assembled nanomaterials can protect therapeutic drugs from degradation, enhance drug solubility, and allow controlled release, thereby increasing drug concentration and therapeutic efficacy at the tumor. They can also promote the immune system's recognition and attack of tumor cells by inducing tumor cells to produce specific markers (such as CRT and HMGB1). 3) The self-assembled nanoplatform achieves the co-delivery of multiple immune signals in particulate form, reprogramming the immune response targeting specific antigens or specific immune cells (such as delivering tumor antigens or adjuvants, regulating TAMs phenotype, blocking immunosuppressive factors such as TGF-β and IDO, and reducing the immunosuppressive effects of Tregs and MDSCs), reshaping the TME (such as improving the hypoxic environment, regulating the tumor metabolic environment (clearing GSH and reducing lactate accumulation)), and activating regulatory mechanisms such as inflammatory signaling pathways. 4) The successful construction of self-assembled nanoplatforms allows for the combined use of cancer immunotherapy with various treatment methods such as CT, CDT, PDT, PTT, RT, and SDT, further amplifying the effects of immunotherapy.

Although the application of self-assembled nanoplatforms in cancer immunotherapy has shown significant advantages, there are also some challenges: 1) The stability of self-assembled nanomedicines within the body is a critical concern. They must maintain structural and assembly stability *in vivo* to avoid premature disassembly or degradation. Furthermore, self-assembled nanoplatforms in blood circulation may be affected by protein adsorption, clearance by the reticuloendothelial system (RES), and renal excretion, limiting their bioavailability and duration of action. 2) High heterogeneity of tumor tissue and adaptability of TME. The immune system status varies among patients, leading to significant differences in the immune activation effects of self-assembled nanoplatforms, which can affect treatment consistency and predictability. The TME is often highly immunosuppressive,

characterized by elevated levels of Treg cells, M2-type macrophages, and MDSCs, which may weaken the ability of self-assembled nanoplatforms to activate the immune system. Although some nanoplatforms rely on the EPR effect to enter tumor tissues, this effect exhibits considerable variability in clinical settings. In tumors with low blood flow or high interstitial pressure, the efficiency of nanoparticle delivery may be limited. Additionally, many nanoplatforms rely on DCs, T cells, or macrophages for delivery, but the activity, uptake efficiency, and homing ability of these immune cells can influence the final therapeutic outcome. 3) The production of self-assembled nanomedicines requires precisely controlled conditions and high-quality raw materials, which may lead to high production costs and limit the feasibility of large-scale production. 4) The safety and toxicity of self-assembled nanomedicines require further evaluation. Long-term or high-dose use may lead to potential toxic reactions. The safety assessment in current research mostly stops at evaluating the damage to organs (heart, liver, spleen, lungs and kidneys) after a short treatment and evaluating various indicators through blood routine and blood biochemical analysis. However, if gold nanoparticles remain in the body for a long time, they may produce bioaccumulation, and their long-term toxicity and excretion pathways still need further study. As a novel type of treatment, the regulatory and regulatory framework for self-assembled nanomedicines is still imperfect. This may affect the speed of its research and development, approval and application.

The focus on self-assembled nanotherapeutics based on cancer immunotherapy is expected to expand in the next few years. Nanocarriers, with their flexible structure and the design of nanomaterials, will provide additional benefits for cancer treatment. Therefore, an increasing number of self-assembled nanoplatforms are designed to enhance the effect of immunotherapy, and more strategies for combining traditional immunotherapy with therapeutic methods are emerging. This suggests that we should actively explore the interaction and subsequent reactions between these materials and biological organisms in future work to promote their clinical transformation and provide new potential for cancer treatment.

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Author contributions

Wenfei Xu: Writing - original draft; Shuxuan Zhu and Zhaogang Sun: Writing - review & editing. Jun Ye and Hongqian Chu: Conceptualization, Funding acquisition, Supervision, Writing - review & editing. All authors have read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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