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Research progress of paclitaxel nanodrug delivery system in the treatment of triple-negative breast cancer

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ABSTRACT

Triple-negative breast cancer (TNBC) is the most aggressive subtype of breast cancer, characterized by the loss or low expression of estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2) and progesterone receptor (PR). Due to the lack of clear therapeutic targets, paclitaxel (PTX) is often used as a first-line standard chemotherapy drug for the treatment of high-risk and locally advanced TNBC. PTX is a diterpenoid alkaloid extracted and purified from Taxus plants, functioning as an anticancer agent by inducing and promoting tubulin polymerization, inhibiting spindle formation in cancer cells, and preventing mitosis. However, its clinical application is limited by low solubility and high toxicity. Nanodrug delivery system (NDDS) is one of the feasible methods to improve the water solubility of PTX and reduce side effects. In this review, we summarize the latest advancements in PTX-targeted NDDS, as well as its combination with other codelivery therapies for TNBC treatment. NDDS includes passive targeting, active targeting, stimuli-responsive, codelivery, and multimode strategies. These systems have good prospects in improving the bioavailability of PTX, enhancing tumor targeting, reducing toxicity, controlling drug release, and reverse tumor multidrug resistance (MDR). This review provides valuable insights into the clinical development and application of PTX-targeted NDDS in the treatment of TNBC.

1. Introduction

According to global statistics for 2022, there are nearly 20 million new cases of cancer and 9.7 million deaths from cancer. Female breast cancer is the second and fourth leading cause of cancer morbidity and mortality worldwide, accounting for 11.6 % of all cancer cases and 6.9 % of deaths [1,2]. The 2011 St. Gallen consensus divided breast cancer into four subtypes: Luminal A (ER+/PR+, HER-2-), Luminal B (ER+/PR+, HER-2+), HER2-positive (ER-/PR-/HER-2+) and Basal-like (ER-/PR-/HER-2-). Basal-like type is also defined as triple negative breast cancer (TNBC) [3,4]. TNBC is a clinically representative type of breast cancer with poor prognosis, often termed the 'king of breast cancer', accounting for 10 %–20 % of all breast cancers. The 5-year survival rate of advanced TNBC is only 11 %. TNBC mostly occurs in young patients before menopause, and the risk of organ metastasis and brain metastasis is high [5,6]. Due to the absence of specific targets for TNBC, the current clinical treatment primarily involves chemotherapy [7].

Among various chemotherapeutic agents, paclitaxel (PTX) is a diterpenoid alkaloid widely used in the treatment of TNBC treatment [8]. PTX contains 11 stereocenters and a four-ring skeleton formed by 17 carbon atoms. It was discovered by American chemist M. E. Wall et al. from the bark of Taxus plants [9]. S. B. Horwitz et al. [10] demonstrated that PTX exerts anticancer effects by inducing tubulin polymerization, inhibiting spindle formation in cancer cells, and preventing mitosis. In 1992, PTX was approved by the FDA to become the first natural plant for the treatment of cancer [11]. Despite being one of the most widely used anticancer drugs in clinical practice, its poor solubility and potential organ damage at effective therapeutic doses lead to immunotoxicity, hypersensitivity, etc, which greatly limit its clinical application [12].

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At present, the listed PTX preparations include Taxol®, Lipusu, Abraxane® and Cynviloq™, of which Lipusu, Abraxane® and Cynviloq™ are nano-preparations. Taxol® relies on the nonionic surfactant polyoxyethylene castor oil (Cremophor EL) as a solubilizer to improve the solubility of PTX, but Cremophor EL has side effects such as hypersensitivity and neurotoxicity, causing pain to patients in clinical use [13]. Lipusu is the only listed PTX liposome preparation in the world, which overcomes the clinical defects such as dissolution, compatibility and safety of Taxol®, and is used for the treatment of clinical breast cancer and ovarian cancer [14]. Abraxane® is an albumin nanoparticle that was first approved by the U.S. FDA in 2005 for the treatment of breast cancer and was approved by China's National Food and Drug Administration for the treatment of metastatic breast cancer after failure of combined chemotherapy or recurrence within 6 months of adjuvant chemotherapy for breast cancer [15]. Abraxane® significantly increased the solubility of PTX without anti-allergic pretreatment and reduced the toxicity of PTX [16,17]. Cynviloq™ is a PTX micelle made from mPEG-PDLLA, a chemical polymer material. It has been marketed in India, South Korea and China for the treatment of breast cancer and non-small cell lung cancer (NSCLC) [18].

Although the clinical application of nano-preparations has significantly improved the physicochemical properties, bioavailability, efficacy and safety of PTX, the further development and application of nanotechnology are still subject to multiple biological barriers composed of tumor microenvironment (TME). In-depth understanding and resolution strategies for these barriers are crucial for optimizing the design of nano-preparations and improving their clinical efficacy. Complex TME is mainly composed of tumor cells, cancer-associated fibroblasts, immune cells, angiogenesis and extracellular matrix (ECM), and the interaction between these elements forms a complex biological barrier. In tumor treatment, the therapeutic agent needs to penetrate the vascular wall and ECM to enter the TME. In this process, various biological barriers limit the distribution and penetration of drugs and affect the therapeutic effect. Therefore, overcoming these biological barriers is one of the key challenges to improve the therapeutic effect of tumors [19]. First of all, the enhanced permeability and retention (EPR) effect of abnormal tumor vascular structure formation will affect the uniform distribution of drugs in tumor tissues. Secondly, the physical barrier formed by ECM in TME further limits the diffusion of drugs and affects the delivery efficiency of drugs. In TME, cancer stem cells (CSCs), as a specific cell subset, can survive and proliferate under the regulation of TME through the ability of self-renewal and differentiation, and produce drug resistance to treatment, thus playing a key role in the occurrence and development of tumors, and immunosuppressive cells such as Tumor-Associated Macrophages (TAMs) further affect the effect of drug immunotherapy by affecting immune response [20]. The characteristics of the tumor cell membrane and the internal environment (such as hypoxia and acidity) also inhibit the activity of the drug and increase the drug resistance of the tumor. Finally, the high heterogeneity of TME leads to significant differences in the treatment response of cells in different parts, which further leads to the complexity of tumor treatment [21]. In addition, TNBC is typically marked by high immune cell infiltration, the potential for a robust immune response, and a lack of ER, HER2, and PR expression, rendering it unsuitable for specific targeted therapies. TNBC cells demonstrate a higher metabolic rate and pronounced anaerobic metabolism, resulting in elevated lactic acid levels and hypoxia within the TME, which increase the likelihood of drug resistance and metastasis. These unique TME characteristics facilitate the development of NDDS for the treatment of TNBC. The passive targeting of NDDS can enhance the accumulation of PTX in tumor tissues by using the EPR effect of tumor. The active targeting is modified by targeting ligands or monoclonal antibodies on the surface of nanocarriers to achieve accurate recognition and binding of tumor markers, improve drug selectivity and reduce adverse reactions [22]. Intelligent NDDS can respond to TME-specific conditions (such as pH changes and specific enzyme activity) to trigger the precise controlled release of drugs. In addition, the integration of different targeting and release mechanisms through codelivery and multimode delivery strategies can enhance the therapeutic effect of various drugs on cancer, reduce toxicity and reverse drug resistance, and improve the accuracy and effectiveness of treatment [23,24]. Therefore, NDDS has become a promising strategy to solve the limitations of PTX and overcome the TME-related biological barrier to achieve effective PTX delivery for the treatment of TNBC [25].

In this review, we summarize the latest advancements in PTX targeted therapy for TNBC over the past five years, along with research on PTX-based combination strategies. Most importantly, we comprehensively summarized targeted drug delivery systems based on different targeted delivery mechanisms, including active targeting, passive targeting, and stimulus-responsive drug delivery systems. Additionally, we highlighted codelivery systems that combine PTX with other therapies, such as chemotherapy, traditional Chinese medicine (TCM), inhibitor therapy, biotherapy, and phototherapy. Finally, we summarized the synergistic mechanisms of PTX-based multimodal strategies in the treatment of TNBC, such as PTX-chemotherapy-immunotherapy, PTX-PDT-immunotherapy. Overall, this study aims to summarize the reported PTX targeted delivery systems, clarify their advantages and disadvantages in the treatment of TNBC, and explore the prospects and challenges of clinical transformation, so as to provide a reference for the clinical development of safe, efficient and controllable PTX in the treatment of TNBC (Fig. 1).

2. Passive targeting nanodrug delivery system

Passive targeting is a drug delivery method based on the anatomical and physiological differences between different organs and tissues [26]. The difference in microvascular structure between normal tissues and solid tumors provides a possible solution for cancer treatment. Solid tumors have high retention and high permeability to macromolecules due to their close blood vessels and wide vascular wall gaps. Nanomaterials can enter and achieve passive targeted delivery of drugs in tumor tissues, which is called EPR effect [27]. Passive targeting agents accumulate drugs at the tumor site to exert anti-tumor effects. In recent years, PTX-based passive targeted agents for TNBC treatment include prodrug liposomes, Polyglycerol carbonate nanoparticles, Protein nanoparticles, Polymer micelles, etc. (Table 1).

2.1. Prodrug liposomes

Liposomes, as a highly biocompatible and biodegradable drug carrier, can carry both water-soluble drugs and fat-soluble drugs [28]. In order to further improve the compatibility of PTX with liposomes, it is a promising strategy to form prodrug liposomes by covalently combining drugs with long-chain fatty acids to encapsulate liposomes [29]. Wu et al. [30] designed lipids with different chain lengths of myristic acid (MA, 14C), palmitic acid (PA, 16C) and stearic acid (SA, 18C) to synthesize liposomes (PTX-MA-L, PTX-PA-L and PTX-SA-L) by ester bonds with PTX, respectively. The three prodrug liposomes increased the drug loading of PTX (about 7.4 %). The accumulation of PTX in the tumor site of PTX-PA-L was higher than that of other groups, and it had the strongest tumor inhibition effect on 4T1 tumor-bearing mice (78.44 %).

2.2. Polyglycerol carbonate nanoparticles

Polyglycerol carbonate is used to form nanoparticles because of its good biocompatibility and biodegradability, and can be further degraded into glycerol and carbon dioxide combined with chemotherapeutic drugs [31]. Robert C et al. [32] designed nanoparticles (PGC-PTX + PTX NPs) composed of poly (1,2-glycerocarbonate)--graft-succinic acid-paclitaxel (PGC-PTX). The loading amount of PTX in PGC-PTX + PTX NPs was ~81 wt%, which could significantly inhibit the tumor growth of 4T1 metastatic breast cancer mice. The obvious adipose tissue area appeared in the tumor site, and the lung metastasis of the

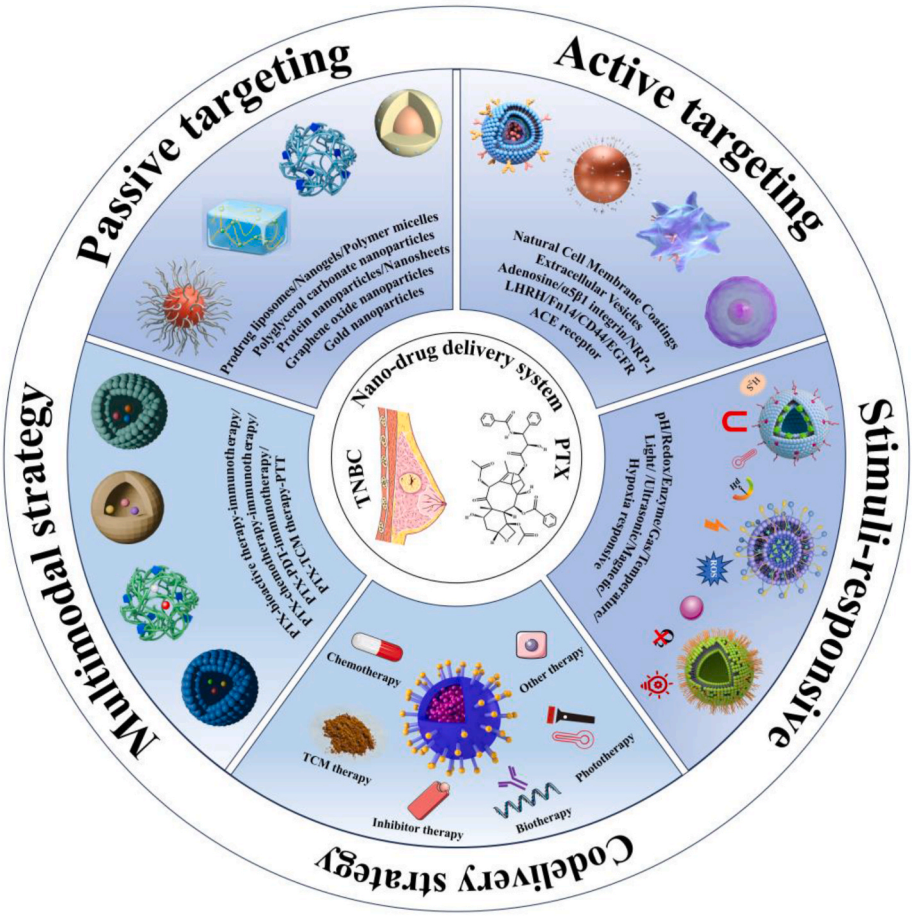

Fig. 1. The classification diagram of NDDS based on PTX in the treatment of TNBC.

tumor was further reduced by reducing NETosis and increasing NK activity (Fig. 2).

2.3. Protein nanoparticles

Protein nanoparticles have become a promising nanocarrier in recent years due to their biodegradability, low immunogenicity and good biocompatibility [33]. Zhang et al. [34] designed two natural proteins (milk casein and rice protein) to self-assemble into protein nanoparticles to deliver PTX (PTX@CaRs) by topological transformation. The three treatment groups of PTX@CaRs could significantly inhibit the tumor growth of 4T1 heterogeneous tumor mice, and the tumor inhibition rate (TIR) could be increased to 73 %–108 %.

2.4. Polymer micelles

Polymer micelles (PMs) is a micro-nano structure formed by self-assembly of block copolymers, which can encapsulate poorly soluble drugs and increase their solubility [35]. The small size reduces the recognition of the liver and the reticuloendothelial system (RES), prolongs the circulation time, and selectively accumulates at the tumor site, thereby improving the anticancer efficacy and solving the non-targeted problem of traditional chemotherapy [36,37]. Chen et al. [38] designed amphiphilic peptide (AmP) and drug excipient TPGS to self-assemble into mixed micelles to improve the solubility of PTX (PTX@TPGS-AmP). PTX@TPGS-AmP could significantly prolong the blood circulation of PTX, and $AUC_{0\text{-}t}$ was 3.6 times that of Taxol, and significantly inhibited tumor growth in 4T1 mice (TIR = 73.0 %). Xu et al. [39] designed PTX-loaded CS-BT-HBS-CB micelles with high drug loading (15.7 %) and high encapsulation efficiency (86.4 %), and maintained a high degree of stability in blood circulation. The micelles loaded with PTX had a significant anti-tumor effect on 4T1 tumor-bearing mice (TIR = 66.9 %) and low systemic toxicity.

2.5. Nanogels

Nanohydrogels have become an important carrier system due to their unique physical and chemical properties and biocompatibility. Their three-dimensional network structure enables them to have high drug loading capacity and adjustable sustained release characteristics, which can effectively control the drug release rate. Nanohydrogels have promising application potential in cancer treatment [40,41]. Wang et al. [42] designed an injectable hydrogel PTX@BN@Gel loaded with PTX, which showed significant cytotoxicity to 4T1 cells (IC_{50} = 2.29 μg/mL). The anti-tumor effect of PTX@BN@Gel containing 10 mg/mL and 20 mg/mL PTX on 4T1 Balb/c mice was significantly stronger than that of PTX, which significantly promoted apoptosis and had good safety.

2.6. Nanosheets

As a two-dimensional material with large area and small thickness, nanosheets can effectively adsorb and load drugs, so they have wide application potential in cancer treatment [43]. Yang et al. [44] prepared PTX-loaded hexagonal boron nitride carbon nanosheets BCNNSs-PEG-PTX showed more significant cytotoxicity than PTX on MDA-MB-231 cells and significantly induced apoptosis.

2.7. Graphene oxide nanoparticles

Graphene oxide (GO), as an oxidation derivative of graphene, has

Table 1
Passive **targeting** NDDS of PTX.

Nanodrug delivery system	Features	Pharmacokinetics/Tissue Distribution/Efficacy	Year, Ref.
PTX-MA-L, PTX-PA-L and PTX-SA-L	EE > 95 %, DL ≈ 7.4 %.	TIR of 4T1 mice: PTX-PA-L (78.44 %) > PTX (55.39 %) > PTX-MA-L (54.99 %) > PTX-SA-L (51.80 %).	2024 [30]
PGC-PTX + PTX NPs	DL~81 wt%.	Cytotoxicity: IC_{50} = 87.75 ng/mL (4T1 cells), IC_{50} = 20.82 ng/mL (MDA-MB-231 cells). TIR of 4T1 mice: ↑.	2024 [32]
PTX@CaRs	DL: CaR1.0 NPs, CaR2.0 NPs and CaR3.0 NPs were 25.67, 22.63 and 19.13 mg/g protein.	Cytotoxicity (4T1 cells): PTX@CaR3.0 (IC_{50} = 0.08 μM) > PTX@CaR2.0 (IC_{50} = 0.13 μM) > PTX@CaR1.0 (IC_{50} = 0.16 μM). TIR of 4T1 mice: PTX@CaR3.0 > PTX@CaR2.0 > PTX@CaR1.0 > PTX.	2023 [34]
PTX@TPGS-AmP	DL = 7.32 %, EE = 69.78 %.	Cytotoxicity (4T1 cells): PTX@TPGS-AmP (IC_{50} = 48.9 ng/mL) > PTX@TPGS (IC_{50} = 137.3 ng/mL) > Taxol (IC_{50} = 287.6 ng/mL) > PTX (IC_{50} = 826.1 ng/mL). Pharmacokinetic: blood circulation, $T_{1/2}$ ↑. TIR of 4T1 mice: PTX@TPGS-Amp > PTX.	2024 [38]
PTX-loaded CS-BT-HBS-CB micelles	DL = 15.7 %, EE = 86.4 %.	TIR of 4T1 mice: PTX-loaded CS-BT-HBS-CB micelles (66.9 %) > PTX (49.6 %).	2022 [39]
PTX@BN@Gel	Cumulative release rate of 30 days: PTX@BN@Gel (20 mg/kg) = 53.5 %, PTX@BN@Gel (10 mg/kg) = 33.1 %.	Cytotoxicity (4T1 cells): IC_{50} = 2.29 μg/mL. TIR of 4T1 mice: PTX@BN@Gel (20 mg/kg) > PTX@BN@Gel (10 mg/kg); PTX@BN@Gel (20 mg/kg) > PTX (20 mg/kg); PTX@BN@Gel (10 mg/kg) > PTX (10 mg/kg).	2021 [42]
BCNNSs-PEG-PTX	DL = 110.2 ± 8.4 μg/mg.	Cytotoxicity (MDA-MB-231 cells): BCNNSs-PEG-PTX > PTX. Cytotoxicity of BCNNSs-PEG-PTX on MDA-MB-231 cells: 72 h (23.24 %) > 48 h (40.78 %) > 24 h (68.52 %). Cytotoxicity of PTX on MDA-MB-231 cells: 72 h (29.69 %) > 48 h (53.82 %) > 24 h (73.63 %).	2020 [44]
Z-G/Ptx	Higher affinity for Ptx.	Cytotoxicity (MDA-MB-231 cells): Z-G/Ptx (20.4 %) > Ptx (45.8 %).	2024 [46]
Au-P	Size: 128 nm. Zeta potential: PTX = 15.5 ± 0.9 mV.	Apoptosis rate (MDA-MB-231 and 4T1 cells): Au-P > PTX. TIR of 4T1 mice: ↑.	2022 [48]

become a well-known nanostructured material due to its large specific surface area, excellent loading capacity and photothermal effect. It has broad application potential in drug delivery, bioimaging and cancer diagnosis [45]. Lorenzo Francesco Madeo et al. [46] designed Zno-graphene oxide nanoparticles (Z-G/Ptx) for PTX delivery. Z-G/Ptx had significant cytotoxicity to MDA-MB-231 cells. GO material could also inhibit the proliferation of CSCs and further enhance the inhibitory effect of PTX on tumors, and GO material was not toxic to normal cells.

2.8. Gold nanoparticles

Gold is one of the metals with the lowest chemical reactivity, and its excellent electrical conductivity has attracted much attention. Gold nanoparticles have shown wide potential in cancer treatment and biomedical applications due to their unique optical properties, good biocompatibility, and excellent drug carrier [47]. Satish Kumar Vemuri et al. [48] prepared PTX-loaded gold nanoparticles (Au-P). Au-P could significantly enhance the cytotoxicity of 4T1 and MDA-MB-231 cells and induce apoptosis, and inhibit tumor cell metastasis by increasing the expression of E-cadherin in cells. It showed significant tumor inhibition effect on 4T1 tumor-bearing mice in vivo.

3. Active targeting nanodrug delivery system

Traditional chemotherapeutic drugs are often accompanied by serious side effects in the treatment of TNBC, which brings great challenges to clinical treatment [49]. The continuous development of cancer bioinformatics and proteomics has made a significant contribution to the study of overexpressed receptors on the surface of cancer cells [50]. These receptors or antigens can specifically bind to complementary ligands on the surface of nanoparticles to achieve selective targeting [51]. Drug-loaded nanocarriers are rapidly internalized into cells through receptor-mediated endocytosis to exert tumor inhibition [52]. In addition to receptor-mediated targeting, biomimetic targeting strategies have also received extensive attention in tumor therapy [53]. Biocarriers such as extracellular vesicles (EVs), cell membranes and viruses have become an ideal choice for researchers to design highly targeted and selective nanocarriers due to their excellent properties in biocompatibility, immunogenicity, and mimicking the structure and function of biological systems. These carriers can exhibit superior aggregation and selectivity in the TME, further improving the therapeutic effect of drugs and reducing damage to normal tissues [54]. In recent years, a large number of researchers have designed and constructed a series of active targeted NDDS loaded with PTX to target the treatment of TNBC, so as to improve the effectiveness of PTX treatment and reduce its toxicity (Table 2).

3.1. Cellular receptors for actively targeted ligands in nanodrug delivery system

3.1.1. Adenosine receptor (AR)

Adenosine (ADN) plays an important role in cell regulation through G protein-coupled receptors, which include four subtypes: A1, A2A, A2B and A3 [55]. Studies have shown that A2B receptor is highly expressed in MDA-MB-231 cells and can be used as a potential molecular biomarker for tumor diagnosis and prognosis [56]. Dasharath Chaudhari et al. [57] designed ADN-modified nanoparticles (PTX ADN-PEG-PLGA NPs) for targeted therapy of TNBC. TNBC cells had higher PTX uptake for ADN-modified nanoparticles than ADN-unmodified NPs, which significantly increased the cytotoxicity and apoptosis index of MDA-MB-231 (IC_{50} = 3.42 μg/mL) and 4T1 (IC_{50} = 3.16 μg/mL) cells. PTX ADN-PEG-PLGA NPs could significantly inhibit tumor growth in 4T1 xenograft mice and showed the lowest tumor load (0.372 ± 0.124 %).

3.1.2. α5β1 integrin receptor

Integrin α5β1, or the fibronectin receptor, is a crucial mediator in various cancers. Its expression imbalance is closely linked to cancer onset, chemotherapy resistance, and poor prognosis [58]. Qiu et al. [59] encapsulated PTX into ATN peptide-modified nanomicelles (ATN-MPTX). Compared with free PTX, ATN-MPTX had more significant targeting and stronger uptake in 4T1 cells with high expression of α5β1 integrin, significantly increased the expression of calreticulin (CRT) on tumor cells, reduced $CD206^+$ M2M, and increased M1M to 42.9 %. M2M was reprogrammed into M1M to reshape the immune environment, and

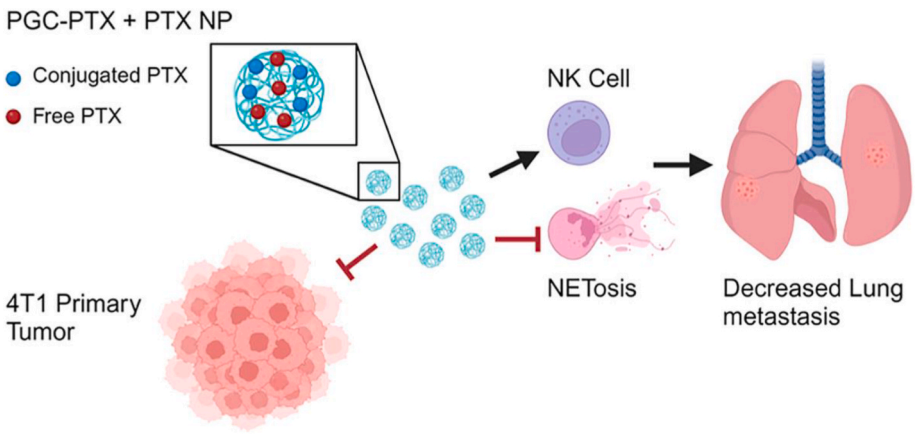

Fig. 2. Schematic Illustration of PGC-PTX + PTX NP. Reproduced with permission from reference. Biomacromolecules 25(3) (2024) 1800–1809 [32]. Copyright © 2024 American Chemical Society.

Table 2
Active targeting NDDS of PTX.

Nanodrug delivery system	Ligand/Antibody	Receptor/Antigen	Pharmacokinetics/Tissue Distribution/Efficacy	Year, Ref.
PTX ADN-PEG-PLGA NPs	ADN	AR	Cytotoxicity and apoptosis rate (MDA-MB-231 and 4T1 cells): PTX ADN-PEG-PLGA NPs > PTX. Pharmacokinetic: AUC $_{(0-\infty)}$, $t_{1/2}$ ↑. AUC $_{(0-\infty)}$: PTX ADN-PEG-PLGA NPs (107,894 ± 4081 ng/mL × h) > Intaxel® (21,521 ± 927 ng/mL × h) > Nanoxel® (54,635 ± 2576 ng/mL × h). TIR of 4T1 mice: PTX ADN-PEG-PLGA NPs > Nanoxel® > Intaxel® > Control.	2023 [57]
ATN-MPTX	ATN	Integrin α5β1	Cytotoxicity (4T1 cells): TN-MPTX > PTX. In vivo distribution: ATN-MPTX (6.14 % ID/g) > PTX. Pharmacokinetics: $t_{1/2\beta}$, AUC $_{(0-\infty)}$ ↑. TIR of 4T1-luc mice: ATN-MPTX > MPTX > PTX.	2022 [59]
PTX-SM-TAR NPs	A7R	NRP-1	Cytotoxicity (4T1-Cherry-Luc cells): PTX-SM-TAR NPs > PTX. TIR of 4T1-mCherry-luc mice: PTX-SM-TAR NPs (43.24 %) > PTX (28.47 %) > TAR (7.81 %).	2023 [62]
PTX-LHRH-DCMs	LHRH	LHRH-R	Cellular uptake (MDA-MB-231 and MDA-MB-435 cells): LHRH-DCMs > non-targeted DCMs. TIR of MDA-MB-231 mice: ↑. Median survival time (MDA-MB-231 mice): PTX-LHRH-DCMs (25 mg/kg) (90 days) > PTX-DCMs (25 mg/kg) (82 days) > PTX-LHRH-DCMs (10 mg/kg) (55 days) > PTX-DCMs (10 mg/kg) group (50 days) > PTX (42 days) > PBS control (32 days).	2021 [66]
PLGA-PEG-ITEM4-PTX	ITEM4	Fn14	Cytotoxicity (231-luc cells): IC_{50} = 0.13 μM. TIR of 231-luc mice: PLGA-PEG-ITEM4-PTX > PLGA-PEG-IgG-PTX > albumin-bound PTX > normal saline. Median survival time (231-luc mice): PLGA-PEG-ITEM4-PTX (68 days) > PLGA-PEG-IgG-PTX (52 days) > Abraxane (45 days) > saline (37 days).	2020 [68]
PTX NC@lipid−PEG−FA	FA	CD44	Cytotoxicity (4T1-luc cells): PTX NC@lipid−PEG−FA > PTX NC@lipid−PEG > PTX NC. Intracellular distribution: PTX NC@lipid−PEG−FA > PTX NC@lipid−PEG > PTX NC. TIR of situ 4T1 mice: NC@lipid−PEG−FA > PTX NC@lipid−PEG > PTX NC > PTX.	2021 [71]
4WJ-X-24 PTXs-$EGFR_{apt}$ nanoparticles	$EGFR_{apt}$	EGFR	Cytotoxicity (MDA-MB-231 cells): 4WJ-X-24PTXs-$EGFR_{apt}$ nanoparticles > 4WJ-X24 PTXs. Apoptosis rate (MDA-MB-231 cells): 4WJ-X-24 PTXsEGFR$_{apt}$ nanoparticles (45.1 %) > 4WJ-X-24 PTXs (37.3 %) > PTX (24.6 %) > 4WJ-X-$EGFR_{apt}$ (8.3 %). TIR of TNBC mice: ↑.	2020 [74]
BPP-PTX	BPP9a	ACE	Cytotoxicity: MDA-MB-231 cells (IC_{50} = 9.5 nM) > MDA-MB-468 cells (IC_{50} = 12.3 nM) > HEK293T cells (IC_{50} = 616.1 nM). Biodistribution of MDA-MB-468 mice: BPP-PTX (PTX = 10458 ng/g) > PTX (PTX = 2250 ng/g). TIR of TNBC orthotopic mice: BPP-PTX (9.6 μmol/kg) > BPP-PTX (2.4 μmol/kg) > PTX.	2021 [77]
Ab-LP-PTX	Ab	Exogenous HER2 EVs	Release rate: 24 h = 45 %. Cytotoxicity (MDA-MB-231 cells): ↑. Apoptosis rate (MDA-MB-231 cells): Ab-LP-PTX (97.8 %) > LP-PTX (40.3 %) > PTX (15.2 %) > PBS (1.76 %). TIR of BT-474EV cultured MDA-MB-231 mice: ↑.	2021 [80]
PTX/Res-R8-Lip@MP	Macrophage membrane	Macrophages receptors	Cytotoxicity (4T1 cells) ↑. Caspase 3 and BAX ↑, Bcl-2 and IL-1β expression levels ↓.Tumor microsphere formation rate: PBS (100 %) > Res-R8-Lip (38.46 ± 7.69 %) > PTX-R8-Lip (26.92 ± 3.85 %) > PTX/Res-R8-Lip (14.10 ± 2.22 %) > PTX/Res-R8-Lip@MP (11.54 ± 3.85 %). Anti-tumor resection recurrent mice: ↑.	2020 [82]
PD-1@PTX_2 NPs	PD-1 cell membrane	PD-1 cell membrane receptors	TIR of 4T1 mice: 71.3 %. Survival time of mice ↑. Ki67 positive cells ↓. CRT positive cells ↑. TNF-α and IFNγ ↑. $CD8^+$ T cells ↑, Treg infiltration in tumors ↓.	2024 [83]

had a stronger tumor inhibitory effect on 4T1-luc mice, significantly reducing lung metastasis.

3.1.3. Neuropilin-1 (NRP-1) receptor

NRP-1 is a non-tyrosine kinase transmembrane glycoprotein receptor that plays an important role in angiogenesis, tumor proliferation and metastasis [60]. Studies have found that NRP-1 is involved in the immune regulation of TNBC and can be used as a potential biomarker and therapeutic target [61]. Wang et al. [62] designed a new fusion peptide TAR modified PTX nanoparticles (PTX-SM-TAR NPs) formed by tumor targeting peptide A7R and cell penetrating peptide TAT. PTX-SM-TAR NPs selectively targets new blood vessels by binding to NRP-1, facilitating endocytosis and significantly accumulating in tumor tissues. The tumor inhibitory effect of PTX-SM-TAR NPs (43.24 %) on mice carrying 4T1-mCherry-luc cells was significantly stronger than that of free PTX (28.47 %).

3.1.4. Luteinizing hormone releasing hormone (LHRH) receptor

LHRH is a hormone decapeptide, as a promising target ligand [63]. The LHRH receptor (LHRH-R) is overexpressed in various cancers. Immunohistochemical analysis of 69 human TNBC samples revealed that LHRH-R was positive in 34 cases (49 %), indicating its potential as a therapeutic target for TNBC [64,65]. Xiao et al. [66] designed nanoparticles targeting LHRH receptors to deliver PTX. PTX-LHRH-DCMs showed significantly enhanced cytotoxicity and cellular uptake in LHRH-R overexpressed MDA-MB-231 and MDA-MB-435 cells through receptor-mediated endocytosis. In three TNBC animal models, (D-Lys)-LHRH peptide modification promotes the accumulation and internalization of DCM in breast cancer tissues and cells, significantly improves PTX delivery to exert significant anti-tumor effects and reduce systemic toxicity.

3.1.5. Fibroblast growth factor-inducible 14 (Fn14) receptor

Fn14, as a member of the tumor necrosis factor receptor superfamily, plays a key role in the development of cancer. Fn14 is often expressed in tumor cells [67]. Jimena G. Dancy et al. [68] designed PTX-DART nanoparticles (PLGA-PEG-ITEM4-PTX) targeting the cell surface receptor Fn14 to improve the treatment of TNBC. PLGA-PEG-ITEM4-PTX specifically binds to Fn14-positive MDA-MB-231-luc cells and significantly enhances cytotoxicity and uptake. In vivo, it showed significant tumor inhibition on primary and brain metastatic TNBC mice tumor models.

3.1.6. Cluster of differentiation 44 (CD44) receptor

The ability of CSCs to self-renew, resistance to chemotherapy and radiotherapy, and the ability to drive tumor recurrence and metastasis make it a key factor to be considered in tumor treatment. CD44 is a glycoprotein that mediates cell-cell and cell-matrix interactions, and its high expression is often used as a marker of CSCs [69]. Studies have shown that overexpressed CD44 receptors in tumor cells can be specifically recognized by folic acid (FA) [70]. Zhao et al. [71] designed FA-modified PEGylated PTX nanocrystals PTX NC@lipid-PEG-FA. The tumor inhibitory effect of PTX NC@lipid-PEG-FA on in situ 4T1 nude mice was significantly stronger than that of PTX NC@lipid-PEG and PTX NC (Fig. 3).

3.1.7. Epidermal growth factor receptor (EGFR)

RNA-based nanotechnology is due to its diverse structure and tumor targeting ability, making it a promising biomaterial for NDDS [72]. EGFR is overexpressed in various cancers such as breast cancer and lung cancer, which promotes tumor angiogenesis and becomes one of the most promising tumor markers for active targeting nanomedicine [73]. Guo et al. [74] designed 4WJ-X-24 PTXs-EGFR$_{apt}$ nanoparticles with tumor targeting ability. The apoptosis rate of 4WJ-X-24 PTXs-EGFR$_{apt}$ nanoparticles (45.1 %) on MDA-MB-231 cells was higher than that of 4WJ-X-24 PTXs (37.3 %), and it could be significantly enriched in tumor sites. The 4WJ-X-24 PTXs-EGFR$_{apt}$ nanoparticles with 8 mg/kg PTX has a good inhibitory effect on tumor growth in orthotopic TNBC xenograft model mice.

3.1.8. Angiotensin converting enzyme (ACE) receptor

ACE is a key enzyme that regulates blood pressure through the renin-

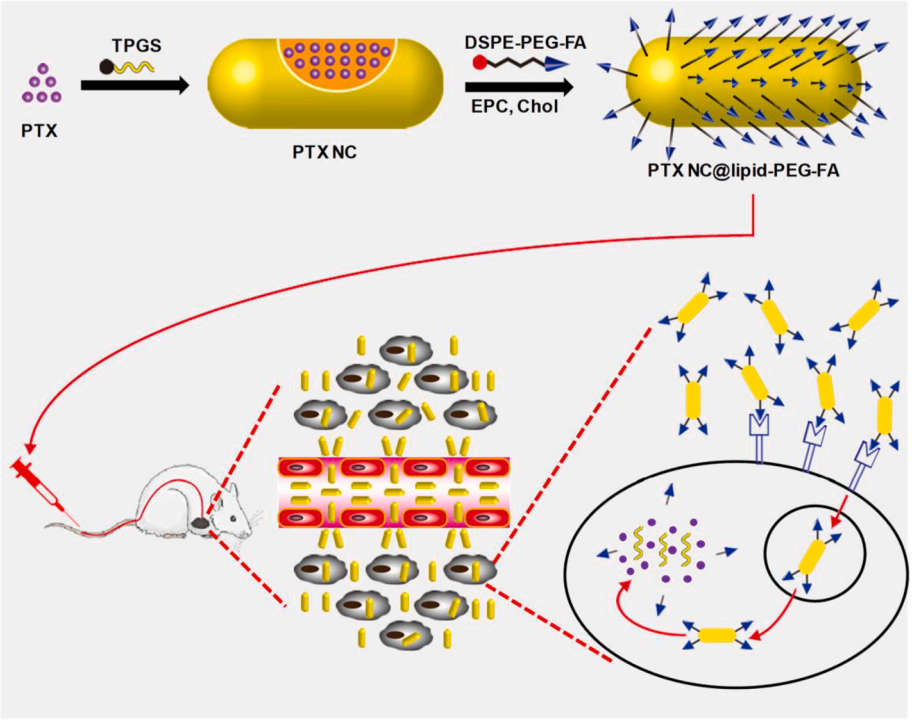

Fig. 3. Overview Showing the Preparation of PTX NC@lipid−PEG−FA and Its Use in Tumor-Targeted Chemotherapy. Reproduced with permission from reference. ACS applied materials & interfaces 13(12) (2021) 14577–14586 [71]. Copyright © 2021 American Chemical Society.

angiotensin system (RAS) and is abnormally expressed in some cancer tissues and tumor blood vessels [75]. Studies have found that the incidence of breast cancer patients treated with ACE inhibitors has a certain degree of reduction [76]. Guo et al. [77] developed a peptide-drug conjugate (BPP-PTX) by linking vasoactive BPP9a to PTX to target ACE for TNBC treatment. BPP-PTX had a more significant anti-tumor effect on nude mice carrying MDA-MB-468 cells and reduced the toxicity of PTX compared with free PTX.

3.2. Biomimetic targeting in nanodrug delivery systems

3.2.1. Extracellular vesicles (EVs)

Due to the lack of ER, PR and HER2 receptors, TNBC greatly limits the choice of treatment options. Studies have shown that EVs secreted by tumors are the key to the communication between tumor cells and stromal cells in local and distal microenvironments [78]. EV can fuse with the cell membrane, and the membrane antigen carrying EV will be integrated into the plasma membrane of the recipient cells [79]. Zachary Quinn et al. [80] fused HER2+ extracellular EVs from HER2-overexpressing BT-474 cells with EV plasma membrane, further endowing TNBC cells with sufficient HER2 on the surface of MDA-MB-231 to deliver PTX (Ab-LP-PTX) through anti-HER2 antibody (Ab) modified liposomes for targeted therapy of TNBC. The cytotoxicity of Ab-LP-PTX on EV-educated MDA-MB-231 cells (IC_{50} = 9.9 nM) was significantly stronger than that of MDA-MB-231 cells without EV-educated (IC_{50} = 173 nM). Ab-LP-PTX significantly inhibited the tumor growth of EV-educated MDA-MB-231 cells transplanted tumor mice.

3.2.2. Natural cell membrane coatings

Natural cell membranes, such as macrophage membrane, erythrocyte membrane, have good biocompatibility, targeting and immune escape ability. Thus, coating synthesized nanocarriers with cell membranes or their components mimics cellular characteristics for precise drug delivery. Biomimetic nanoparticles camouflaged with cell membranes hold great promise in tumor therapy [81]. Qiu et al. [82] designed octaarginine (R8) modified macrophage liposome (PTX/Res-R8-Lip@MP) co-loaded with PTX and RES. Macrophage-encapsulated preparations can more effectively transfer PTX and RES to 4T1 tumor cells, significantly inhibit the proliferation of 4T1 mice and residual tumor cells after tumor resection, and reduce tumor-related inflammatory factors. Hu et al. [83] designed PD-1 receptor cell membrane-coated PTX dimer nanoparticles (PD-1@PTX_2 NPs) to enhance the therapeutic effect on TNBC. PD-1@PTX_2 NPs can significantly enhance the cytotoxicity to 4T1 cells by binding to PD-L1 ligands overexpressed on 4T1 cells. It also significantly inhibited tumor growth in 4T1 transplanted tumor mice (TIR = 71.3 %), promote the infiltration of $CD8^+$ T cells in tumor tissues (increased by 3.2 times), and reduce the infiltration of Treg (decreased by 73.7 %).

4. Stimuli-responsive nanodrug delivery systems

Nanotechnology has significantly improved the bioavailability of PTX under the action of EPR effect and targeting ligands, showing good potential in TNBC targeted therapy [84]. In addition, the therapeutic effect of nanomedicine is also related to the unique pathological stimulation of tumors, such as acidity, redox and other microenvironments. Therefore, developing drug stimuli-responsive delivery systems that react to these microenvironmental factors offers an opportunity for selective targeting of tumor cells (Table 3).

4.1. pH-responsive

Compared with normal cells (pH = 7.35–7.45), tumor cells (pH = 6.5–6.8) produce more acidic TME than normal cells due to their abnormal growth, faster metabolism and preference for glycolysis [85].

Table 3
Stimuli-responsive NDDS of PTX.

Nanodrug delivery system	Stimulus-response properties	Efficacy	Year, Ref.
PTX-LH2(M) or PTX-LH2(C)	pH responsive: PTX release >70 %.	TIR of MDA-MB-231 mice: PTX-LH2 (M) > PTX-LH2 (C) > PTX.	2021 [87]
PSPA NPs	Redox-responsive.	Cytotoxicity (4T1 cells): PSPA NPs > PSP NPs. ROS generation (4T1 cells) ↑. ATP ↓. $O_2^{\bullet-}$↑. TIR of 4T1 mice: ↑.	2023 [90]
PTX-LHRH-DCMs	Redox-responsive.	Cellular uptake (MDA-MB-231 and MDA-MB-435 cells): LHRH-DCMs > non-targeted DCMs. TIR of MDA-MB-231 mice: PTX-LHRH-DCMs > PTX-DCMs. Safety evaluation: WBC, RBC, ALT, AST, TBIL, CREA, BUN in the normal range.	2021 [66]
PTX/Bio-NG	Enzyme-responsive (PTX release): Lipase and Hyals (80.2 %) > Hyals (62.5 %) > Lipase (34.9 %).	Pharmacokinetics: AUC_{0-t}: PTX/Bio-NG > PTX/NG > PTX; $t_{1/2\beta}$: PTX/Bio-NG > PTX/NG > PTX. TIR of 41 mice: PTX/Bio-NG (94 %) > PTX/NG (73 %) > Taxol (59 %).	2022 [93]
PEG-PAMPTX	Gas-responsive (PTX release): PEG-PAMPTX (80 %) > PEG-PHPTX (10 %).	Cytotoxicity (MDA-MB-231 cells): PEG-PAMPTX (IC_{50} = 0.10 ± 0.05 μg/mL) > PTX (IC_{50} = 5.20 ± 0.60 μg/mL). TIR of MDA-MB-231 mice: PEG-PAMPTX (79.35 %) > PTX (61.23 %) > PEG-PHPTX (33.92 %).	2022 [96]
PTX/Pt/BTNPs	Light-responsive.	Cytotoxicity (4T1 cells): IC_{50} = 264.5 ng/mL. TIR of 4T1 mice: PTX/Pt/BTNPs + hv ↑.	2021 [98]
PTX-NCS-gel	Temperature-responsive: 33.1 °C gelation.	Cytotoxicity (4T1-luc cells): PTX-NCS-gel (72 h, IC_{50} = 0.03 μg/mL) > PTX-NCS-gel (24 h, IC_{50} = 2.49 μg/mL) > PTX-NCS-gel (48 h, IC_{50} = 6.15 μg/mL). TIR of 4T1-luc mice: ↑.	2022 [100]
PTX-URE	Ultrasonic-responsive.	Cellular Uptake (MDA-MB-231 Cells): increased by 10.6 times. Cytotoxicity (MDA-MB-231 cells): ↑.	2024 [102]
PTX-CUR-LP-NB	Ultrasonic-responsive.	Cytotoxicity (MDA-MB-231 cells): ↑. ROS production ↑. TIR of MDA-MB-231 mice: ↑.	2021 [103]
MAPSULES	Magnetic-responsive.	Cytotoxicity (MDA-MB-231 cells): ↑. Accumulation of tumor site (MDA-MB-231 mice): ↑. TIR of MDA-MB-231 mice: ↑.	2023 [105]
PHDS-NF/PQ	Hypoxia-responsive: PTX release >70 %.	Cytotoxicity (4T1 cells): PHDS-NF/PQ > PHDS-N/PQ > PHDS/PQ. Cellular uptake (4T1 cells): ↑. TIR of 4T1 mice: PHDS-NF/PQ > PTX.	2022 [107]
D_{High}-PEI-(A + P)/PTX	Hypoxia-responsive (PTX release): 24 h (63 %) > 12 h (50 %).	Cytotoxicity (4T1 cells): ↑. Apoptosis rate (4T1 cells): 53.19 %. TIR of 4T1 mice: ↑.	2021 [108]

The acidic TME makes it possible to selectively target 'smart' controlled-release nanomedicines for tumor tissues or cells [86]. Nam et al. [87] designed a pH-activated cell penetrating peptide dimer LH2 with histidine residues to deliver PTX to form a non-covalent complex (PTX-LH2(M)) or a covalent complex (PTX-LH2(C)). PTX-LH2(M) released about 50 % of PTX within 5 h under acidic conditions. PTX-LH2(M) and PTX-LH2(C) had significant anti-tumor effects on MDA-MB-231 cell xenograft mice.

4.2. Redox-responsive

Reactive oxygen species (ROS) are chemicals produced by the human body from oxygen. Studies have shown that tumor tissues contain high levels of ROS and reduced glutathione (GSH), and the concentration of GSH is 4 times that of normal tissues [88,89]. Therefore, based on the abnormal ROS and GSH in the tumor, the redox-responsive PTX nano-delivery system has potential application prospects in the targeted therapy of TNBC. Hao et al. [90] combined PTX with copper chelating agent by disulfide bond to form redox-responsive PTX prodrug nanoparticles (PSPA NPs). Under simulated intracellular redox conditions, PSPA NPs could release PTX at 10 mM dithiothreitol (DTT) and 10 mM H_2O_2. PSPA NPs showed a significant tumor inhibition effect on 4T1 mice, causing more karyopyknosis and nuclear ablation (Fig. 4). Xiao et al. [66] designed a tumor microenvironment responsive PTX NDDS (PTX-LHRH-DCMs) to promote the release of PTX in the presence of GSH, and had a significantly enhanced anti-tumor effect on MDA-MB-231 transplanted tumor mice, prolonging the survival time of mice.

4.3. Enzyme-responsive

The abnormal expression of related genes in the occurrence and development of tumors will significantly affect the expression and activity of some enzymes in TME. For example, overexpressed enzymes in TNBC, including matrix metalloproteinases (MMPs) and hyaluronidase, can lead to tumor invasion and metastasis [91]. Therefore, the enzyme-responsive NDDS has become a promising solution for the treatment of cancer [92]. Gao et al. [93] designed an enzyme-sensitive hyaluronic acid nanogel to deliver PTX (PTX/Bio-NG). In the presence of hyaluronidase and/or lipase, PTX in PTX/Bio-NG could be rapidly released, and 80.2 % of PTX could be released within 48 h. PTX/Bio-NG could significantly accumulate in the tumor site and had a significantly enhanced anti-tumor effect on 4T1 tumor-bearing mice (TIR = 94 %).

4.4. Gas-responsive

Hydrogen sulfide (H_2S) is an important endogenous gas signal molecule, which is significantly up-regulated in breast cancer, colon cancer and other cancers [94]. H_2S can specifically reduce azides to amines, which plays an important role in the development of tumor-specific prodrugs [95]. Xiang et al. [96] designed H_2S-responsive block copolymer prodrug PEG-PAMPTX self-assembled into micelles. Under the condition of NaHS (10 mM), the azide group in PEG-PAMPTX was reduced to amino group by high level of H_2S, which promoted the release of PTX, and about 80 % of PTX was released within 24 h. It also showed good tumor inhibition effect on MDA-MB-231 orthotopic tumor mice (TIR = 79.35 %) and reduced damage to healthy tissues.

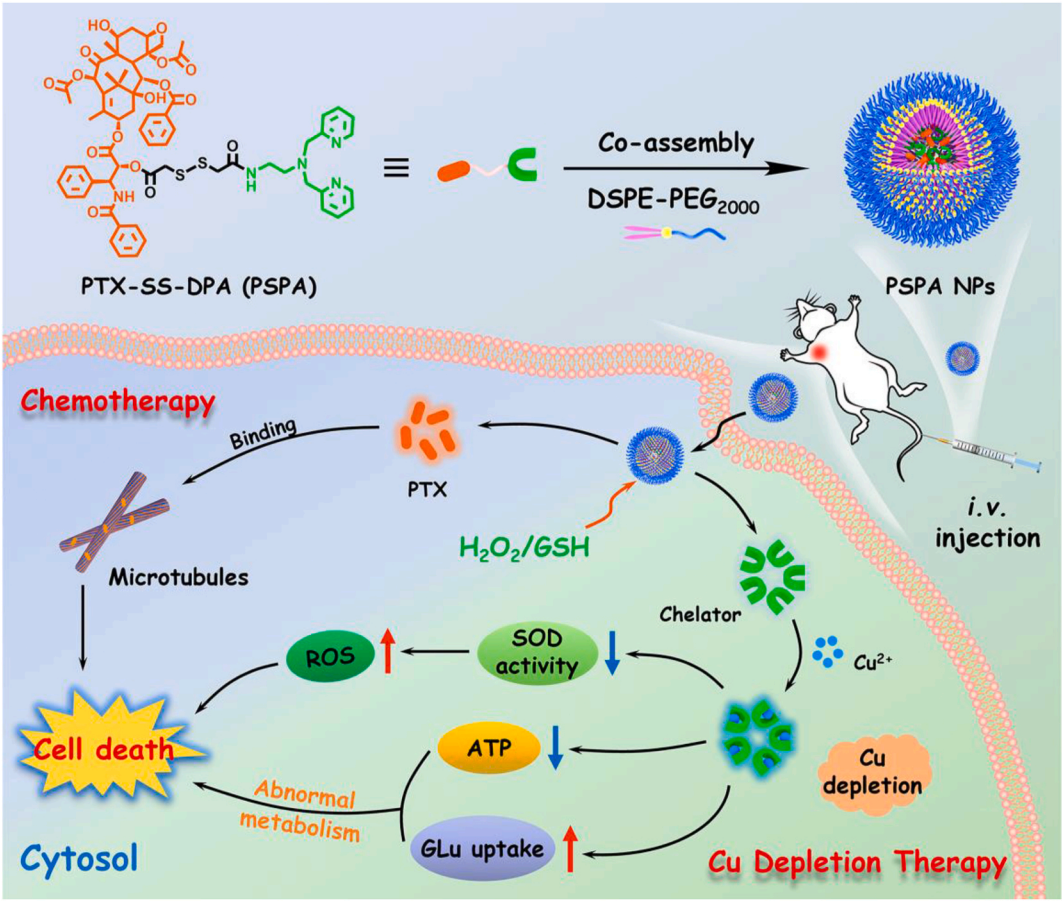

Fig. 4. Illustration of the Preparation of PSPA NPs and Combination of Chemotherapy and Copper Depletion for TNBC Treatment. Reproduced with permission from reference. ACS nano 17(13) (2023) 12383–12393 [90]. Copyright © 2023 American Chemical Society.

4.5. Light-responsive

As an easy-to-produce and remote-controllable non-invasive external stimulator, light plays a key role in light-responsive NDDS based on cancer therapy (such as photodynamic therapy, PDT). Its characteristics enable the system to accurately release drugs at specific sites and times, thereby improving the efficacy of anti-tumor drugs and reducing the impact on surrounding normal tissues [97]. Long et al. [98] designed a BODIPY-derived triangular molecule BTAEA self-assembled nanoparticle PTX/Pt/BTNPs. PTX/Pt/BTNPs showed a good accumulation effect on the tumor site of 4T1 Balb/c mice, and significantly inhibited tumor growth under infrared light irradiation.

4.6. Temperature-responsive

The increased metabolic activity of tumor cells and the formation of new blood vessels lead to the temperature of the tumor site higher than that of normal tissues, which provides an important biological basis for the thermal response delivery system. In particular, thermal responsive nanohydrogels have temperature sensitivity, reversibility and good biocompatibility. Embedding drugs into thermosensitive hydrogels can effectively inhibit tumor recurrence after surgery or during treatment, and reduce damage to surrounding healthy tissues [99]. It has great application prospects in preventing postoperative tumor recurrence and metastasis. Fan et al. [100] prepared a thermosensitive hydrogel (PTX-NCS-gel) constructed by poloxamer 407, poloxamer 188 and carbomer 974P loaded with PTX nanocrystals to overcome postoperative recurrence and metastasis of tumors. At 33.1 °C, the gel can be transformed from liquid to semi-solid. The release of PTX in PTX-NCS-gel was slow and persistent, and 93.7 % of PTX was released within 6 h. PTX-NCS-gel showed significant tumor inhibition on Balb/c mice carrying 4T1-luc cells without recurrence and no obvious nodules in the lungs.

4.7. Ultrasonic-responsive

As an economical, non-invasive and efficient technology, ultrasound has been widely used in clinical diagnosis and treatment. Therefore, ultrasound-based NDDS play an important role in cancer treatment, which can increase the permeability of tumor tissue and achieve controlled release of drugs [101]. Gayoung Kim et al. [102] designed an ultrasound-assisted drug delivery system (PTX-URE) using ultrasound-responsive emulsion (URE) as a carrier to deliver PTX. PTX-URE had higher echogenicity and drug release characteristics. Under ultrasound treatment, the toxicity of PTX-URE to MDA-MB-231 cells was significantly enhanced, which was 11.2 % higher than that without ultrasound. Prateek Badwaj et al. [103] designed ultrasound, pH and temperature triple-responsive liposomes for codelivery of Cur and PTX, and coupled liposomes with nanobubbles to form the 'theranostic platform' (PTX-CUR-LP-NB). Ultrasound treatment enhanced the accumulation of PTX and Cur in PTX-CUR-LP-NB at the tumor site of MDA-MB-231 tumor-bearing mice and significantly inhibited tumor growth.

4.8. Magnetic-responsive

Magnetic nanoparticles are an effective drug delivery system with good magnetic responsiveness and targeted delivery efficiency, which are usually made of iron oxide, cobalt, nickel and other materials [104]. Due to their excellent chemical stability and high resistivity, these nanoparticles are widely used in the magnetic response NDDS of anticancer drugs. Arnon Fluksman et al. [105] designed magnetic responsive metal iron-based magnetic surface plasmon nanocapsules (MAPSULES) loaded with PTX to improve the therapeutic effect of PTX. The magnetophoresis force and magnetic driving ability test results showed that the capture efficiency of MAPSULES is more than 10 times higher than that of superparamagnetic magnetite nanocubes. MAPSULES significantly improved the anti-tumor effect on MDA-MB-231 tumor-bearing mice and reduced the therapeutic window of PTX under the action of magnetic concentration.

4.9. Hypoxia-responsive

Hypoxia is a prominent feature of the TME, which promotes rapid tumor proliferation by regulating signaling pathways such as angiogenesis and invasion, and may lead to multidrug resistance, further promoting tumor metastasis and recurrence. This phenomenon also provides a new idea for the development of stimulus-responsive targeted delivery systems for hypoxic tumors [106]. Xu et al. [107] prepared a mixed micelle (PHDS-NF/PQ) co-loaded with PTX and quantum dots (QDs). As a hypoxia-responsive motif, 2-(2-nitroimidazole) eth- ylamine is converted into hydrophilic aminoimidazole (AI) by enzyme catalysis under hypoxia to further promote the release of PTX. Within 48 h, the release of PTX under hypoxic conditions (77 %) was significantly stronger than that under normoxic conditions (31 %). PHDS-NF/PQ had obvious red fluorescence in the hypoxic site of tumor and showed significant anti-tumor effect on 4T1 mice.

Yin et al. [108] prepared a photosensitive hypoxia-sensitive zwitterionic carrier (D_{High}-PEI-(A + P)/PTX) to achieve hypoxia-responsive release of PTX. Under light conditions, about 50 % of PTX was released from D_{High}-PEI-(A + P)/PTX within 12 h, and PpIX could produce a large amount of ROS under light conditions to induce aggravation of the disease and homogenize the hypoxic microenvironment, achieving precise and controllable release of PTX at the tumor site, and significantly enhance the inhibition and anti-metastasis ability of 4T1 tumor cells.

5. Codelivery system for PTX combined with other therapies

Tumor is one of the major problems that threaten human health worldwide. Due to factors such as tumor heterogeneity, structure, and intercellular signal transduction, the efficacy of a single drug in preclinical and clinical studies of cancer is often unsatisfactory [109,110]. Traditional combination therapy is difficult to control the time of different therapeutic drugs reaching the tumor site, resulting in non-selective toxicity. Therefore, simultaneous delivery of multiple drugs in a single nano-delivery system can improve tumor targeting and achieve synergistic anti-tumor effects, especially in the treatment of TNBC [111,112]. In recent years, the combination of PTX based on NDDS has achieved good results in the treatment of TNBC. In this regard, the synergy of PTX with chemotherapy, active ingredients of TCM, inhibitors, biological therapy, immunotherapy, phototherapy and other therapies is reviewed in detail (Table 4).

5.1. PTX combined with chemotherapy

PTX-based chemotherapy is a common method for clinical or preclinical treatment of TNBC [113]. Studies have shown that compared with single PTX treatment, combined treatment significantly improves the efficacy of PTX on TNBC and overcomes drug resistance [114]. PTX can be co-delivered with different chemotherapeutic drugs, such as gemcitabine (GEM) [115], Doxorubicin (DOX) [116]. As an anti-metabolic drug for cancer treatment, GEM improves overall survival and progression-free survival in patients. However, it is easy to be metabolized by deaminase, has low bioavailability and is prone to drug resistance, which limits its clinical application [117]. Yang et al. [115] designed nanoparticles co-loaded with PTX and GEM (P/G NPs) to enhance the therapeutic effect on TNBC (Fig. 5). The cytotoxicity of P/G NPs on MDA-MB-231 cells (IC_{50} = 0.48 μM) was significantly higher than that of free drugs, and the cell migration rate at 24 h (5.99 %) was significantly lower than that of free drugs PTX (13.87 %) and GEM (16.99 %), and a large number of late apoptotic cells were observed.

Table 4
Codelivery NDDS of PTX combined with other therapies.

Nanodrug delivery system	Drug	In vitro and in vivo model	Pharmacokinetics/ Efficacy/Safety	Year, Ref.
P/G NPs	PTX 5 mg + GEM 2 mg	In vitro: MDA-MB-231 cells.	Cell migration rate: control group (22.49 %) > GEM (16.99 %) > PTX (13.87 %) > PTX + GEM (11.82 %) > P/G NPs (5.99 %).	2023 [115]
PSN/DOX$_{5:1}$ LPs	PTX prodrug (PSN) and DOX = 5:1	In vitro: 4T1 cells. In vivo model: 4T1 tumor-bearing mice.	In vitro cytotoxicity: ↑; CI_{50} value was 0.08. Anti-tumor effect in vivo: ↑. Safety evaluation: ALT, AST, BUN, CR no significant change.	2021 [116]
PC NDs	PTX solution 0.4 mL + Cur solution 0.1 mL	In vitro: 4T1 cells, MDA-MB-231 cells. In vivo: situ female Balb/c mice model carrying MDA-MB-231 cells.	Cytotoxicity (4T1 cells): PC NDs (IC_{50} = 3.87 ± 0.14 μM) > PTX/Cur mixture (IC_{50} = 4.05 ± 0.13 μM) > PTX (IC_{50} = 16.52 ± 0.16 μM). Cytotoxicity (MDA-MB-231 cells): PC NDs (IC_{50} = 2.58 ± 0.11 μM) > PTX Cur mixture (IC_{50} = 2.79 ± 0.10 μM) > PTX (IC_{50} = 7.34 ± 0.19 μM). Anti-tumor effect in vivo: ↑. No histopathological changes were observed.	2021 [122]
CS/LyP-1-PC Lip	PTX and CTS = 1:2	In vitro: 4T1 cells. In vivo: situ and metastatic Balb/c mice tumor model carrying 4T1 cells.	Cytotoxicity and apoptosis rate (4T1 cells): ↑. Anti-tumor effect in vivo: ↑. Biocompatibility: good biocompatibility.	2023 [126]
HA-UA/PTX NPs	PTX, UA	In vitro: MDA-MB-231 and 4T1 cells. In vivo: ectopic mice tumor model carrying 4T1 cells.	Cytotoxicity (MDA-MB-231 and 4T1 cells): ↑. Apoptosis rate (MDA-MB-231 and 4T1 cells): HA-UA/PTX NPs > PTX + UA > free PTX > UA > HA-UA. Anti-tumor effect in vivo: ↑. Hemolysis study: PTX + UA (28.9 %) > free PTX (21.33 %) > UA (13.25 %) > HA-UA/PTX NPs (5.46 %).	2024 [129]
HA-PTX + RTV-NMF	PTX 1.0 mg + RTV 0.25 mg	In vitro: MDA-MB-231 cells.	Cytotoxicity (MDA-M-231 cells): ↑. Cellular uptake (MDA-MB-231 cells): HA-PTX + RTV-NMF > HA-PTX-NMF.	2021 [131]
PH-RL@NEs	PTX, HCQ	In vitro: 4T1 cells. In vivo: 4T1 orthotopic mice tumor recurrence and metastasis model.	Cytotoxicity (4T1 cells): ↑. Cell migration and invasion (4T1 cells): PH-RL@NEs (3.92 %) > PH-RL (4.91 %) > H-RL (13.96 %) > P-RL (14.70 %) > PBS group (62.74 %). Anti-tumor effect in vivo: ↑. Ncadherin and Vimentin ↓. E-cadherin ↑.	2022 [135]
tLyP-1-rHDL-PTX/ GANT61 NP	PTX and GANT61 = 0.5:1.6	In vitro: MDA-MB-231 cells. In vivo: highly metastatic in situ MDA-MB 231 luc mice tumor model.	Cytotoxicity (4T1 cells): ↑. Anti-tumor effect in vivo: ↑.	2021 [139]
PTX@MOF/ siDDIT4-AS1	50 μL PTX solution (10 mg/mL) + 62.5 μL siDDIT4-AS1 (20 μm)	In vitro: MDA-MB-231and MDA-MB-436 cells. In vivo: MDA-MB-231 Balb/c nude mice model.	Expression of DDIT4-AS1 ↓. Anti-tumor effect in vivo: ↑. Safety evaluation: blood biochemical indexes (ALT, AST, CREA2, UREAL) were normal.	2023 [143]
PTX/miR124-NP	PTX 0.5 μg/mL + miR124 100 pmol/mL	In vitro: MDA-MB-231 cells. In vivo: MDA-MB-231 mice orthotopic tumor model.	Expression of E-cadherin ↑, N-cadherin, MMP-9 and Vimentin ↓. Anti-tumor effect in vivo: TIR = 85.3 %. Safety evaluation: AST, ALT did not appear abnormal.	2021 [151]
siRNA@M-/ PTX-CA-OMVs	DSEP-PEG-CA-PTX + siRNA	In vitro: 4T1 cells. In vivo: 4T1-luc TNBC xenograft mice model.	Anti-tumor effect in vivo: ↑. Cleaved caspase3 ↑, ki67 signal ↓. T lymphocytes ($CD8^+$/$CD45^+$) ↑, dendritic cells ($CD80^+CD86^+$/$CD11c^+$)↑, Treg ($CD25^+Foxp3^+$/$CD4^+CD45^+$) ↓.	2021 [154]
PNP-TA + INP-TA	PTX 10 mg/mL + IMQ 4.16 mg/mL	In vivo: Balb/c nude mice popliteal lymph node metastasis model carrying 4T1-luc.	Anti-tumor effect in vivo: INP-TA + PNP-TA > INP + PNP. $CD4^+$ T and $CD8^+$ T cells ↑.	2022 [157]
PTX/ CXB@Lip-cRGD	PTX 1 μM + CXB 5 μM	In vitro: 4T1 cells. In vivo: 4T1 Balb/c mice in situ model; 4T1 Balb/c mice attack and lung metastasis model.	Anti-tumor effect in vivo: ↑. M1 macrophages ↑, M2 macrophages ↓. TNF-α and IFN-γ ↑, IL-10 ↓. Effector memory $CD8^+$ T cells ($CD62L^-CD44^+$) in spleen ↑. Anti-TNBC invasion and lung metastasis: PTX/CXB@Lip-cRGD > PTX@Lip-cRGD.	2024 [160]
pep-PAPM@PTX	PTX and PAP/ pep-PAP = 1:10	In vitro: 4T1 cells. In vivo: 4T1 Balb/c mice tumor model.	Cytotoxicity (4T1 cells): ↑. Expression of PD-L1: ↓. Anti-tumor effect in vivo: pep-PAPM@PTX (78 %) > pep-PAPM (57 %) > PTX (41 %) > pep (30 %).	2022 [164]
POx-PTX/PLX	PTX and CSF1R inhibitor PLX 3397 = 1:1 (75 mg/kg PTX and 75 mg/kg PLX3397)	In vitro: 4T1 cells. In vivo: 4T1 orthotopic mouse tumor and secondary tumor model.	Cytotoxicity (4T1 cells): POx-PTX/PLX (IC_{50} = 0.72 μg/mL) > POx-PTX (IC_{50} = 25.9 μg/mL) > POx-PLX (IC_{50} = 151.3 μg/mL). Anti-tumor effect in vivo: ↑.	2023 [168]

(continued on next page)

Table 4 (*continued*)

Nanodrug delivery system	Drug	In vitro and in vivo model	Pharmacokinetics/ Efficacy/Safety	Year, Ref.
			$CD8^+$ T cells and $CD4^+$ T cells: ↑.	
NGP@MI	PTX 4 mg/kg + IL-2 2.5 mg/kg	In vitro: 4T1 cells. In vivo: 4T1 female Balb/c mice in situ tumor and metastasis model, bilateral subcutaneous 4T1 female Balb/c mice tumor model.	Accumulation of tumor sites: ↑, mature DCs mature: ↑. Cellular uptake (4T1 cells): ↑. Maturation of BMDCs: NGP@MI (69.1 %) > PTX (64.2 %). Anti-tumor effect in vivo: NGP@MI (21.6 %) > NG@MI (21.1 %) > PTX + IL-2 (15.2 %) > PTX (13.5 %) > IL-2 (9.5 %). $CD3^+CD8^+CD44^+$ cells: ↑.	2022 [171]
PSMT NPs	PTX prodrug (PSSP) and 1 MT = 1:1.2	In vitro: 4T1 cells. In vivo: 4T1 ectopic Balb/c mice tumor model.	Cytotoxicity and apoptosis rate (4T1 cells): ↑. DC maturation ($CD80^+CD86^+$DC production): PSMT NPs (50.5 %) > PTX+1 MT (42.6 %) > PTX (40.9 %). Anti-tumor effect in vivo: ↑. Infiltration of $CD4^+$ T and $CD8^+$ T cells ↑, TNF-α, IFN-α and IL-6 ↑.	2024 [174]
PTX-ILips	PTX and αCD47 = 2:1	In vitro: MDA-MB-231 cells. In vivo: MDA-MB-231 xenograft Balb/c mice model.	Cytotoxicity (MDA-MB-231 cells): ↑ Anti-tumor effect in vivo: ↑.	2021 [177]
PTX-SUN micelles	PTX and SUN = 1:5	In vitro: MDA-MB-231 cells.	Cytotoxicity (MDA-MB-231 cells): PTX-SUN micelles (IC_{50} = 1.76 μM) > PTX (IC_{50} = 11.49 μM). Apoptosis rate (MDA-MB-231 cells): PTX-SUN micelles (93.5 %) > PTX-SUN (90.1 %) > SUN (24.7 %) > PTX (15.6 %). DC maturation ↑.	2022 [179]
PPTP@PTX_2 NPs	PTX_2 and PPTP = 1:0.8	In vitro: 4T1 cells. In vivo: 4T1 Balb/c xenograft mice model.	Apoptosis rate (4T1 cells): PPTP@PTX_2 NPs + L (58 %) > PPTP NPs + L (34.9 %). Biological distribution of tumor: PPTP@PTX_2 NPs > PPT@PTX_2 NPs. Anti-tumor effect in vivo: ↑.	2023 [182]
THPP-(S-S-PTX)$_4$-RGD NPs	PTX, THPP	In vitro: MDA-MB-231 cells. In vivo: MDA-MB-231 mice tumor model.	Apoptosis rate (MDA-MB-231 cells): laser irradiation + THPP-(S-S-PTX)$_4$-RGD NP (97.5 %) > laser irradiation + THPP-(S-S-PTX)$_4$ NPs (86.3 %) > THPP-(S-S-PTX)$_4$ NPs (40.7 %). Anti-tumor effect in vivo: ↑.	2023 [185]
MoS_2@PTX-CS-K237	PTX 50.00 mg + MoS_2 0.35 g	In vitro: MDA-MB-231 cells. In vivo: MDA-MB-231 xenograft mice tumor model.	Cytotoxicity (MDA-MB-231 cells): MoS_2@PTX-CS-K237 + NIR (0.67 ± 0.1 μg/mL) > MoS_2@PTX-CS-K237 (2.8 ± 0.3 μg/mL) > PTX-CS-K237 (4.5 ± 0.5 μg/mL) > PTX (7.2 ± 0.7 μg/mL) > MoS_2 (112.6 ± 10.6 μg/mL). Anti-tumor effect in vivo: tumor volume: 22 ± 2 mm^3.	2024 [187]
PSPA NPs	PTX, copper chelate	In vitro: 4T1 cells. In vivo: 4T1 Balb/c mice tumor model.	Cytotoxicity and apoptosis rate (4T1 cells): PSPA NPs > PSP NPs. Anti-tumor effect in vivo: ↑. Safety evaluation: no significant change in blood indexes.	2023 [90]
HSA-NH NPs	PTX 5 mg + HSA-NH solution (2 mL)	In vitro: 4T1 cells. In vivo: 4T1 Balb/c mice tumor model.	Cytotoxicity (4T1 cells): HSA-NH NPs > HSA-AH NPs > PLGA NPs > HSA NPs > HSA-AH NPs. MMP-9 expression ↓. CSCs ↓. Median survival time of mice: HSA-NH NPs (55 days) > HSA-AH NPs (41 days) > HSA NPs (37 days) > PLGA NPs (32 days) > Taxol (31 days) > Abraxane (30 days) > saline group (25 days).	2023 [190]
tPTX-SS-PARA NPs	PTX, PARA	In vitro: 4T1 cells. In vivo: 4T1 Balb/c mice tumor model.	Cytotoxicity (4T1 cells): tPTX-SS-PARA NPs > PTX-SS-PARA NPs > PTX-SS-PARA > PARA. Anti-tumor effect in vivo: tPTX-SS-PARA NPs > PTX-SS-PARA NPs > PTX.	2024 [193]

DOX liposomes are the first nanomedicine approved by the FDA, but the drug loading capacity is only 11 % and the release efficiency at the tumor site is low, which limits the anti-tumor effect [118]. Wang et al. [116] designed a dual-delivery liposome (PSN/$DOX_{5:1}$ LPs) co-loaded with ROS-sensitive PTX prodrug (PSN) and DOX. In the presence of excessive ROS in 4T1 cells, PSN/$DOX_{5:1}$ LPs showed good synergistic anti-tumor activity by rapid release of PTX and sustained release of DOX (CI = 0.08), which could significantly inhibit the tumor growth of 4T1 tumor-bearing mice in vivo.

5.2. PTX combined with active ingredients of TCM therapy

For centuries, TCM has been widely used alone or as a complementary method for cancer treatment. Compared with traditional therapies, TCM has obvious advantages such as mild, low toxicity, small side effects, low economic burden, and prolonged survival of patients [119]. It has great potential in cancer treatment [120]. Cur is an anti-tumor drug with good safety and low cost. Studies have shown that the combination of PTX and Cur can eliminate the CSCs of TNBC and play a synergistic anti-tumor effect [121]. Zuo et al. [122] designed self-assembled engineered nanomedicines (PC NDs) co-loaded with PTX and Cur to enhance the effective and safe treatment of TNBC. PC NDs had higher therapeutic

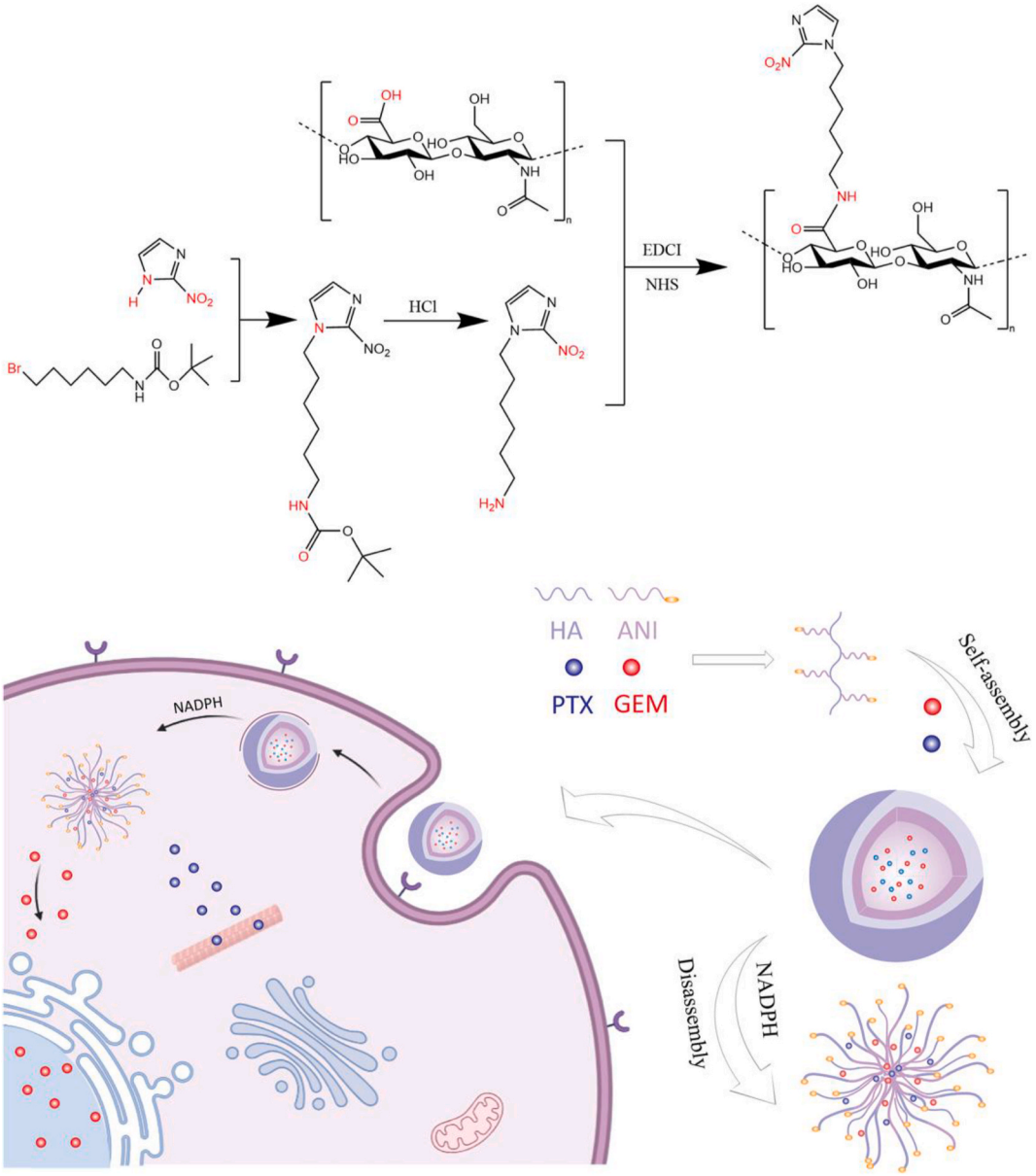

Fig. 5. Schematic diagram of the preparation of P/G NPs and their application in combination chemotherapy. Reproduced with permission from reference. Discover nano 18(1) (2023) 119 [115]. Copyright © Springer Science + Business Media, LLC, part of Springer Nature.

efficiency (inhibition rate of 80.36 %) and lower metastasis rate in 4T1 tumor-bearing mice, and no systemic poisoning was observed.

Studies have shown that signal transducer and activator of transcription 3 (STAT3) is involved in the occurrence, invasion and metastasis of TNBC [123]. Cryptotanshinone (CTS) is a bioactive component of Salvia miltiorrhiza. CTS has the potential to inhibit the phosphorylation of STAT3 and treat breast cancer [124,125]. Luo et al. [126] designed LyP-1 and chondroitin sulfate (CS) double-modified liposomes (CS/LyP-1-PC Lip) co-loaded with PTX and CTS. CTS can increase the sensitivity of PTX to 4T1 tumor cells, inhibit STAT3 activation, reduce the infiltration of immunoregulatory T cells, M2 TAM and bone marrow-derived suppressor cells and the number of immune factors (TGF-β, IL-10), and stimulate immune response. When PTX: CTS = 1:2 (CI = 0.606), CS/LyP-1-PC Lip synergistically enhanced the anti-TNBC tumor effect in vitro and in vivo, and significantly inhibited tumor lung metastasis.

Studies have shown that ursolic acid (UA) exerts anti-tumor effects by inducing apoptosis, inhibiting angiogenesis and metastasis, and increasing the sensitivity of tumor cells to PTX through a variety of mechanisms [127,128]. Reena Sharma et al. [129] designed the enzyme-responsive polymer prodrug HA-UA/PTX NPs for codelivery of PTX and UA, which has the strongest TIR (~90 %) in 4T1 mice and low toxicity risk to mice.

5.3. PTX combined with inhibitor therapy

As a P-glycoprotein (P-gp) inhibitor, ritonavir (RTV) can increase the concentration of P-gp substrate, inhibit the expression of P-gp, reduce the metabolism of PTX and improve bioavailability by inhibiting the metabolic enzyme CYP3A4 [130]. Vrinda Gote et al. [131] designed hyaluronic acid (HA) modified mixed nanomicelles to co-load PTX and P-gp inhibitor RTV (HA−PTX + RTV−NMF) to overcome the MDR of TNBC treatment. RTV reversed the resistance of MDA-MB-231 cells to PTX and significantly increased the uptake of PTX by inhibiting P-gp and CYP3A4-mediated PTX metabolism.

Autophagy is a cytoprotective mechanism that facilitates tumor

proliferation and metastasis. Inhibiting autophagy to reduce CSCs offers a novel approach for postoperative tumor treatment [132]. Hydroxychloroquine (HCQ) is an autophagy inhibitor. The combination of chemotherapy drugs can enhance the sensitivity of tumor cells to drugs, enhance anti-tumor and anti-metastasis effects [133,134]. Ren et al. [135] designed neutrophil-mediated liposomes (PH-RL@NEs) co-loaded with PTX and HCQ. PTX and HCQ co-loaded liposomes down-regulated the levels of N-cadherin and Vimentin, up-regulated the level of E-cadherin, inhibited tumor autophagy, reduced the number of stem cells ($CD44^+/CD24^-$), and synergistically killed the tumors of mice with recurrence after in situ 4T1 surgery.

GANT 61 is an inhibitor of the sonic hedgehog (SHH) signaling pathway, which is abnormally activated in TNBC [136,137]. The combination of PTX and GANT61 as a potential method for TNBC treatment and inhibition of metastasis, but there are low bioavailability and systemic toxicity limitations, which greatly limit its clinical application [138]. Jiang et al. [139] designed tLyP-1 peptide and apolipoprotein A-1 modified double-targeted recombinant high-density lipoprotein nanoparticles co-loaded with PTX and GANT61 (tLyP-1-rHDL-PTX/GANT61 NP) for the treatment of metastatic TNBC (Fig. 6). Codelivery of PTX and GANT61 nanoparticles synergistically inhibited tumor growth and lung metastasis in highly metastatic MDA-MB-231 luc breast cancer mice. Additionally, GANT61-mediated GLI1 inhibition disrupts TNBC cell metastasis by targeting several downstream regulatory pathways.

5.4. PTX combined with biotherapy

Cancer biotherapy leverages the human immune system and biological agents to target cancer cells, resulting in minimal side effects [140]. Cancer biotherapy research has been widely used in breast cancer and lung cancer [141]. Currently, biological agents are classified into two main categories: non-specific agents, such as therapeutic peptides, enzymes [142], and genes [143], referred to as 'bioactive therapy', and specific agents, including vaccines, immune checkpoint blockade (ICB) antibodies, and immunomodulators, known as 'immunotherapy'. The combination of biological therapy and chemotherapy has become a potential cancer treatment [144]. In this section, PTX-based bioactive therapy and chemoimmunotherapy for TNBC will be introduced in detail.

5.4.1. PTX combined with biological activity therapy

Studies have shown that autophagy-related proteins are abnormally elevated in TNBC cells, and autophagy is closely related to drug resistance [145]. Inhibition of autophagy can reduce the resistance of TNBC to chemotherapeutic drugs, siRNA is an important RNA interference tool [146,147]. RNA sequencing revealed that DNA damage-inducible transcript 4 antisense RNA1 (DDIT4-AS1) was highly expressed in TNBC. Jiang et al. [143] designed a siRNA/drug core-shell nanoparticle system for codelivery of PTX and DDIT4-AS1 (PTX@MOF/siDDIT4-AS1) to enhance the therapeutic effect of anti-TNBC. PTX@MOF/siDDIT4-AS1 showed significant tumor inhibitory effect on tumor-bearing mice carrying MDA-MB-231 cells and showed strong inhibitory effect on organoid tumors derived from breast cancer patients.

As a multifunctional anti-tumor miRNA, miR124 is down-regulated in TNBC [148]. Studies have shown that overexpression of miR124 can effectively inhibit the growth and metastasis of TNBC and enhance the sensitivity to PTX [149,150]. Chen et al. [151] designed a stepwise degradable calcium phosphate composite liposome nano-system (PTX/miR124-NP) for codelivery of PTX and miR124 to treat advanced TNBC (Fig. 7). PTX and miR124 in PTX/miR124-NP showed a good synergistic ratio at 0.5 μg/mL: 100 pmol/mL. PTX/miR124-NP had a significant anti-tumor effect on MDA-MB-231 orthotopic tumor mice

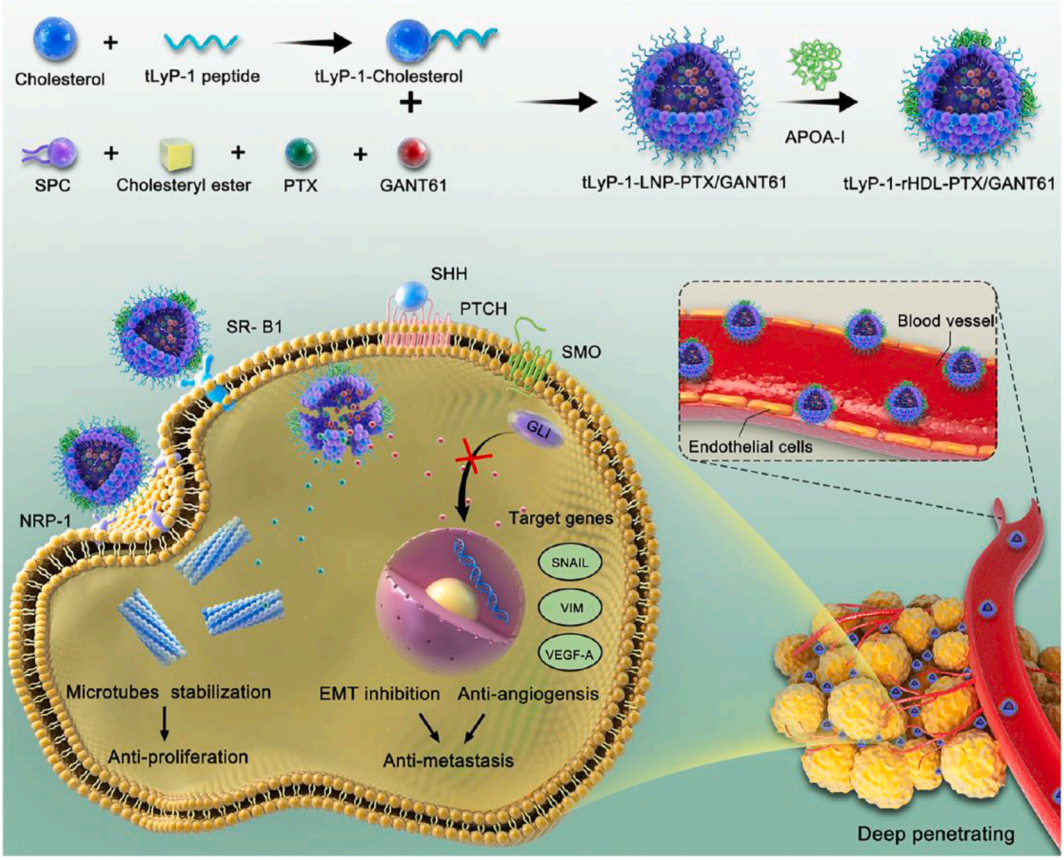

Fig. 6. Schematic Illustration of the Structure and Antitumor Mechanisms of tLyP-1-rHDL-PTX/GANT61 NPs in the Context of TNBC Therapy. Reproduced with permission from reference. ACS applied materials & interfaces 13(30) (2021) 35248–35265 [139]. Copyright © 2021 American Chemical Society.

(TIR = 85.3 %) and inhibited metastasis.

Regulated in development and DNA damage-response 1 (Redd1) is a stress-induced protein [152]. Oxidative stress caused by TAM can up-regulate Redd1 to promote tumor growth and metastasis, while chemotherapy drugs can kill tumor cells to overcome oxidative stress and down-regulate Redd1 [153]. Guo et al. [154] designed a pH-responsive codelivery system (siRNA@M-/PTX-CA-OMVs) for codelivery of PTX and Redd1-siRNA (Fig. 8). The sequential release of PTX and Redd1 at the tumor site in siRNA@M-/PTX-CA-OMVs, siRNA-mediated macrophage metabolic regulation and direct tumor killing induced by PTX chemotherapeutic drugs, increased cleaved caspase3 signal in tumor tissues, decreased ki67 signal, and played a synergistic anti-TNBC role and inhibited liver metastasis.

5.4.2. PTX combined with immunotherapy

5.4.2.1. PTX-nanovaccine. As a promising complement to cancer therapy, tumor vaccine therapy trains the patient's immune system to induce a specific anti-tumor immune response, target and kill cancer cells with few side effects, and form an immune memory to prevent tumor recurrence. The emergence of nanovaccines has significantly enhanced the accuracy and effectiveness of cancer vaccination strategies [155]. Small molecule TLR7/8 agonists can activate antigen presenting cells (APCs) and directly kill tumor cells by recruiting cytotoxic T lymphocytes (CTLs). Imiquimod (IMQ) is one of the small molecule TLR7/8 agonists approved by the FDA for the treatment of breast cancer and colorectal cancer [156]. Liu et al. [157] designed tannic acid (TA) modified nanoparticles (PNP-TA + INP-TA) for the delivery of PTX and IMQ. TA-modified PTX can enhance the accumulation of tumor in situ and metastatic sites in immunodeficient 4T1 Balb/c mice. TA-mediated IMQ and PTX nanoparticles combined to exert a strong tumor-specific T cell response and significantly inhibit tumor growth and lung metastasis.

Studies have shown that prostaglandin E2 (PGE2) levels are elevated after PTX treatment of cancer, and PGE2 has immunosuppressive effects on a variety of immune cells in TME. Inhibition of PGE2 production in tumor cells enhances PTX-induced immunogenic cell death (ICD) and immune response [158]. Celecoxib (CXB), a selective cyclooxygenase-2 (COX-2) inhibitor, is commonly used clinically to inhibit the synthesis of PGE2 [159]. Qian et al. [160] designed cRGD-modified liposomes co-loaded PTX and CXB (PTX/CXB@Lip-cRGD) to achieve effective immunotherapy for TNBC (Fig. 9). The CXB in PTX/CXB@Lip-cRGD can activate DC-mediated immune effect, induce anti-tumor immune vaccine effect, further enhance PTX-induced ICD, and significantly inhibit tumor growth and lung metastasis in orthotopic TNBC mice (TIR = 81.1 %).

5.4.2.2. PTX-immune checkpoint blockade (ICB). ICB therapy is a commonly used methods for the treatment of cancer against the programmed cell death-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway [161]. Studies have shown that anti-PD-L1 peptides are promising alternatives to PD-1/PD-L1 blocking antibodies; however, the low response rate of ICB significantly limits clinical application [162]. Chemotherapy drugs can induce ICD and reduce the infiltration of immunosuppressive cells to enhance tumor immunogenicity [163]. Hu et al. [164] designed a synergistic drug delivery system (pep--PAPM@PTX) that co-delivers PTX and surface-modified anti-PD-L1 peptide (pep) (Fig. 10). Pep-PAPM@PTX intratumoral infiltration of CTL was 1.47 times that of pep treatment and significantly inhibited tumor growth in 4T1 tumor-bearing mice (TIR = 78 %) and promoted tumor cell apoptosis and necrosis.

5.4.2.3. PTX-immunosuppressive environmental regulator. The immunosuppressive environment produced by TAM in TME can induce the occurrence, invasion and metastasis of TNBC [165]. Improving immunosuppressive TME is an effective way to overcome the obstacles of immunotherapy [166]. Antibodies or small molecules can inhibit the regulation of colony-stimulating factor 1 (CSF-1) on the proliferation and survival of macrophages and their precursors, which can inhibit the growth of breast cancer [167]. Lim et al. [168] designed POx polymeric micelles (POx-PTX/PLX) co-loaded with PTX and CSF-1 receptor (CSF1R) inhibitor PLX 3397. POx-PTX/PLX has a good anti-tumor effect on 4T1, T11-apobec and T12 three immunocompetent in situ TNBC mice

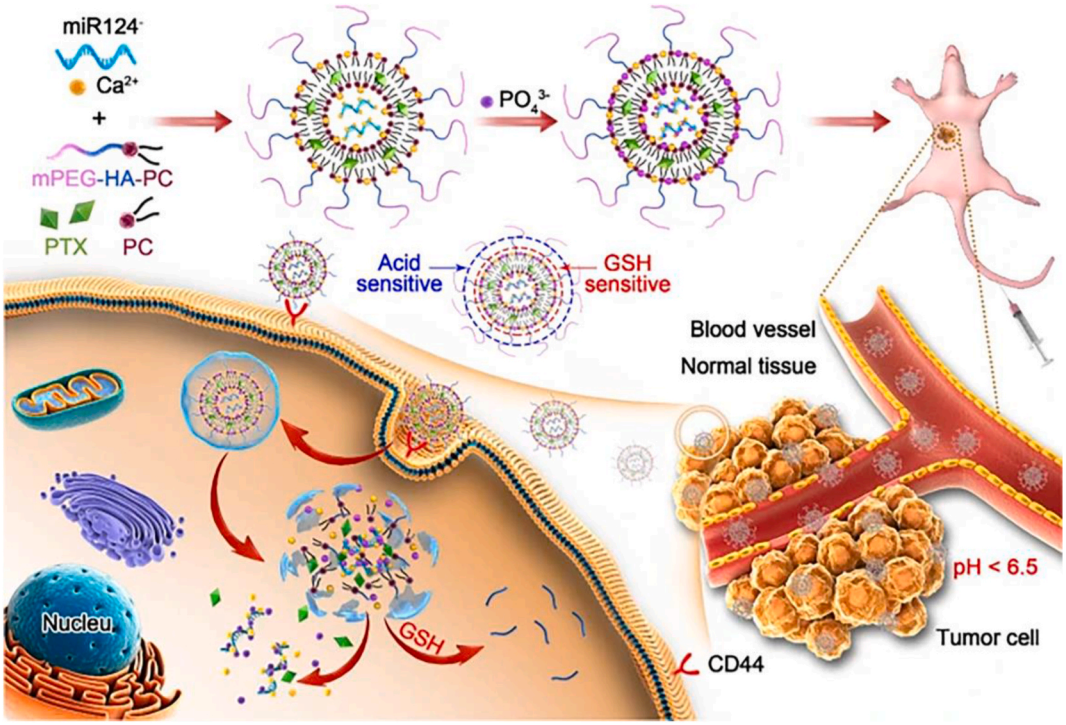

Fig. 7. Schematic Illustration of PTX/miR124-NP. Reproduced with permission from reference. Journal of nanobiotechnology 19(1) (2021) 55 [151]. Copyright © 2024 BioMed Central Ltd unless otherwise stated. Part of Springer Nature.

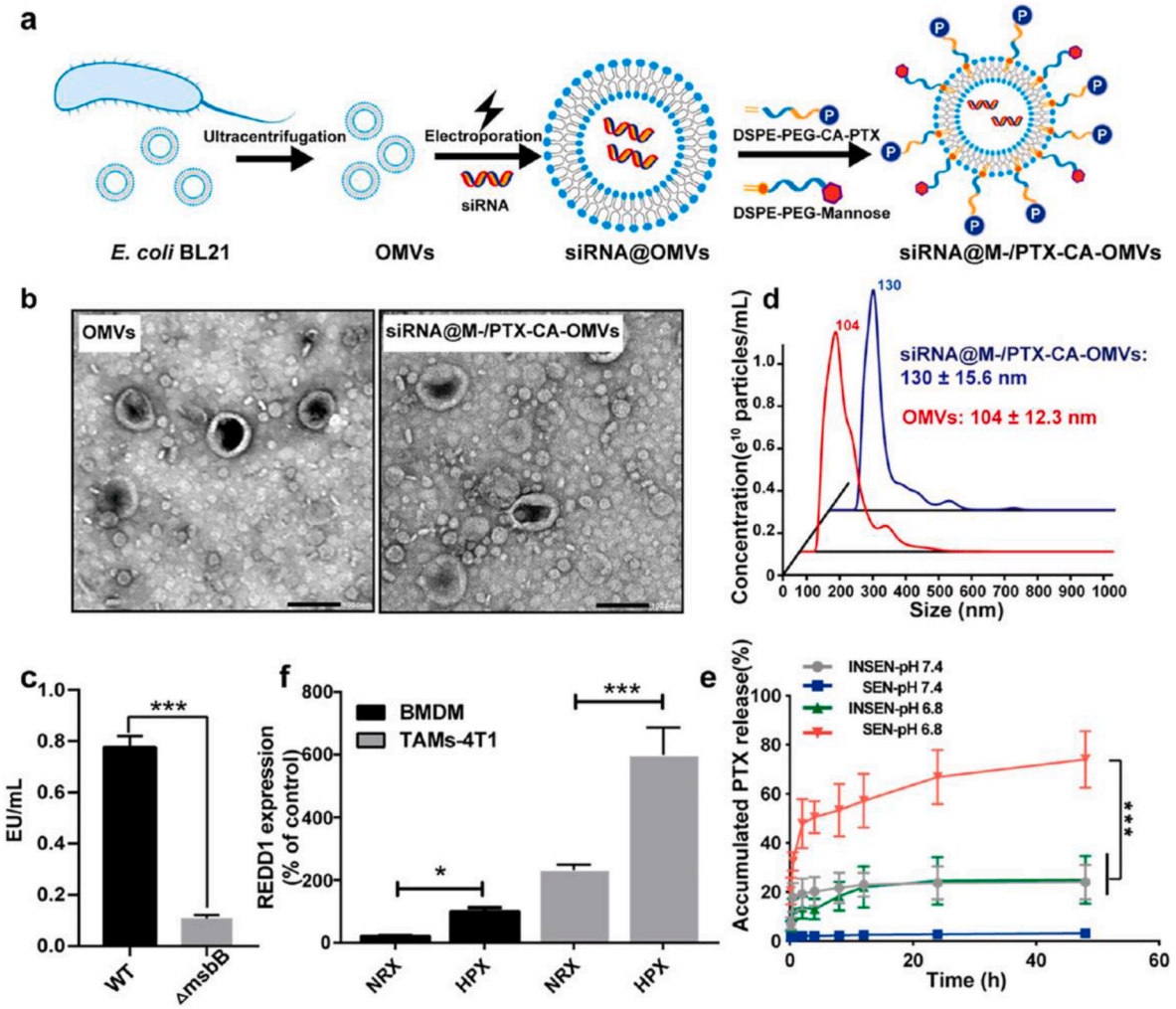

Fig. 8. (a) Preparation of siRNA@M-/PTX-CA-OMVs; (b) TEM images ofOMVs and siRNA@M-/PTX-CA-OMVs (scale bar = 100 nm); (c) LAL assay of OMVs; (d) NTA results ofOMVs and siRNA@M-/PTX-CA-OMVs; (e) PTX release of siRNA@M-/PTX-CA-OMVs (SEN) and siRNA@M-/PTX-OMVs (INSEN) in PBS (pH 7.4) and PBS (pH 6.8); (f) Redd1 mRNA expression in BMDM and TAM-4T1 in normoxic (NRX) or hypoxic (HPX) culture detected by RT-qPCR; Data were presented as the mean ± SD (*P < 0.05, ***P < 0.001). Reproduced with permission from reference. ACS nano 15(8) (2021) 13826–13838 [154]. Copyright © 2021 American Chemical Society.

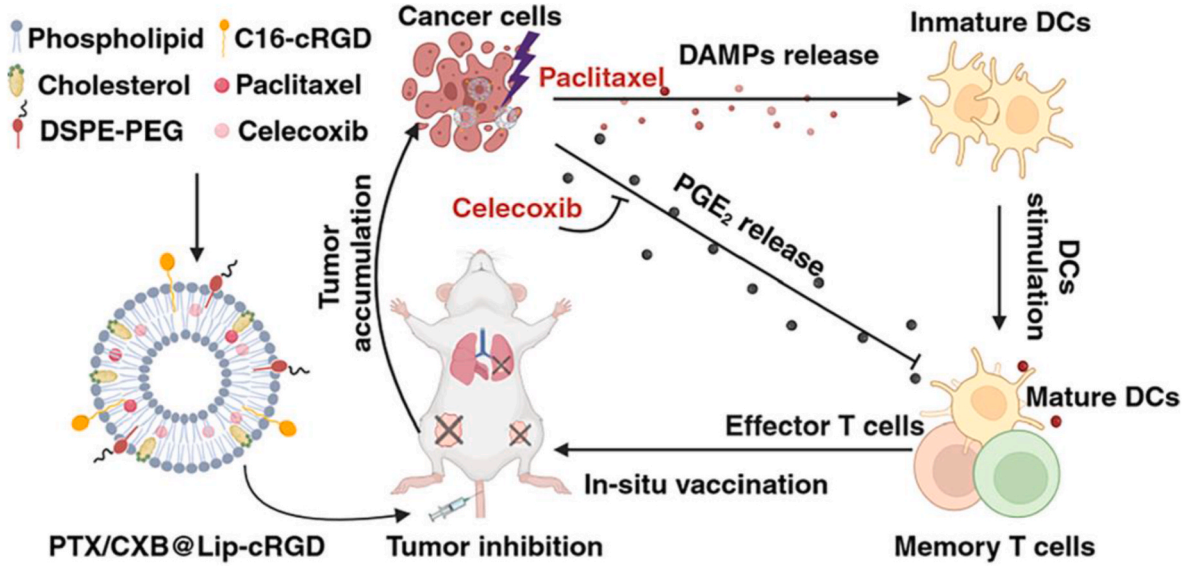

Fig. 9. Schematic Illustration of PTX/CXB@Lip-cRGD. ACS nano 18(24) (2024) 15864–15877 [160]. Reproduced with permission from reference. Copyright © 2024 American Chemical Society.

by repolarizing immunosuppressive TME and enhancing T cell immune response, inhibiting lung metastasis, and increasing $CD4^+$ and $CD8^+$ T cell levels.

The immunomodulator interleukin-2 (IL-2), as a key cytokine that drives immune-mediated cancer cell killing, exerts an anti-tumor immune response by regulating the proliferation and survival of lymphocytes in TME, and PTX has a pleiotropic immune effect on TME [169, 170]. Shang et al. [171] designed a cancer cell membrane-coated pH-responsive nanogel (NGP@MI) for codelivery of PTX and IL-2. NGP@MI increased the number of anti-tumor immune memory T lymphocytes ($CD3^+CD8^+$ $CD44^+$) in the 4T1 reactivated mice model, effectively initiated the anti-tumor immune response, induced the production of immunosuppressive memory $CD8^+$ T lymphocytes ($CD3^+CD8^+$ $CD44^+CD62L^-$), showed significant tumor inhibition (74.7 %), and prolonged the median survival time of mice to 39 days.

Studies have found that chemotherapy drugs can increase the expression of indoleamine 2,3-dioxygenase (IDO) on tumor and tumor-associated immune cells, leading to the failure of immunotherapy. Various IDO inhibitors have been used to reverse ITME and activate the immune system [172]. The combination of chemotherapy drugs and IDO inhibitors is expected to overcome immunosuppression and enhance the therapeutic effect on cancer [173]. Li et al. [174] combined PTX prodrug (PSSP) with IDO inhibitor (1-methyl-tryptophan, 1 MT) to form self-carrier nanoparticles (PSMT NPs) to enhance the therapeutic effect on TNBC. PTX in PSMT NPs interfered with cell mitosis, promoted cell apoptosis, produced ICD effect, promoted DC maturation ($CD80^+CD86^+$), and 1 MT significantly inhibited the growth of subcutaneous xenograft tumors in 4T1 mice by inhibiting IDO activity and PTX synergistically activating cytotoxic T lymphocytes (CTL).

TAM can differentiate into M1-like and M2-like functional phenotypes. M1 TAM plays an anti-tumor role by initiating an immune response, while M2 TAM is an alternative activated macrophage that increases tumor or is associated with tumor invasion and metastasis [175]. Anti-CD 47 (αCD47) can bind to signal regulatory protein α (SIRPα) to promote TAM polarization into M1 macrophages to exert anti-tumor effects [176]. Chen et al. [177] designed matrix metalloproteinase 2 (MMP2)-responsive immunoliposomes (PTX-ILips) for codelivery of PTX and αCD47 (Fig. 11). Codelivery liposomes promote MMP2-responsive release of αCD47 in the TME, polarize M2 macrophages into M1-type to enhance phagocytosis of tumor cells and activate systemic T cell immune response. It showed obvious chemotherapy and immunotherapy effects on MDA-MB-231 orthotopic tumor model mice, and inhibited tumor growth and lung metastasis.

Sunitinib (SUN) is a multi-target receptor tyrosine kinase inhibitor, which can inhibit the growth of tumor blood vessels and tumor extracellular matrix components and reshape immunosuppressive TME [178]. Qin et al. [179] designed PTX and SUN co-loaded nano-micelles (PTX-SUN micelles) to enhance the chemoimmunotherapy of TNBC. The PTX and SUN of PTX-SUN micelles had the strongest synergistic effect at a molar ratio of 1:5 (CI = 0.67), which produced synergistically enhanced anti-tumor activity and apoptosis (93.5 %) on MDA-MB-231 cells, induced DC maturation (41.9 %), and effectively enhanced tumor immunogenicity.

5.5. PTX combined with phototherapy

In recent years, phototherapy, as a local and non-invasive method to achieve cancer treatment, has gradually become one of the main means of cancer treatment [180]. Phototherapy is divided into photodynamic therapy (PDT) and photothermal therapy (PTT). PDT has been clinically approved for the treatment of cancer, and photosensitizer (PS) enhances the necrosis and apoptosis of cancer cells by producing toxic ROS [181]. Commonly used PS includes tetraphenylporphyrin (TPP) [182], chlorin e6 (Ce6), etc. In PTT, the photothermal agent (PTA) absorbs light under the irradiation of external light and converts it into heat to kill tumor cells [183].

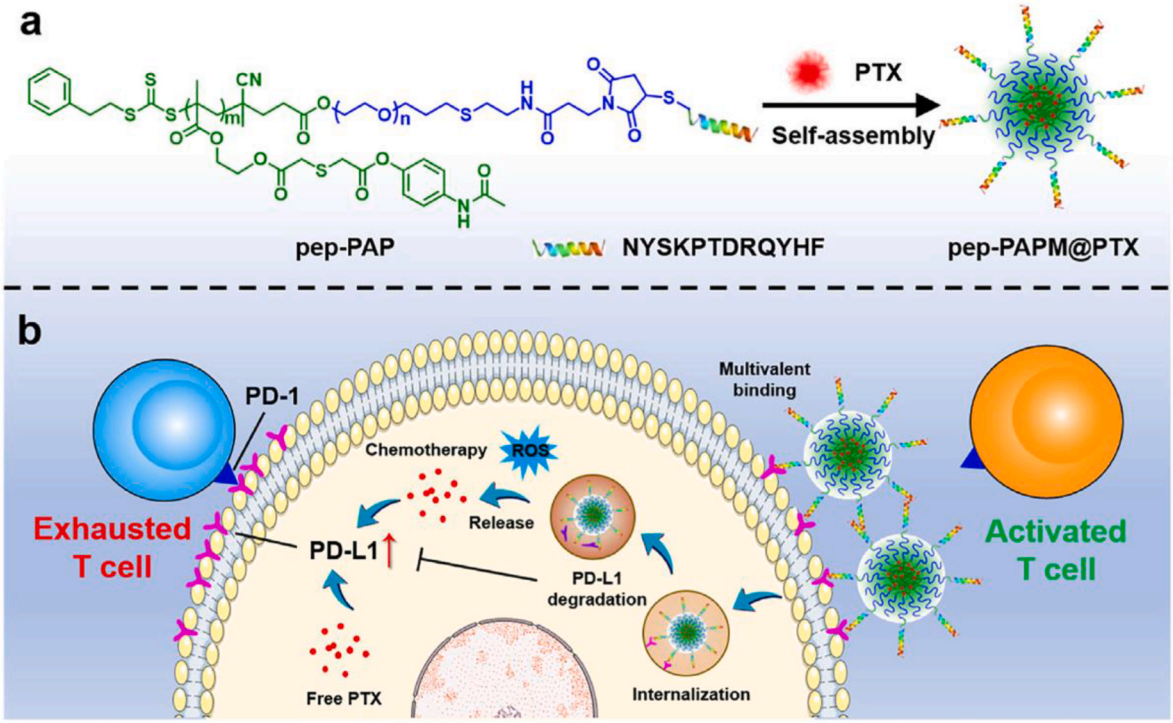

Fig. 10. Schematic illustration of the PD-L1-targeting ROS-responsive micelle for combined immunotherapy and chemotherapy. (a) The anti-PD-L1 peptide modified amphiphilic block polymer pep-PAP self-assembled with PTX in water to form mi-celles (pep-PAPM@PTX). (b) pep-PAPM@PTX binded the cell surface PD-L1 multivalently and drove its recycling to lysosome degradation, thus down-regulating PD-L1 expression. Meanwhile, pep-PAPM@PTX released PTX in response to elevated ROS levels, exerting cell-killing abilities to synergize immunotherapy. Reproduced with permission from reference. Materials today. Bio 14 (2022) 100284 [164]. Reproduced with permission from reference.

5.5.1. PTX combined with PDT

Studies have found that the synergistic therapeutic effect of chemotherapy combined with phototherapy can reduce the dose of chemotherapeutic drugs and reduce the side effects [184]. Zhang et al. [182] designed nanoparticles for codelivery of photosensitizer tetraphenyl porphyrin (TPP) and PTX (PPTP@PTX_2 NPs) (Fig. 12). Under laser irradiation, PPTP@PTX_2 NPs can significantly induce tumor cell apoptosis and necrosis in 4T1 mice through the combined treatment of PDT therapy and PTX chemotherapy to inhibit tumor growth and metastasis.

Ma et al. [185] designed a photosensitizer 5,10,5,20-tetra (4-hydroxyphenyl)-porphyrin (THPP) and PTX to self-assemble into nanoparticles (THPP-$(S\text{-}S\text{-}PTX)_4$-RGD NPs) through disulfide bonds. The inhibitory effect of THPP-$(S\text{-}S\text{-}PTX)_4$-RGD NPs on the tumor of MDA-MB-231 tumor-bearing mice was significantly enhanced under laser irradiation. Obvious nuclear shrinkage and apoptosis were observed, and the expression of vascular endothelial cell marker CD31 was inhibited to prevent tumor metastasis.

5.5.2. PTX combined with PTT

Molybdenum disulfide (MoS_2) has become a promising solution for cancer PTT due to its semiconductor properties, efficient loading, and excellent absorption and light conversion characteristics in the near-infrared (NIR) region [186]. Wang et al. [187] designed nanoparticles for codelivery of PTX and MoS_2 (MoS_2@PTX-CS-K237). The PTX in MoS_2@PTX-CS-K237 was rapidly released under the action of tumor environment and NIR laser irradiation, which had a significant inhibitory effect on MDA-MB-231 mice tumors and promoted tumor cell apoptosis (85.2 ± 8.8 %).

5.6. PTX combined with other therapy

As a cofactor of most metal enzymes or proteins, copper is widely involved in a variety of metabolic processes. Studies have shown that the proliferation, angiogenesis and immune escape of TNBC are closely related to copper metabolism-related signaling pathways [188]. Hao et al. [90] designed redox-responsive nanoparticles (PSPA NPs) co-loaded with PTX and copper chelating prodrugs to enhance the therapeutic effect on TNBC. The copper chelating agent in PSPA NPs reduced the activity of superoxide dismutase (SOD) in 4T1 cells, reduced the production of ATP, increased the demand for glucose through the consumption of intracellular copper, further increased cell death induced by oxidative stress and abnormal metabolism, and synergistically enhanced the tumor inhibition of 4T1 tumor xenograft mice with PTX.

Metformin is an anti-glycolytic drug. Studies have shown that it plays an important role in the treatment of cancer and can reduce the occurrence of breast cancer [189]. Jiang et al. [190] designed a metformin-modified PTX albumin nanoparticles for the treatment of metastatic cancer (HSA-NH NPs). The metformin in HSA-AH NPs penetrates the tumor site, regulates the metabolism of 4T1 cells and exerts a synergistic anti-tumor activity with the chemotherapeutic drug PTX (554.49 ± 45.87 ng/mL), significantly increased the expression of E-cadherin and inhibited the epithelial-mesenchymal transition (EMT) of tumor cells.

Studies have found that the genes in the ferroptosis metabolic pathway in TNBC have changed, and ferroptosis plays a key role in the treatment as a new type of programmed cell death [191]. The abundant GSH in tumor can play an important role in inhibiting ferroptosis as a substrate of glutathione peroxidase 4 (GPX4). Paracetamol (PARA), as a

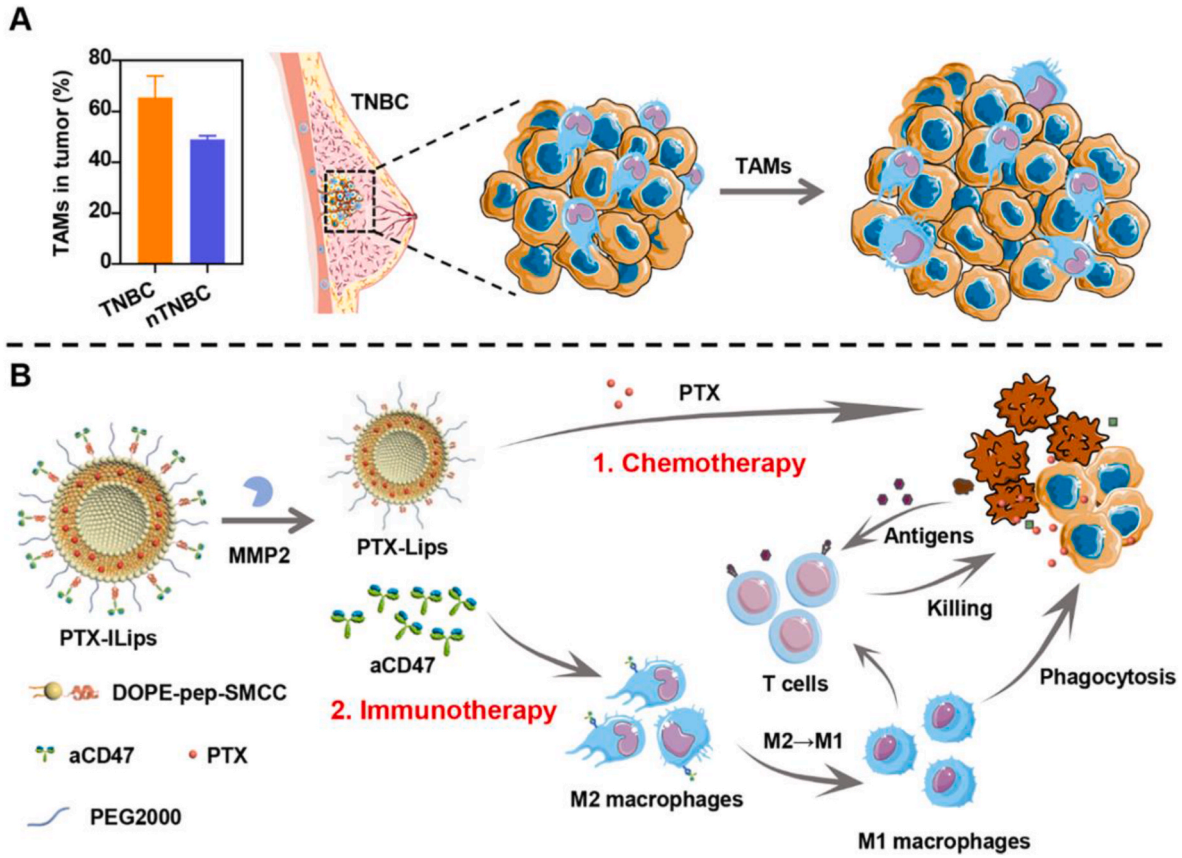

Fig. 11. (A) Tumor-Associated Macrophages (TAMs) Promoting Tumor Growth in Triple-Negative Breast Cancer (TNBC) and (B) PTX-lLips Designed for the Enhanced Efficacy of Immunochemotherapy against TNBC. Reproduced with permission from reference. Nano letters 21(14) (2021) 6031–6041 [177]. Copyright © 2021 American Chemical Society.

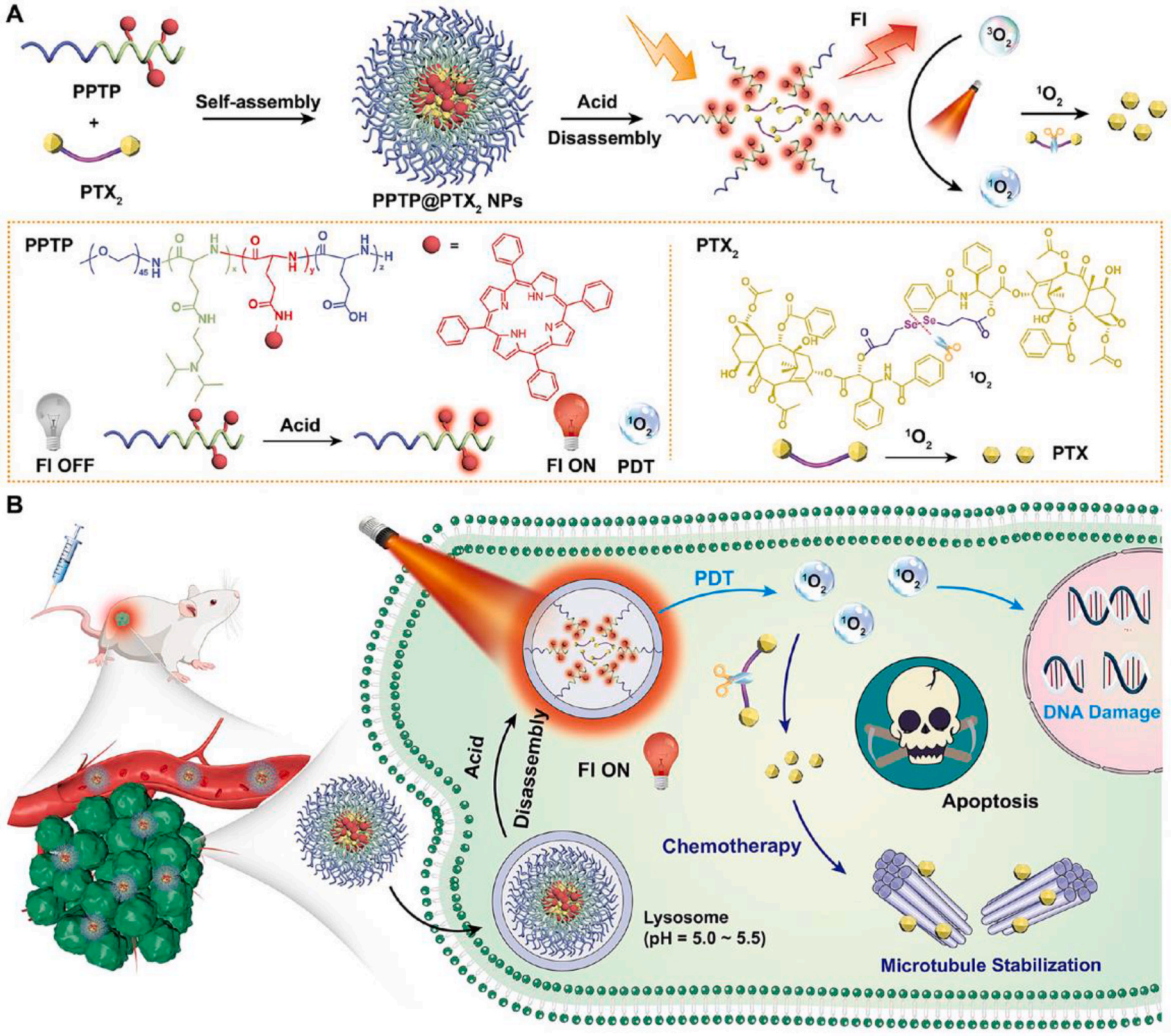

Fig. 12. Schematic Illustration of Combinatory Cancer Therapy by Chemo-Photodynamic Therapya. (A) Self-assembly process and acid-responsive fluorescence and photoactivity capability of PPTP@PTX_2 NPs. (B) Upon intravenous injection, PPTP@PTX_2 NPs passively accumulated at the tumor site and dissociated to release paclitaxel dimeric prodrug. Then, upon 660 nm laser irradiation, TPP-mediated PDT was activated in the intracellular acidic microenvironment, thereby having an enhanced antitumor effect in combination with PTX2-mediated chemotherapy. Reproduced with permission from reference. ACS applied materials & interfaces 14 (35) (2022) 39787–39798 [182]. Copyright © 2022 American Chemical Society.

widely used drug in clinical practice, can quickly react with GSH and induce ferroptosis [192]. Li et al. [193] designed disulfide-linked PTX and PARA prodrugs to self-assemble into nanoparticles (tPTX-SS-PARA NPs). The tPTX-SS-PARA NPs could significantly reduce the level of GSH in 4T1 cells, inhibit GPX4 activity, increase MDA level and mitochondrial morphological changes, and significantly induce ferroptosis in 4T1 cells, showing significant tumor inhibition.

6. Multimodal synergistic delivery system of PTX

In addition to the above-mentioned PTX-based codelivery system combination therapy, the multimodal synergistic therapy of PTX-based NDDS for TNBC has also been widely studied (Table 5), such as PTX-chemotherapy-chemotherapy, PTX-chemotherapy-immunotherapy, PTX-inhibitor-inhibitor therapy, etc.

6.1. PTX-chemotherapy-chemotherapy

Sara El-Sahli et al. [194] designed polymer-lipid mixed nanoparticles (PVC-NP) co-loaded with PTX, verteporfin and combretastatin A4 (CA4). Verteporfin could reduce the accumulation of CSCs after PTX and CA4 treatment, inhibit the up-regulation of carcinogenic YAP signal, and increase the inhibitory effect of CA4 on tumor angiogenesis, significantly inhibit the tumor growth of TNBC xenograft nude mice, and had no effect on the body weight of mice (Fig. 13).

6.2. PTX-chemotherapy-immunotherapy

He et al. [195] designed a nanoparticle delivery system modified by αPD-L1 co-loaded with DEC and PTX (DEC/PTX NPs@αPD-L1). The DEC/PTX NPs@αPD-L1 delivers nanoparticles to tumors, blocks PD-L1 on the surface of tumor cells, and enhances $CD8^+$ T cell-mediated immune response. By inhibiting the expression of DNMT1 in 4T1/PTX cells, DEC regulates the EMT process and CSC-like characteristics of tumor cells, and reverses PTX resistance and tumor metastasis. PTX exerts a direct killing effect on tumors, inhibits Treg cells to remodel TME, and synergistically inhibits tumor and lung metastasis in 4T1 tumor-bearing mice with DEC and αPD-L1.

Guo et al. [196] designed integrin-targeted micelles (ATN-mG/P) co-loaded with GEM and PTX combined with polymer CpG (Nano CpG) to effectively regulate 'cold' TME for the treatment of TNBC. In ATN-mG/P, PTX and GEM synergistically enhanced the apoptosis of 4T1 cells, induced effective ICD, stimulated the maturation of bone marrow-derived dendritic cells (MDSC, $CD80^+CD86^+$mDC), and

synergistically reversed immunosuppressive TME. ATN-mG/P combined with Nano CpG further promoted a strong anti-tumor immune response, significantly inhibited the tumor growth and lung metastasis of post-operative recurrent metastatic 4T1 mice, of which 3/5 mice were completely cured and tumor-free.

Gao et al. [197] designed a macrophage camouflage nano inducer co-loaded with PTX and demethylation drug Decitabine (DAC) combined with PD-1 blocking therapy (P/D-mMSNs/αPD-1) to improve the therapeutic effect on TNBC. DAC combined with PTX can significantly enhance the cytotoxicity and apoptosis of 4T1 cells and reduce the expression of DNMT3. P/D-mMSNs induced ICD-induced anti-tumor immunity, resulting in higher CRT expression (52.93 ± 2.93 %), ATP secretion (35.31 ± 2.91 nmol/L) and significantly reduced HMGB1 fluorescence intensity in 4T1 cells. Chemical immunotherapy combined with DAC can further enhance T cell infiltration and reverse T cell exhaustion, thereby triggering an effective anti-tumor immune response and significantly enhancing the anti-tumor effect on 4T1 tumor-bearing mice (TIR = 90.04 ± 4.34 %).

6.3. PTX-inhibitor-inhibitor therapy

Zhang et al. [198] designed pH-responsive nanomicelles (P/A/B@NM) co-loaded with PTX, CXCR4 antagonist AMD3100 and PD-1 inhibitor BMS-1. PTX in P/A/B@NM enhances cytotoxicity and induces ICD. AMD 3100 blocks the CXCL12/CXCR4 axis to change TME. BMS-1 blocks PD-1/PD-L1 signaling between CAF, tumor cells and immune cells to reduce T cell exhaustion. Synergistic activation and amplification of T cell-mediated anti-tumor immunity significantly inhibited tumor growth and lung metastasis in 4T1 orthotopic tumor-bearing mice, and prolonged the survival time of mice (51-day survival rate 70 %).

Andrew Sulaiman et al. [199] designed Wnt inhibitor PRI-724 and YAP/methoxyvalerate inhibitor simvastatin (PS-HNPs) co-loaded polymer nanoparticles combined with PTX (Pacli + PS-HNPs) for the treatment of TNBC. PRI-724 and simvastatin effectively eliminate clinical PTX-induced CSCs enrichment and tumor regeneration by regulating Wnt and YAP signals. The combination of PTX can further prevent the growth of PTX-resistant and PTX-sensitive TNBC xenografts.

6.4. PTX-PDT-immunotherapy

He et al. [200] designed albumin nanoparticles containing MnO_2 to co-deliver photosensitizer IR780, IDO-1 inhibitor NLG919 and PTX dimer ($BMIP_2N$ NPs). The ROS produced by $BMIP_2N$ NPs, inhibition of TNF-α expression and MnO_2 catalyzed oxygen can enhance the synergistic effect of IR780 and PTX-mediated photodynamic and

Table 5
Multimodal synergistic NDDS of PTX.

Multitherapy category	Nanodrug delivery system	Therapeutic Agent	Therapeutic efficiency	Year, Ref.
PTX-chemotherapy-chemotherapy	PVC-NP	PTX, verteporfin, combretastatin (CA4)	Cytotoxicity (MDA-MB-231 cells): ↑. Inhibition of CSCs enrichment ↑. Anti-PDX organ-type climbing slice culture cell viability ↑. Anti-tumor effect in vivo: ↑.	2021 [194]
PTX-chemotherapy-immunotherapy	DEC/PTX NPs@αPD-L1	PTX, DEC, αPD-L1	Cytotoxicity (4T1/PTX cells): ↑. CRT expression level ↑, DC maturation rate ↑. Safety evaluation: no change in liver and kidney indexes. Anti-tumor effect in vivo: ↑. N-cadherin ↑, vimentin ↑, E-cadherin ↓.	2023 [195]
PTX-chemotherapy-immunotherapy	ATN-mG/P + NanoCpG	PTX, GEM, NanoCpG	DC maturation rate: ATN-mG/P > mG/P. In vivo anti-4T1-luc mice: ↑. Maturation rate of BMDC: ATN-mG/P + NanoCpG > mG/P + NanoCpG. $CD8^+$ T cells and $CD4^+$ T cells in the spleen and tumor: ↑. Tumor necrosis factor-α and interferon-γ ↑. Immunosuppressive MDSCs, Treg and IL-10 ↓.	2023 [196]
PTX-chemotherapy-immunotherapy	P/DmMSNs/αPD-1	PTX, DAC, αPD-L1	DNMT 3 ↓. Caspase 3, CRT, ATP, DC maturation ↑. Proportion of $CD8^+$ T cells: P/DmMSNs/αPD-1 > P/D-mMSNs > P-mMSNs. CTL rate: P/DmMSNs/αPD-1 > P-mMSNs. Anti-tumor effect in vivo: P/DmMSNs/αPD-1 (90.04 ± 4.34 %) > P/D-mMSNs (72.02 ± 4.10 %) > PTX + DAC+αPD-1 (67.17 ± 7.28 %) > P-mMSNs (56.26 ± 8.17 %).	2023 [197]
PTX-inhibitor-inhibitor therapy	P/A/B@NM	PTX, AMD3100, BMS-1	Cytotoxicity (MDA-MB-231 cells): IC_{50} = 105 μg/mL. Anti-tumor effect in vivo: ↑. Safety evaluation: no change in liver and kidney indexes. CXCL12、CCL-2 and VEGF-A ↓, $CD8^+$ T cells ↑, Infiltration of FoxP3+Tregs cells ↓.	2023 [198]
PTX-inhibitor-inhibitor therapy	PTX + PS-HNPs	PTX, Wnt inhibitor PRI-724, YAP/mevalonate inhibitor simvastatin	Inhibition of PTX-induced ALDH + CSCs enrichment: ↑. Anti-tumor effect in vivo: ↑. CSCs ↓.	2020 [199]
PTX-PDT-immunotherapy	$BMIP_2N$ NPs	PTX, IR780, NLG919	Cellular uptake (4T1 cells): $BMIP_2N$ NPs > IR780. Apoptosis rate (4T1 cells): $BMIP_2N$ NPs + L (61.1 ± 2.5 %) > BIP_2N NPs + L (47.8 ± 0.7 %) > IR780 (36.3 ± 2.0 %). CRT exposure, ATP release, HMGB1 migration, DC maturation rate ↑. Anti-tumor effect in vivo: ↑. Ki67 ↑. Safety evaluation: no change in liver and kidney indexes.	2024 [200]
PTX-bioactive therapy-immunotherapy	PP/siAXL@EXO	PTX, siAXL, EXO	Cytotoxicity and apoptosis rate (4T1/PTX) ↑. CRT, ATP, HMGB1 levels, mature DC cells ($CD80^+CD86^+$) ↑. CSCs ↓. Anti-tumor effect in vivo: PP/siAXL@EXO > PTX-PLL. Safety evaluation: no significant difference in liver and kidney function.	2023 [201]
PTX-chemodynamic therapy-enzyme therapy	NanoMn-GOx-PTX	PTX, Gox, Mn^{2+}	Cytotoxicity (4T1 cells): ↑. Generation of ROS: NanoMn-GOx-PTX > NanoMn-Gox. Anti-tumor effect in vivo: NanoMn-GOx-PTX (66.56 %) > NanoMn-Gox-PTX (44.27 %) > GOx (38.08 %) > $MnCl_2$ (31.11 %) > PTX (23.68 %) Mice spleen $CD8^+$ T cells, DC maturation ↑. Proinflammatory cytokines TNF-α and IL-6 ↑.	2022 [142]

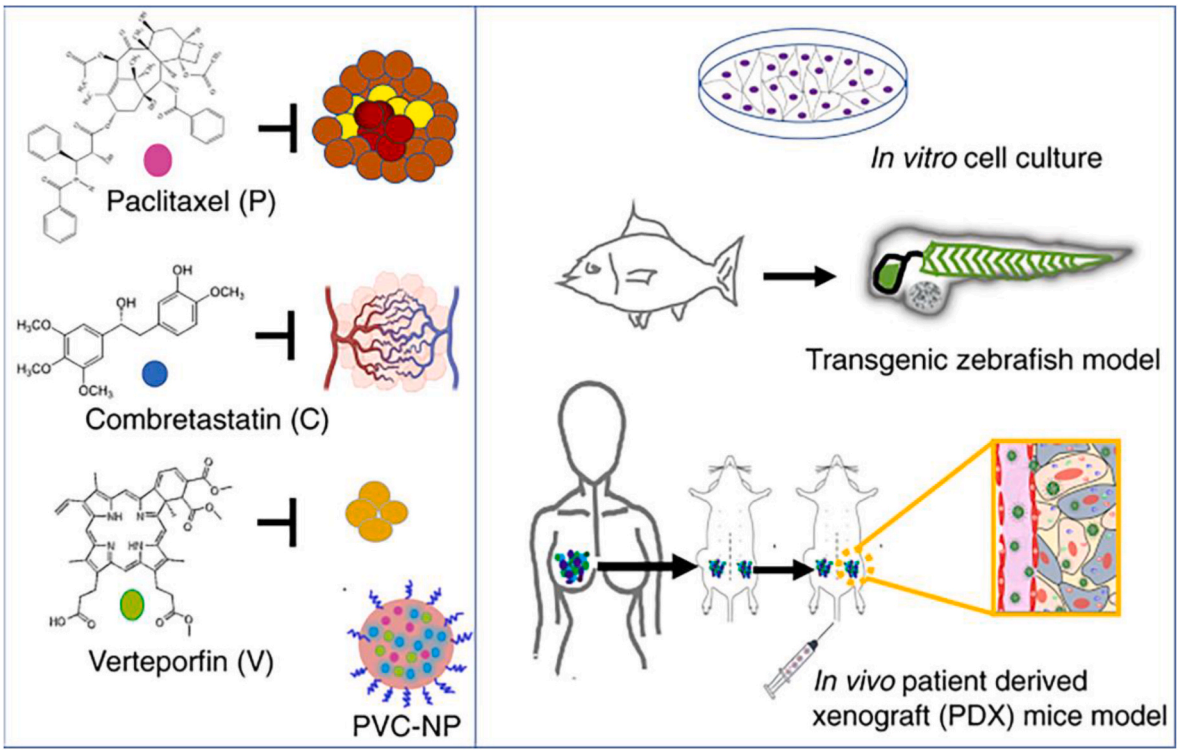

Fig. 13. A schematic representation of experimental design using cell culture, transgenic zebrafish, and patient-derived xenograft models to study bulk cancer cells, angiogenesis, and CSCs. PDX: patient-derived xenograft, and engrafted in mice again for in vivo transplantation and for in vitro organotypic slice culture. Biorender was used to construct part of the figure. Reproduced with permission from reference. Cell Death Dis 12(1) (2021) 8 [194]. Creative Commons Attribution 4.0 International License. Copyright © 2024 Springer Nature Limited.

chemotherapy, showing the highest DC maturity (80.2 ± 11.3 %), further activating anti-tumor immunity. The remission of hypoxia can also down-regulate the expression of PD-L1 in tumor cells and the tumor infiltration of TNF-α secreted by M2 TAM, reshape immunosuppressive TME, increase the lethality of anti-tumor CTL and the inhibitory effect of NLG919 on IDO-1, which has a significant tumor inhibitory effect on 4T1 mice.

6.5. PTX-bioactive therapy-immunotherapy

Chen et al. [201] designed GSH-responsive PTX-poly-L-lysine (PTX-PLL, PP) loaded with AXL-siRNA (siAXL) prodrug micelles to be encapsulated in a T cell-derived exosome delivery system (PP/siAXL@EXO) for the treatment of TNBC. PP/siAXL@EXO exosome-mediated PD-L1 can reverse T cell immunosuppression and EMT. The release of siAXL in the acidic environment of tumor cells overcomes the drug resistance of PTX, synergistically increases the proportion of mature DC cells ($CD80^+CD86^+$) with PTX, induces ICD to establish a positive feedback immune cycle dominated by $CD8^+$ T cells, and establishes a lasting tumor-specific immune memory response to significantly inhibit the growth, metastasis and recurrence of 4T1/PTX tumors.

6.6. PTX-chemodynamic therapy-enzyme therapy

Glucose oxidase (GOx) can selectively and efficiently consume glucose in tumor cells and produce H_2O_2 [202]. Chemodynamic therapy (CDT) is an effective cancer treatment strategy, Mn^{2+}-mediated Fenton-like reaction converts H_2O_2 into ROS and induces tumor cell necrosis and apoptosis [203]. Zhu et al. [142] designed manganese nanoparticles co-loaded with GOx and PTX (NanoMn-GOx-PTX) to exert synergistic anti-tumor effects and reduce the amount of PTX. NanoMn-GOx-PTX could significantly enrich in the tumor site of 4T1 tumor-bearing mice to exert synergistic anti-tumor effect (TIR = 44.27 %) and good biocompatibility.

7. Conclusion and future perspectives

TNBC is a clinically representative type of breast cancer with poor prognosis. Due to its lack of specific targets, chemotherapy is currently the main clinical treatment. PTX is one of the main chemotherapeutic drugs for the treatment of early and metastatic TNBC. However, PTX has the disadvantages of poor water solubility and potential organ damage, immunotoxicity, hypersensitivity and neurotoxicity caused by effective therapeutic doses. In recent years, the continuous development of PTX-based preparations has provided a promising solution for TNBC treatment, but there are still problems such as poor tumor targeting and side effects of intravenous injection. Therefore, the development of new PTX drug delivery systems for the treatment of TNBC is urgently needed. This article reviews the emerging research progress of PTX-based NDDS in the treatment of TNBC, including passive targeting delivery systems, active targeting delivery systems, stimuli-responsive delivery systems, codelivery systems and multimodal delivery systems.

Although NDDS have shown significant potential in tumor therapy and have gradually become an important tool for modern medicine, with the increase of system complexity, the difficulty of achieving its clinical transformation has also increased [204]. The passive targeting delivery system mainly depends on the EPR effect to improve the therapeutic effect of TNBC, which has the advantages of simplified design and preparation, low price, and high bioavailability. It is relatively easy to achieve clinical transformation. PTX passive nanoagents currently approved for market include Lipusu, Abraxane® and Cynviloq™. Studies have shown that multiple combination therapy strategies based on PTX nano-preparations have shown good efficacy and safety in clinical trials. For example, a new adjuvant chemotherapy of PTX liposome combined with epirubicin showed a significant clinical effect in patients with TNBC cancer [205]. Compared with Abraxane® + GEM

(nab-P/G) or GEM + carboplatin (G/C), Abraxane® + carboplatin (nab-P/C) showed significant activity in metastatic TNBC and significantly prolonged progression-free survival (PFS) (NCT03414582) [206]. KN046 + Abraxane® showed good tolerance and clinical efficacy in patients with PD-L1 positive metastatic TNBC (NCT03872791) [207]. Treponemab + Abraxane® has been approved by the National Drug Administration (NMPA) for fully validated PD-L1 positive (CPS ≥1) recurrent or metastatic TNBC [208]. A phase 3 clinical trial of Cynviloq™ also showed good clinical efficacy and overall safety in the treatment of patients with metastatic breast cancer [209]. In addition, a phase 3 clinical trial (CTR20232332) is evaluating the efficacy of Cynviloq™ in the treatment of HER2 metastatic breast cancer that has failed at least two chemotherapy regimens. Although the passive nano-delivery system has made significant progress in drug delivery, approved nano-preparations and ongoing clinical trials have also shown good preliminary results, it still faces several key challenges. In order to avoid the recognition of NDDS by kidney and RES, we need to control the size and surface properties of nanoparticles, which may lead to uneven distribution of drugs in tumor tissues. In addition, safe and effective carriers are also one of the necessary conditions for clinical transformation of biological agents [210]. These problems need to be further overcome in clinical transformation.

The active targeting delivery system based on ligand-receptor specific recognition provides a feasible solution for the efficient administration of PTX in the treatment of TNBC. Studies have shown that G protein A2B receptor, Integrinα5β1, PD-1 protein are closely related to the occurrence, invasion and metastasis of TNBC, and become potential targets for targeted therapy. The active targeting strategy opens up new possibilities for TNBC treatment, especially in achieving precise treatment and overcoming drug resistance [211]. However, there are still many challenges in the process of clinical transformation. The success of active targeting tumor drugs is closely related to carriers, ligands, receptors and therapeutic drugs. The number of ligands and the density of target cell receptors are one of the determinants of tumor specificity. The low abundance of nanodrugs makes parameter characterization complicated [212]. At the same time, most studies are based on peptides, aptamers, etc., targeting ligands by pre-ligation, and ligand density optimization is not performed, which may lead to weak targeting ability to cancer. In addition, it is also important to ensure the maintenance of the therapeutic function and biological activity of the nanoplatform after surface modification. Biomimetic delivery systems such as carriers based on red blood cells, stem cells, macrophages, and platelets represent an innovative development in nanomedicine. By using the cell membrane of autologous cells to disguise nanoparticles, it can significantly improve the biocompatibility and targeting of drug delivery, enhance the therapeutic effect of drugs and reduce the toxic and side effects on normal tissues, thereby improving the therapeutic effect on TNBC [213]. However, the transformation of clinical applications still faces some technical and institutional obstacles, including the complexity of the extraction and application of endogenous cell envelope technology, high manufacturing costs, lack of clinical safety verification, and strict requirements for regulatory and ethical review. Therefore, we need to accelerate the transformation of active targeted drug delivery systems to clinical treatment of TNBC by optimizing the design of ligands and target proteins, developing suitable three-dimensional tumor models, and establishing standard production processes [214].

TME-based PTX stimulus-responsive delivery system is also an effective strategy for the treatment of TNBC. The drug delivery carrier designed by the difference between tumor cells and normal cells can achieve precise control of drug release, reduce the leakage of normal tissues and side effects, and provide a potential great prospect for improving the safety and efficacy of PTX in the treatment of TNBC. Thermosensitive nanohydrogel is a special drug delivery preparation, which usually exists in liquid state. When it is exposed to specific temperature conditions at the site of administration, it will undergo a 'sol-gel' phase transition, thereby transforming into a gel state. This process can release drugs in a controlled manner [215]. OncoGel™ is a PTX nanohydrogel made by Micromed based on PLGA-PEG-PLGA thermosensitive biodegradable gel material. It has the characteristics of targeted sustained release, which can effectively reduce the dosage (6 g/L PTX), significantly increase the treatment of breast cancer and reduce systemic toxicity, and the efficacy can last for about 6 weeks [216,217]. A phase 1 clinical study of OncoGel™ showed that it has good tolerance and preliminary anti-tumor activity in patients with incurable solid tumors, and effectively limits PTX to the injection site, reducing systemic exposure [218]. Phase 2 clinical results of OncoGel™ showed that it showed good tolerance in patients with inoperable esophageal cancer, and could achieve sustained local release and enhanced anti-tumor activity when combined with radiotherapy [219]. In addition, the incidence of recurrence and metastasis after tumor surgery is extremely high, and the mortality rate after recurrence is significantly increased. The stimulus-responsive hydrogel nano-delivery system shows unique advantages in accurately targeting the release of drugs to inhibit recurrence, which provides new hope for the therapeutic effect of inhibiting tumor recurrence and metastasis [220]. Of course, due to the complexity of the TME, there are still many problems to be further overcome in the process of clinical transformation of the stimuli-responsive delivery system. The single stimulus of nanomaterials has the problems of low specificity and slow response. Establishing an accurate drug delivery system with multiple stimulus responses and combining intelligent technology to respond to effective stimulus signals in real time is one of the keys to tumor treatment. Tumor heterogeneity in gene expression, TME characteristics and drug resistance of tumor cells in different patients and the same patient, we need to combine 3D, patient-derived xenograft (PDX) and other models to evaluate the stimulus response delivery system [221]. At the same time, the degradation of biomaterials must also be considered. Therefore, in order to promote its clinical transformation, we need more accurate design and preparation process optimization based on multidisciplinary cooperation to accelerate the transformation of PTX-based stimulus response delivery system to TNBC clinical treatment [222].

NDDS of PTX combined with chemotherapeutic drugs, active ingredients of TCM, inhibitors, biotherapy, phototherapy and multimodal synergistic therapy can enhance therapeutic effect, reduce drug dose, reverse drug resistance of tumor cells, reduce toxicity and adverse effects on the body by regulating different signal pathways. Meanwhile, the combination of co-administration system with accurate tumor diagnosis and multimodal imaging can better adapt to the specific condition and physiological changes of patients, which provides a good research idea and application prospect for PTX-based NDDS in the clinical treatment of TNBC. Vyxeos (CPX-351), a liposome formulation that co-delivers daunorubicin and cytarabine, has been approved for the treatment of newly diagnosed treatment-related acute myeloid leukemia (t-AML) or acute myeloid leukemia with dysplasia-related changes (AML-MRC) [223]. In addition, an anti-advanced solid tumor irinotecan hydrochloride and fluorouracil compound liposome (LY01616) developed by Nanjing Luye Pharmaceutical Co., Ltd is currently undergoing clinical trials (CTR20210414) in China. Therefore, the codelivery system based on PTX is also expected to achieve clinical translation. Of course, there are still several issues to be considered in the clinical translation of codelivery systems or multimodal delivery systems: Firstly, determining the optimal ratio of drugs is the key to achieving synergy. Due to the different properties of different drugs, the choice of nanocarriers is also one of the key factors to maintain the optimal ratio of drugs. At the same time, the combined treatment of multiple drugs will increase the complexity of pharmacokinetic characteristics, and it is necessary to maintain the consistency of pharmacokinetic characteristics and in vivo distribution of drugs to target the lesion site. The complex preparation process and cost of NDDS may limit its large-scale application [224]. The biocompatibility of the carrier material, the metabolic pathway in vivo, the interaction with biological substances (such as proteins, blood, etc.),

and the long-term safety are of great importance for the clinical treatment of TNBC [225].

Overall, PTX-based NDDS has a good prospect in the treatment of TNBC, but it still faces many challenges in clinical transformation. The clinical ideal PTX-based NDDS should accurately and stably deliver the drug to the TNBC tumor target site, overcome drug resistance and achieve precise controlled release of the drug, and the delivery carrier has good biocompatibility and degradability to achieve the win-win goal of maximizing the therapeutic effect and minimizing adverse reactions [226]. With the continuous development of nanotechnology, the combination with cutting-edge fields such as computational models, artificial intelligence, 3D printing, DNA sequencing, and precision oncology has opened up new opportunities for PTX-based NDDS in the diagnosis and treatment of TNBC. We believe that in the near future, PTX-based NDDS can provide a safer, more accurate, more effective and smarter strategy for the treatment of TNBC.

CRediT authorship contribution statement

Jia-xin Qiao: Writing – original draft, Methodology, Conceptualization. **Dong-yan Guo:** Methodology, Investigation, Funding acquisition. **Huan Tian:** Writing – review & editing, Investigation. **Zhan-peng Wang:** Methodology, Investigation. **Qiang-qiang Fan:** Methodology, Conceptualization. **Yuan Tian:** Writing – review & editing. **Jing Sun:** Writing – review & editing, Conceptualization. **Xiao-fei Zhang:** Supervision. **Jun-bo Zou:** Conceptualization. **Jiang-xue Cheng:** Writing – review & editing. **Fei Luan:** Supervision. **Bing-tao Zhai:** Writing – review & editing, Funding acquisition, Conceptualization.

Consent for publication

All authors have reviewed the final version of the manuscript and approved it for publication.

Availability of data and materials

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Declaration of competing interest

The authors declare no competing interests.

Abbreviations

TNBC: triple-negative breast cancer, ER: estrogen receptor, HER2: human epidermal growth factor receptor, PR: progesterone receptor, PTX: paclitaxel, NDDS: nanodrug delivery system, MDR: multidrug resistance, NSCLC: non-small cell lung cancer, TME: tumor microenvironment, ECM: extracellular matrix, EPR: enhanced permeability and retention, CSCs: cancer stem cells, TAMs: Tumor-Associated Macrophages, TCM: traditional Chinese medicine, TIR: tumor inhibition rate, RES: reticuloendothelial system, GO: Graphene oxide, EVs: extracellular vesicles, AND: adenosine, CRT: calreticulin, NRP-1: Neuropilin-1, LHRH: Luteinizing hormone releasing hormone, LHRH-R: LHRH receptor, Fn14: Fibroblast growth factor-inducible 14, CD44: cluster of differentiation 44, FA: folic acid, EGFR: epidermal growth factor, ACE: angiotensin converting enzyme, ROS: reactive oxygen species, GSH: glutathione, DTT: dithiothreitol, MMPs: metalloproteinases, H_2S: hydrogen sulfide, QDs: quantum dots, GEM: gemcitabine, DOX: doxorubicin, Cur: curcumin, STAT3: signal transducer and activator of transcription 3, CTS: cryptotanshinone, CS: chondroitin sulfate, UA: ursolic acid, P-gp: P-glycoprotein, RTV: ritonavir, HCQ: hydroxychloroquine, ICB: immune checkpoint blockade, Redd1: regulated in development and DNA damage-response 1, IMQ: imiquimod, TA: tannic acid, PGE2: prostaglandin E2, ICD: immunogenic cell death, CXB: celecoxib, COX-2: cyclooxygenase-2, PD-1: programmed cell death-1, PD-L1: death ligand-ligand 1, IDO: indoleamine 2,3-dioxygenase, CTL: cytotoxic T lymphocytes, IL-2: immunomodulator interleukin-2, PDT: photodynamic therapy, PTT: photothermal therapy, PS: photosensitizers, PTA: photothermal agent, TPP: tetraphenyl porphyrin, MoS_2: molybdenum disulfide, SOD: superoxide dismutase, EMT: epithelial-mesenchymal transition, GPX4: glutathione peroxidase 4, APAP: paracetamol, CA4: combretastatin A4, GOx: Glucose oxidase, CDT: chemodynamic therapy.

Data availability

Data will be made available on request.

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