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Nanoparticle drug delivery systems and their applications as targeted therapies for triple negative breast cancer

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ABSTRACT

The therapeutic effect of highly malignant triple negative breast cancer (TNBC) is negatively affected by the formation of tumor cell resistant clone and the severe toxicity of chemotherapy drugs to normal tissues. In accordance with research findings, in the comprehensive targeted therapy of TNBC, the nano delivery system effectively suppresses and kills tumor cells on the basis of its unique targeting properties as well as the ability to co-load, deliver, and release chemotherapeutic drugs, active gene fragments and immune enhancing factors, etc. When combined with photothermal ablation therapy, the synergism and toxicity reduction effect of chemotherapy drugs, the inhibition of tumor proliferation related genes as well as activation of immune system can be achieved. Nanoparticle delivery systems present a totally new way of drug design and usage, and change the pharmacokinetic characteristics of conventional chemotherapeutic drugs with significantly reduced adverse effects of some otherwise very toxic chemodrugs via targeted delivery. In this paper, a detailed review was carried out focusing on the research progress of nanoparticle delivery system in the comprehensive targeted therapy of TNBC. We also summarize the merits, shortcomings, perspectives and future developments of nanoparticle-drug delivery systems.

1. Introduction

Triple-negative breast cancer (TNBC) is a term that has historically been applied to cancers that lack expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC tends to behave more aggressively than other types of breast cancers. Unlike other breast cancer subtypes (i.e., ER-positive, HER2-positive subtypes), there are no approved targeted treatments available, although immunotherapy (in combination with chemotherapy) is available for those

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with advanced TNBC that has over-expressed programmed cell death ligand 1 (PD-L1). Chemotherapy is recommended for women with TNBC tumor sizes larger than 0.5 cm or with lymph node positive TNBC (regardless of tumor sizes). Anthracycline-, alkylator-, and taxane-based chemotherapy regimens are the standard regimens for TNBC. These patients have a higher risk of relapse as compared to other breast cancer phenotypes, partly because of the development of drug resistance in TNBC. It was reported to be associated with the increase of drug efflux pump caused by abnormally elevated gene expression, the decrease of intracellular drug concentration, the decrease of drug uptake caused by the change of phospholipid structure in cell membrane, and the shielding/changing of drug target [1-3]. Therefore, the therapeutic outcome of conventional chemodrug therapy is poor for the treatment of TNBC. Medicinal chemotherapy is considered to be an effective approach for the treatment of breast cancer, which, however, is accompanied by disadvantages, such as damages to normal tissues around the tumor or even other organs, resulting in severe myelosuppression and cardiotoxicity. Nowadays, the treatment process of TNBC has been developed via chemodrugs delivery by nanomaterials, the construction of nano treatment system [4], precise gene diagnosis [5], gene therapy [6], photothermal therapy [7], medicinal chemotherapy [8] and immunotherapy [9] on the basis of rapid development of nanomedicines. With its unique physical and chemical properties to co-load a variety of chemotherapy drugs, suppressive gene fragments and immune enhancers, etc., the nanoparticle delivery system can contribute to less adverse reactions, via targeted delivery, in the treatment process via specific photothermal ablation of tumor cells, which is an important tumor treatment strategy under research and development.

According to Marques et al. [10], the two mechanisms by which nanocarriers can deliver drugs to tumors, are passive accumulation and active targeting [11]. Passive accumulation exploits some physicochemical properties of nanoparticles and, mainly, the pathophysiological features of cancers [12,13]. Firstly, the size and the surface of nanoparticles must be controlled to avoid both renal clearance and scavenging by the mononuclear phagocyte system (MPS) and reticuloendothelial system (RES) and, thus, maximize blood circulation time [14,15]. It was well-reported in the literature that nanoparticles with hydrodynamic diameters smaller than ~ 5.5 nm will be removed easily through renal clearance [16,17], whereas those with sizes larger than 50–100 nm tend to be removed by hepatic and splenic macrophages and accumulated in liver and spleen [18,19]. Secondly, solid tumors are characterized by an aberrant angiogenesis that leads to a leaky blood vasculature, of which the endothelial cell junctions are incomplete and disordered [20,21]. Nanoparticles with diameters in the range of 100–400 nm are expected to accumulate at tumor sites through the passive enhanced permeability and retention (EPR) effect by convection and diffusion processes[22,23]. In addition, the impaired lymphatic drainage in tumors promotes the retention of the nanocarriers [24,25]. The passive EPR strategy, however, does not work for all tumors, since some certain hypovascular tumors do not exhibit the EPR effect and the permeability of vessels may not be uniform throughout the whole tumor. In addition, passive accumulation may not be able to deliver chemodrugs evenly to the whole tumor tissues, since drug delivery process is in a random manner and is lack of control with uneven drug diffusion into tumor tissues [26-28]. Active targeting of tumors can overcome these limitations.

This review paper summarizes the application of nanoparticle delivery systems in comprehensive treatment of TNBC, and concurrently provides potential references for the TNBC treatment. In the literature, there have been some reviews published in this field in recent years [29-35], for example, Pallabita Chowdhury, et al [33], reviewed various nanoparticle technology mediated delivery of chemotherapeutic agents for TNBC, and they also concluded novel biological and biomimetic nanomedicine for effective clinical translation for breast cancer treatment, including approaches to employ cellular (erythrocytes, leukocytes, neutrophils, monocytes/macrophages, and thrombocytes) and cell membrane cloaked nanoparticles. Vikas Jain, et al [34], discussed various nanocarriers (polymeric nanoparticles and micelles, metallic and inorganic NPs, and lipid-based NPs, etc) used to deliver chemotherapeutic agents to treat breast cancer (BC) and TNBC, and the application of nanomedicine such as CRISPR nanoparticle, exosomes and natural agent-based nanocarriers. Moreover, they also highlighted the role of breast cancer stem cells (BCSCs) in the recurrence of BC and TNBC, and discussed some nano-therapeutics targeting BCSCs. In addition to discussing the nanocarriers and nanoparticles mentioned above in detailed, Lahanya Guha, et al [35], also reviewed the molecular pathways in TNBC. However, when comparing with those articles, the importance and novelty of our review lie in that not only it is comprehensive and detailed, covering almost all the important parts of the above three articles, but it also thoroughly underscored the developments of nanoparticles with ligands responsive to tumor microenvironment, developed nano topical modifications, and clinical trials using nanoparticles. Specifically, we conducted this review focusing on TNBC to make this paper more straightforward.

This review paper summarizes some important literature information which very little or none could be found in the previous review articles; including: 1) in-depth discussion of the molecular biological mechanisms (such as receptors, ligands, signal transduction pathways, etc.) of the nano-drug delivery system acting on breast cancer cells or tissues; 2) full summarization of nanoparticle drug delivery systems from a clinical perspective, elaboration on specific treatment methods and strategies (such as nanoparticle-based gene therapy, photothermal therapy, and immunotherapy), and clinical trials of nanoparticle delivery systems for breast cancer treatment.; 3) focus on the most malignant triple negative breast cancer (TNBC), which cannot be cured using conventional modalities; 4) explicitly pointing out the true beauty and spirits of using nanomedicines for treatment of cancers, such as tumor targeting, multidrug co-delivery, providing a totally new way of drug designs and usages, resolving multi-drug resistance problems, etc; 5) Comprehensive review covering a large number of 515 literature papers published up to December 2022 including many important ones, especially the related clinical applications of nanomedicines in treating TNBC. Therefore, the readers get to know more and in-depth research advances and applications of nano-delivery systems in breast cancer targeted treatment, the various microenvironment-sensitive nano delivery systems, the basic working principles and mechanisms, and clinical applications.

2. Advanced nanoparticles for targeting at TNBC

Some of nanocarriers reported for targeting at TNBC were summarized in Table 1 [36-87]. Targeted drug delivery system was

Table 1
Some of nanocarriers used for targeting of TNBC.

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
Inorganic NP	Photo-thermaltherapy using MWCNTs	To examine whether breast cancer stem cells (BCSCs) are resistant to hyperthermia, and conquer such resistance	BCSCs are sensitive to hyperthermia and lose long-term proliferative capacity; observed complete tumor regression and extended average lifespan.	NA	The combination of MWCNTs and laser exposure led to complete tumor regression and significantly enhanced overall survival (100%) relative to the control groups ($p < 0.05$).	Induction of necrotic death may be therapeutically advantageous, since mechanisms of resistance to apoptotic cell death are bypassed. further studies will be required to elucidate the details of the interaction between NIR-stimulated nanotubes and the cancer cell surface that leads to cell death	[437]
Inorganic nanoparticle	HA-SWCNT-DOX	To develop a carbon nanotube product for targeted delivery of doxorubicin to improve breast cancer treatment	Enhanced uptake of DOX by MDA-MB-231 cells, inhibited cell proliferation, growth, metastasis, and apoptosis,	SWCNTs-DOX-HA achieved a 2.1-fold increase in cellular DOX fluorescent intensity than SWCNTs-DOX.	SWCNTs-DOX, SWCNTs-DOX-HA and free DOX groups were 2.33 ± 0.56 %, 9.25 ± 1.62 %, 37.72 ± 1.03 % and 73.45 ± 1.54 %, respectively. At 48 h, the migration indexes of control, SWCNTs-DOX, SWCNTs-DOX-HA and free DOX were 73.8 ± 0.88 %, 47.4 ± 0.78 %, 28.6 ± 0.32 % and 14.8 ± 0.56 %, respectively	During the application of carbon nanotubes (CNTs) as drug carrier, its toxicity is the key issues of their application in the therapeutic areas	[207]
Inorganic nanoparticle	Mesoporous polymer- Bcl-2siRNA NPs	For targeting of a folic acid receptor of breast cancer	Effective inhibition of sequence- specific Bcl-2mRNA expression, high tumor cell apoptosis.	More than 94% cellular internalization was achieved in the OMPN–PEI1@ siRNAFAM@PEI2 group after 4 h and the fluorescence intensity was much higher (by approximately one order of magnitude) compared with the OMPN–PEI1@siRNAFAM group.	Compared with the group treated by nanoparticles without any PEI coating, the apoptosis rate of the MCF-7 breast cancer cells in the OMPN–PEI1@ siRNA@PEI2 (siRNA, 100 nM) group increased from 13.99% to 28.7%, revealing the significant cell growth inhibition ability of siRNA and the positive effect of the PEI coating on apoptosis efficiency. As the siRNA dose was increased from 100 nM to 150 nM and 200 nM, the apoptosis rate reached 30% and 38.4%.	NA	[75]
Metal nanoparticle	Lipid -conjugated estrogenic (ESC8)	To find an effective therapy against TNBC combining properties of target specificity, efficient tumor killing, and translational relevance	Effective suppression of the TNBC tumor and metastasis, ESC8 inhibited TNBC with IC_{50} ranging from 1.81 to 3.33 μM, combined (ESC8-SLN)-cisplatin therapy inhibits 87% MDA-MB-231 tumor cell growth.	Although the absorptive flux o ESC8 across formulations did not vary significantly, the efflux ratio was shifted to favor increased drug retention in the basolateral compartment (percent efflux ratio, i.e. % ER) of ESC8 was reduced 2–3 times in ESC8-Liposomes (% ER, 42%), ESC8-SLN (% ER, 31%), and ESC8-NLC (% ER, 33%) compared to ESC8 solution (% ER, 89%)	The difference in tumor volume between ESC8-SLN (10 mg/kg/day) and Cisplatin (2 mg/kg, 2x/week) was significant ($P < 0.0001$). And the decrease in tumor volume in ESC8-SLN (10 mg/kg/day) and ESC8-SLN (10 mg/kg/day) + Cisplatin (2 mg/kg, 2x/week, IP injection) group was significant ($P = 0.0002$). Overall, rank in tumor growth inhibition followed the order ESC8-SLN (10 mg/kg/day) + Cisplatin (2 mg/kg,	NA	[438]

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Table 1 (*continued*)

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
					2x/week, IP injection) ≫ ESC8-SLN (10 mg/kg/day) and ESC8-SLN (20 mg/kg/day) ≫>≫ Cisplatin (2 mg/kg, 2x/week) >>> controls.		
Metal nanoparticle	Paclitaxel/cisplatin-ZnO NPs	To clarify antitumor activity of photo-stimulated ZnO-paclitaxel/cisplatin NPs	Reduced toxicity and improved efficacy in killing breast cancer cells.	NA	There was a significant cell killing effect in all three HNSCC cell lines following 15 min of UVA-1 irradiation with 0.2 ug/ml ZnO-NP. The IC50 of single photocatalytic therapy with ZnO-NPs was 1.2 lg/ml in HLaC 78, 1.6 lg/ml in Cal-27, and 1.5 lg/ml in PJ 41.	Besides NP-concentration, shape, configuration, dispersion grade, and surface charge seem to play an important role in NP-cytotoxicity. Further studies on ZnO-NP induced photocata- lytic cell death in cancer cells should address the impact of these values on tumor killing efficiency.	[162]
Metal nanoparticle	cRGD conjugated Fe_2O_3 NPs	To find a novel MRI contrast agent for bone metastasis imaging	Anti-(HER-2) antibody grafted (Fe_2O_3)-polymersomes serve as MRI contrast agents for bone metastasis imaging, enhanced tumor retention.	MRI signal analysis of the tumor tissue showed that naked polymersomes were less retained than the targeted ones (Fig. 2E). Additionally, superior contrast was observed in the tumor bone, when compared with the contralateral femur tissue (Fig. 2C, D), attesting the targeting specificity in a clinically relevant in vivo scenario.	NA	NA	[439]
Metal nanoparticle	Anti-neu MAb-SPIONs	To find a novel biomarker to diagnose small volume metastasis early	Anti-neu MAb-SPIONs can tag both primary and metastatic breast tumors in liver, lung, and bone marrow; SPIONs serve as MRI contrast agent.	NA	NA	NA	[440]
Lipid nanocarrier	LPT-HA-NCs	To expand therapeutic horizon of Lapatinib (LPT)	LPT-HA-NCs upregulate expression of pro-apoptotic proteins, Fas, caspase-3 and caspase-8, suppress tumor growth and prolong lifespan.	The accumulation of both types of NCs was nearly similar at 1 h, but they could not be retained for a time. On the other hand, LPT-HA-NCs were retained in tumor area and the distribution was highest at 24 h. Mice treated with LPT-HA-NCs have very high tumoral distribution than LPT-NCs. The lungs of the mice treated with both types of NCs also showed very high localization of LPT. The comparative accumulation of LPT-HA-NCs in liver, spleen, and kidneys was slightly lesser than LPT-NCs as observed by the lower fluorescent intensity.	LPT-HA-NCs displayed nearly 52, 74.65 and 83.32 percentage reduction in tumor burden than LPT-NCs, free LPT and control groups respectively. Compared to the control group (11.33 ± 2.88 nodules/lung) as 100% lung metastasis, there was only 3% lung metastasis in crude LPT (0.33 ± 0.57 nodules/lung), 0% in LPT-NCs and LPT-HA-NCs as the lungs of these groups denoted complete absence of the nodules.	Though LPT has an acceptable safety the serious liver toxicity is reported with its treatment, but the exact underlying cause remains underdetermined.	[184]
Lipid nanocarrier	γ- PGA-g-PLGA-IG-DOX NPs	To overcome low therapeutic efficacy of chemotherapy against multidrug resistance (MDR) breast cancer	Effective accumulation in MDR cancer cells, inhibition of p-gp activity, suppression of proliferation and growth of MDR cancer cells/ tumors,	Significant accumulation of DOX in cell nuclei was observed for MCF-7 cells treated with free DOX-HC1 and DI-NPs. By contrast, the DOX signal in MCF-7 cells treated with DOX base was relatively low. both free DOX-HCl and	Upon laser irradiation, the tumor volume of the group treated with CP2k-DI-NPs was further reduced to 124.4 ± 22.1 mm3, attesting to the efficacy of the proposed combination therapy against MDR	NA	[441]

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Table 1 (*continued*)

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
				DOX base barely accumulated within the nuclei of the MDR cellsAlthough the DOX species was found in the cytoplasm of MCF-7/MDR cells treated with bare DI-NPs, it was not observed in the nuclei. By contrast, DOX was found in both cytoplasm and nuclei of MCF-7/MDR cells treated with CP-DI-NPs	cancer cells. In contrast with that of the groups treated with free drug and bare DI-NPs with laser, the H&E stained tumor sections of the group treated with CP2k-DI-NPs and laser irradiation exhibited significant reduction in the number of nuclei with enlarged apoptosis region		
Lipid nanocarrier	Polymer-lipid hybrid NP of spsoralen (PSO-PLNs)	To improve the water solubility & bioavailability of spsoralen	In vivo anticancer efficiency of PSO-PLNs was done on MCF-7 breast tumor model with low toxicity and side effect.	PSO-PLNs accumulate passively in the tumor via the enhanced permeability and retention (EPR) effect due to the leaky tumor blood vessels, leading to increased exposure of PSO within the tumor as compared to free drug treatment. In addition, PSO-PLNs enable PSO retention within nanocarriers and extend the circulation time of PSO.	When the nude mice were treated with PSO-PLNs, the tumor inhibition rate was up to 78.10%, which was significantly different from the control group ($p < 0.05$). PSO-PLNs showed more efficient anti-tumor effects than the formulations of free PSO and DOX.	NA	[442]
Lipid nanocarrier	Transferrin (Tf)-polymer-DOX NPs	To improve Dox delivery to DOX-resistant (R) breast cancer cell lines	Effective accumulation in DOX-resistant cancer cell line MDA-MB-231(R), effective inhibition of cancer cell proliferation	The fluorescence intensity of cyanine 5.5 loaded targeted NPs was significantly higher than that of non-targeted NPs and there was minimal ex vivo distribution in the organs examined (heart, liver, spleen, kidney, and lungs) in the targeted NP treatment group.	The MTT assay proved that the cytotoxic effect of Dox/F127&P123-Tf was higher than that of free Dox in not only the Dox-sensitive (OVCAR-3 and MDA-MB-231), but also the Dox-resistant MDA-MB-231(R) cell lines.	NA	[443]
Liposomal nanoparticle	(Cys-Asp-Gly-Phe (3,5-DiF)-Gly-Hyp-Asn-Cys)-liposome (DOX -rapamycin)	To find a new approach to combat the triple-negative breast cancer (TNBC)	Enhanced antitumor activity and efficacy in TNBC xenograft mice model	As shown in Fig. 6A, the mice receiving LXY-LS-DIR displayed a significantly stronger intense fluorescence compared with that of LS-DIR in all time points in tumor tissues. The fluorescence distributing all over the bodies of the mice receiving LXY-LS was weaker than that of mice receiving LS.	The relative tumor volumes of control, free DOX, LS-DOX and LXY-LS-DOX were 6.68 ± 2.21, 4.12 ± 0.78, 3.61 ± 0.65 and 2.42 ± 0.79, respectively. The significant reduced tumor weight also demonstrated the superior inhibition efficacy of LXY-modified liposomes towards LS-DOX (P = 0.026)	HIF-1a down-regulation might be partly account for the anti-tumor effect of RAPA alone but might not completely explain the enhanced anti-tumor efficacy of LXY-LS- DOX plus M−RAPA combinational treatment compared with M-RAPA single treatment.	[444]
Liposomal nanoparticle	Micelle-DOX	To define the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLTs) of NK911	Neutropenia was the predominant haematological toxicity, dose-limiting toxicities (DLTs) = 67 mg m^{-2}, NK911 was well tolerated, recommended phase II dose = 50 mg m^{-2} per 3 wks	NA	A partial response was seen in one patient with metastatic pancreatic cancer who had been treated at a dosage level of 6; the size of the liver metastasis had decreased by more than 50%, compared to the baseline scan, in this patient. The tumour marker (CA19-9 and CEA) levels in this patient had also decreased remarkably.	The value of V1 in humans after the injection of free DXR has not been reported	[445]
Liposomal nanoparticle	PAA-g-PEG-copolymer micelles-DOX	To delay 4 T1 tumor growth and reduce the lung metastases of breast cancer	Effective inhibition of growth of 4 T1 breast cancer cells in vitro, improved DOX bioavailability and reduced	In the process of injected by via tail vein in 4 h, more tumor accumulation and less heart distribution of DOX-	DOX HCl and PAA(8:2)-PEG2000/PAA(8:2)-PEG5000 DOX-incorporated micelles exhibited effective inhibitory	For DOX HCl treated group, obvious organ damage as fragmentation and pathological changes were perceived in heart	[446]

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Table 1 (*continued*)

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
			side effects to heart and other organs	incorporated micelles compared to that of DOX HCl	effect compared to the control groups (PBS and empty micelles), and the inhibitory effect was reflected in a statistically significant reduction in tumor volume at day 23 compared with control groups.	and spleen tis- sues compared with the normal muscle fibers and organ structure from blank mice.	
Liposomal nanoparticle	Liposomes-paclitaxel-irinotecan (EndoTAG-1 and MM-398)	To evaluate safety and efficacy in advanced TNBC	Combination of EndoTAG-1 and standard paclitaxel showed good antitumor efficacy to advanced TNBC.	NA	The PFS rate at week 16 was 59.1% on combination treatment, 34.2% on EndoTAG-1, and 48.0% on paclitaxel. Median PFS reached 4.2, 3.4, and 3.7 months, respectively. After complete treatment (week 41 analysis), median overall survival (OS) was 13.0, 11.9, and 13.1 months for the modified Intention-to-Treat (ITT) population and 15.1, 12.5, and 8.9 months for the per-protocol population, respectively. The clinical benefit rate was 53%, 31%, and 36% for the treatment groups.	A randomized controlled phase III study is mandatory to confirm this therapeutic concept.	[50]
Liposomal nanoparticle	CREKA-liposome-DOX (CREKA-Lipo-Dox)	For the therapy of metastatic breast tumor	Targeting at fibronectin, longer blood circulation time, and better antitumor and anti-metastasis efficacies.	The CREKA-Lipo-Dox increased almost 4-fold uptake amount of Dox compared to the PEG-Lipo-Dox group, and the distribution was well co-located with the fibronectin both in tumor vessels and deeper tumor sites.	When the treatment procedure ended, the average tumor volume of the PEG-Lipo-Dox and the CREKA-Lipo-Dox groups respectively decreased to 150 mm^3 and 60 mm^3. The mice treated with the CREKA-Lipo-Dox showed less lung metastasis nodules than other groups.	NA	[66]
Liposomal nanoparticle	Losartan loaded liposomes (LST-Lip)	For improvement of liposomal paclitaxel	LST-Lip in advance could inhibit the collagen in tumors effectively and did not affect the blood pressure, then PTX-TH-Lip could exert enhanced antitumor efficacy.	The amount of Evans Blue in tumor in LST-Lip group was 1.98 times of that in control group.	Tumor volume reduces 41.73% by TH-Lip (PTX-TH-Lip), and 14.94% by PTX-TH-Lip	NA	[74]
Solid lipid nanocarrier	diallyl disulfide-solid lipid NPs (DADS-SLN)	Targeting at RAGE receptor for improvement of apoptotic activity in TNBC	RAGE antibody-DADS-SLN shows good cytotoxicity against RAGE overexpressing MDA-MB231 cells, RAGE is a promising molecular target in TNBC.	The cellular uptake of DADS-RAGE-SLN is much higher than that of DADS SLN in MDA-MB231 cells ($P < 0.05$).	The percentage of apoptotic cells was higher in DADS-RAGE-SLN (61.8%) when compared to DADS-SLN (45%) and DADS (15%).	This study is a preliminary report of in vitro results, further RAGE-targeted delivery to improve antitumour activity need to confirm in vivo in animal models.	[72]
Solid lipid nanocarrier	Paclitaxel amino lipid-P53 mRNA NPs	To find a combination therapy for the targeting of TNBC	Higher drug loading efficiency than Abraxane® and Lipusu®, good inhibition of orthotopic TNBC cancer cell growth. due to its small size.	NA	PAL P53 mRNA NPs showed significantly stronger inhibition of tumor growth in comparison to other groups. Specifically, one mouse in PAL P53 mRNA NPs group (mouse 779) showed	NA	[447]

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Table 1 (*continued*)

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
					complete tumor elimination after treatments.		
Solid lipid nanocarrier	lipid-polymer excipients-docetaxel (LPHNPs-DTX)	For controlled and sustained delivery of DTX	Good cytotoxicity & high cellular penetration of docetaxel in breast cancer cell lines, improved pharmacokinetics & target specificity	After administration of single dose of LPHNPs DTX, a significant amount ($p < 0.001$) of DTX was detected in tumor of animals in comparison to free DTX after 24 h.	The residual tumor burden was calculated as 69.85%, 31.9% & 138.6% for free DTX, LPHNPs-DTX and normal saline (Untreated control) after 3 weeks of treatment respectively. The repeated dosing of LPHNPs-DTX showed less mortality (33.33%) than mortality seen with free DTX treatment.	NA	[37]
Solid lipid nanocarrier	Tamoxifen (Tam) loaded solid lipid nanoparticles (SLNs)	To investigate its effect on MCF7 Tam-resistant breast cancer cells (MCF7-TamR)	Tamoxifen-loaded solid lipid nanoparticles are a potential treatment against resistant breast cancer cells.	NA	exposure of R ↔ and R ↔ cells to Tam-SLNs for 72 h, led to, cell shrinkage, loss of cellular adhesion, membrane blebbing, small holes, rounding and highly condensed or fragmented chromatin, which is indicative of apoptosis, as the dose of Tam-SLNs was increased.	NA	[65]
Polymeric micelle	Cholecalciferol-PEG nano micelle-doxorubicin (PEGCCF-DOX)	Find a novel approach for treatment of TNBC	Significant reduction in tumor markers including mTOR, c-Myc & Bcl-xl, upregulated preapoptotic marker Bax, enhanced chemotherapy, & apoptosis	Cellular accumulation studies confirmed that PEGCCF was able to concentration-dependently enhance the cellular accumulation of DOX and rhodamine 123 in MDA-MB-231 cells through its P-glycoprotein (P-gp) inhibition activity.	PEGCCF-DOX exhibited 1.8-, 1.5-, and 2.9-fold enhancement in cytotoxicity of DOX in MDA-MB-231, MDA-MB-468, and MDA-MB-231DR (DOX-resistant) cell lines, respectively. PEGCCF causes enhanced chemosensitization and induces apoptosis. Substantially enhanced apoptotic activity of DOX (10-fold) in MDA-MB-231 (DR) cells confirmed apoptotic potential of PEGCCF.	NA	[67]
Polymeric micelle	Folate-PF127-F68 co-micelle-Chrysin	For enhancement of oral bioavailability and anticancer activity against human breast cancer cells	Target at overexpressed folate receptors on MCF-7 cancer cells, significant higher C_{max}, AUC0-t, enhanced anticancer activity	Significant increase in Cmax (2-fold) and AUC0-infinity (3-fold) for CH-MM when compared to A-CH suggested significant improvement in oral bioavailability of CH.	CH-MM showed 5-fold reduction in GI50 value of CH when tested in MCF-7 cells reducing GI50 value of CH significantly.	NA	[77]
Polymeric micelle	β-CD polymer (β-CDP) conjugated RNA-cleaving DZ	To find a good way to deliver RNA-cleaving DZ, and suppression of the c-Myc gene in MCF-7 cell line	The formulation inhibited the growth of SMC cells and MCF-7 cell line.	Results of Real-time-qPCR showed 1.7-fold decrease the expression of c-Myc mRNA after cell transfection of 0.8 μM inclusion complex.	The formulation inhibited the 30–80% growth of SMC cells and MCF-7 cell line. By flow cytometry analysis, apoptosis rate of cancer cells was high (45.6%), with a significant difference compared to control.	NA	[64]
Polymeric micelle	A micellar system using styrene-co-maleic acid (SMA)	To deliver hydrophobic RL71 curcumin, and to improve pharmacokinetic profile for TNBC treatment	Higher toxicity to cancer cells	NA	SMA-RL71 micelles have a cytotoxicity profile comparable to the free drug against several TNBC cell lines. Moreover, the 15% loaded micelles increased the stability of RL71 and	NA	[48]

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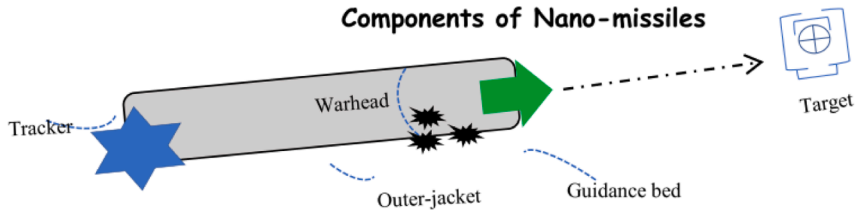
Table 1 (*continued*)

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
					demonstrated higher activity in a tumor spheroid model.		
Polymeric micelle	Transferrin-TPGS micelle	To co-delivery docetaxel (drug) and Au NC (imaging) for detection and treatment of MDA-MB-231-Luc breast cancer	Great advantages for real-time tumor imaging and inhibition of tumor growth with 71.73-fold more effective than Taxotere (®) for MDA-MB-231-luc cancers	The IC50 values demonstrated that the non-targeted and targeted micelles could be 15.31 and 71.73 folds more effective than Taxotere after 24 h treatment with the MDA-MB-231-luc cells.	The tumor size of the saline control, the AuNC control, Taxotere®, the non-targeted (DTX-AuM) and targeted (DTX-AuTfM) theranostic micelles were 373 ± 40.4 mm3, 396 ± 40.1 mm3, 288 ± 32.5 mm3, 180 ± 18.8 mm3 and 86 ± 15.7 mm3, respectively.	NA	[55]
Polymeric nanoparticle	Controlled-drug release NP Gle-Ile-Arg Leu-Arg-Gly (GIRLRG)	To capitalize on the response of tumor cells to XRT	Delayed in vivo tumor tripling time by 55 days in MDA-MB-231 and 12 days in GL261, increasing apoptosis and tumor growth delay	Paclitaxel was found in significantly greater concentrations in the targeted-nanoparticle group with the use of irradiation over all other treatment groups at one and three weeks ($P < 0.05$)	MDA-MB-231 tumor tripling time was delayed 55 days with the nanoparticle-targeted peptide with XRT ($P = 0.0001$), compared to 11–14 days by the three other XRT-treatment groups ($P < 0.05$).	NA	[39]
Polymeric nanoparticle	RGD-solid lipid NP (RGD-SLN)	To inhibit αvβ3 integrin receptor overexpressing tumor cell metastasis	It was shown to inhibit adhesion and invasion of αvβ-3 integrin receptor over-expressed in invasive TNBC tumors.	In vivo whole-body fluorescence imaging revealed that 1 % cRGD on the SLNs' surface had maximum tumor accumulation with extended tumor retention among all formulations tested in an orthotopic MDA-MB-231/EGFP breast tumor model.	RGD-SLNs were demonstrated to inhibit MDA-MB-231 cell adhesion to fibronectin and invasion through Matrigel.	NA	[56]
Polymeric nanoparticle	RGD-polymer lipid-DOX/mitomycin C (RGD-DOX-MMC-PLN)	To develop a dual-targeted nanomedicine for treatment of lung metastases of TNBC	Enhanced cytotoxicity and overall efficacy	At a concentration of 50 mg/ml anti-HER2-modified nanoparticles up-to 85% of the cells showedassociation with nanoparticles.	Compared to non-targeted DMPLN or free drugs, administration of RGD-DMPLN (10 mg/kg, iv) resulted in a 4.7-fold and 31-fold reduction in the burden of lung metastases measured by bioluminescence imaging, a 2.4-fold and 4.0-fold reduction in the lung metastasis area index, and a 35% and 57% longer median survival time, respectively.	NA	[61]
Polymeric nanoparticle	Chitosan (CS)/ polylactide (PLA) NPs of tamoxifen	To deliver tamoxifen to treat TNBC	High encapsulation, sustained released and significant cell death in breast cancer cell.	NA	NA	NA	[36]
Polymeric nanoparticle	AXT050-poly (lactic-co-glycolic acid)-poly ethyleneglycol (AXT050- PLGA-PEG)	To evaluate in vivo in mouse model of an orthotopic human xeno graft triple-negative breast cancer (MDA-MB-231)	Good targeting at integrin avb3 breast cancer cell receptor.	Using labeled AXT050 peptide, the fluorescence signal in the tumor for 10% PLGA-PEG-AXT050 (90% PEG-PLGA) NP at 24 h post injection was 14% of the total fluorescence measured in all harvested organs, a 2.2-fold increase compared to non-targeted 0% PLGA-PEG-AXT050 (100% PEG-PLGA) NP and a 3.5-fold increase from 100% PLGA-PEG-AXT050 in this head-to-head study.	In MDA-MB-231 cells, 50–100% PLGA-PEG-AXT050 NPs encapsulating 1% AXT050 reduced human cancer cell adhesion by 80–81%.	Binding affinity to integrin αvβ3 needs to be improved.	[448]
						NA	[69]

(*continued on next page*)

Table 1 (*continued*)

Nano-carrier	Products	Research Aims	Key Findings	Targeting efficacy	Anti-tumor efficacy	Problems	Ref.
Polymeric nanoparticle	Calcitriol-loaded polymeric nanoparticles	To reduce doses and/or frequency, while retaining the therapeutic activity towards cancer cells	The nanocapsules showed the sustained release of calcitriol with significant accumulation of calcitriol in the tumor cell.	The amount of IV-administered MNPs delivered to the tumors was enough in combination with the field strength to effectively ablate nearly all tumors (78%–90%, results of two independent experiments).	Successfully treated tumors were rapidly liquefied and resorbed in 1–2 days.		
DNA nano structures	DNA- glutathione-Au NCs-actinomycin (DPAu/AMD)	For simultaneous detection and killing of E. coli and Staphylococcus aureus	Challenging to escape the endosome degradation of DNA nanostructure in mammalian TNBC.	NA	NA	NA	[52]
DNA nano structures	Cetuximab -TH (THC3)- doxorubicin (DOX) drug (THDC3)	For biosensing and antibody-mediated targeted drug delivery	Preferential killing of MDA-MB-468 cancer cells; cetuximab targets at EGFR over expressing cancer cells; enhanced targeting & killing of TNBC cancer cells	MDA-MB-468 cells were observed to take up 2.5-fold more of Cy3-THC3 compared to Cy3-TH. 20%, 28%, 34%, and 47% of total cell population that was detected to take in Cy3-TH, Cy3-THC1, Cy3-THC2, and Cy3-THC3, respectively.	NA	NA	[449]
Dendrimers for siRNA delivery	Oligo- (AODNs) -poly(amidoamine) dendrimers G4PAMAM	To demonstrate reduction in tumor vascularization in TNBC xenograft mouse model	Used as a gene vector to deliver AODNs into MDA-MB-231 breast cancer cells with enhanced cellular uptake; high inhibition efficiency of tumor vascularization; protecting DNA from enzyme digestion	Compared to VEGFASODN group, G4PAMAM complex seem to be more efficient in delivering nucleic acid fragments ($P < 0.05$).	The tumor growth was not suppressed obviously until 4 weeks later ($P < 0.05$), and G4/VEGFASODN complex was superior to VEGF-ASODN only ($P < 0.05$).	If the DNA/RNA-PAMAM complex is hard to dissociate in target environment, it can weaken the motive effect of target DNA/RNA.	[40]
Dendrimers for siRNA delivery	PAMAM-siRNA complexes	To identify new therapeutic targets and develop novel treatments to improve patient outcomes	SUM1315 TNBC cells efficiently take up PAMAM-siRNA complexes, leading to significant knockdown of TWIST1 and EMT-related target genes; a valuable adjunctive therapy for TNBC patients	Cellular uptake of AlexaFluor 647-labeled siQ (acting as a surrogate for unlabeled siTwistA and siTwistB) was greater than 90% after 24 h	NA	NA	[54]
Dendrimers for siRNA delivery	G4PAMAM -GdDOTA- DL680	For imaging and drug delivery of TNBC	Effective drug uptake by and imaging of TNBC tumor using (GdDOTA) 42 G4PAMAM-DL680 dendrimeric nanocarrier.	NA	NA	NA	[60]



Delivery system	Therapeutic Drugs	Ligands Target specific	Diagnostic tracker	Currently available Target/therapeutic/Diagnostic Nano-medicine	
Liposomes	Doxorubicin Rapamycin Sorafenib Paclitaxel	Cyclic octapeptide LXY targeting integrin α-3	None	Dual drug Liposome conjugated with ligand LXY	
Micelles	RL71 (curcuminderivative) Docetaxel	None Cetuximab targeting EGFR receptor	None	Sytrene-co-meleic acid (SMA) micelle	Docetaxel entrapped Vitamin-E TPGS micelle conjugated with cetuximab
Dendrimers	Antisense Oligo-Deoxynucleotide (AODNs)	AODNs targeting VEGF receptor	- GdDOTA DL680	AODN conjugated Poly(amidoamine) dendrimer	$(GdDOTA)_{42}$-G4PAMAM-DL680 dendrimer
Polymeric NP	Paclitaxel	Gly-Ile-Arg-Leu-Arg-Gly peptide targeting Glucose regulated protein-78 (GRP78)	None	Paclitaxel encapsulated, GIRLRG conjugated polyester NP	
DNA nanostructures	Doxorubicin	Cetuximab targeting EGFR receptor	Cy3	Doxorubicin loaded DNA tetrahedral conjugated with cetuximab	Cetuximab conjugated Cy3 labeled DNA tetrahedral
Others Delivery systems: Carbon nanotubes (CNT); Nano-conjugates; Nano-diamonds (ND)					

(caption on next page)

Fig. 1. Targeted drug delivery system, including liposomes, micelles, dendrimers, polymeric NP and DNA nanostructures, could be used to deliver different chemodrugs like paclitaxel, doxorubicin and docetaxel, in addition to tracking dye Cy3, as in DNA nanostructure for targeted delivery using the target-specific ligand Cetuxima. Modified and reprinted from ref. [88].

shown in Fig. 1.

2.1. Major types of nanoparticles involved in treating TNBC

2.1.1. Polymeric nanoparticles (PNPs)

PNPs are one of the most recognized nanoparticles widely adopted as a nano drug delivery system, and are the simplest soft materials among nanomedicines [89-92]. Anti-cancer reagents could be encapsulated in the inferior or conjugated on the surface of PNPs, which could deliver and release a required dose of anti-cancer reagents to tumor sites for a long period of time. For example, a Bortezomib (BTZ)-loaded poly (ethylene glycol)-b-(poly lactic acid) (PEG-b-PLA) nanoparticle can deliver poorly water-soluble BTZ to BCSCs and non-CSCs, and exert inhibition of proliferation and initiation of apoptosis. As compared to administration of free BTZ, delivery via nanoparticles could contribute to enhanced uptake and accumulation of BTZ in adherent cells and balloon cells, prolong the cycle half-life of BTZ, and improve drug accumulation in tumor tissues. Subsequently, researchers further encapsulated doxorubicin (DOX) and all-trans retinoic acid (ATRA) in the same PEG-b-PLA nanoparticles. Experimental results indicated that as compared to administration of free drugs alone, the encapsulated ATRA and DOX in nanocarriers had slower in vitro release rates. Besides, the co-delivery of multi-drugs could better inhibit tumor growth in both in vitro and in vivo experiments as compared to a single-drug nanocarrier system [93]. Such dual drugs-loaded nanoparticles possess advantages, such as prolonged blood circulation time, improved pharmacokinetics, and enhanced tumor uptake and anti-tumor effects [94,95]. In another study, Chittasupho et al. loaded the antagonist LFC131 of CXCR4 into PLGA nanoparticles, and embedded DOX to obtain a composite nano drug LFC131-DOX-NPS [96]. Their results showed that the composite LFC131-DOX-NPS could significantly inhibit the proliferation, promote apoptosis of breast cancer cells, and retard the effect of SDF-1A on promotion of metastasis of breast cancer cells [97].

2.1.2. Liposomes and micelles

Liposomes are colloidal nanocarriers composed of amphiphilic phospholipid bilayers, which could load with both hydrophilic and hydrophobic drugs. Liposomes have good biocompatibility, are easy to have surface-modification, and have long circulation time in blood, which is an ideal nano carrier for anti-BCSCs treatment [98-101]. Onivyde® is an irinotecan nano-liposome approved by the FDA of USA in 2015, not a common drug for breast cancer. However, the disease control rate of Onivyde® was reported to be 45.5% in a phase I study of advanced refractory solid tumors including breast cancer [102]. Conjugated hyaluronic acid-Gemcitabine (GEM)-loaded liposomes were used to target at the CD44 + proteins which are expressed on BCSCs. Experimental results showed that the hyaluronic acid-Gemcitabine (GEM)-loaded liposomes could enhance the anti-tumor cytotoxicity, anti-migration and anti-colony forming abilities of GEM. The liposome nanocarrier could also improve the stability of GEM in blood, and significantly reduce the systemic toxicity of GEM to normal healthy cells via targeted delivery of GEM to tumor sites [103].

Polymeric micelles are derived from self-assembled amphiphilic block copolymers, which contain both hydrophilic and hydrophobic components, providing functionalities for surface modification to introduce tumor targeting ability. Polymeric micelles are popular drug nanocarriers for anti-cancer treatment due to their uniformity, small sizes and prolonged blood circulation time [104,105]. In previous studies, PTX-loaded and anti-CD44 + antibody functionalized PLGA-co-PEG polymeric micelles were used to treat breast cancer. Experimental results showed that the encapsulation of PTX into PLGA-co-PEG micelles could enhance its cytotoxicity towards BCSCs as compared to administration of free PTX without nanocarriers [106,107].

Moreover, belonging to the self-assembled micellar nanoarchitecture of heavy-atom-modulated supramolecules, the multi-iodinated boron dipyrromethene micelles with tunable photoconversion and efficient cytoplasmic translocation were used for potent suppression against TNBC. Specifically, Tetra-iodinated boron dipyrromethene micelles (4-IBMs) showed an enhanced anti-tumor efficiency by inducing over-expression considerable apoptotic proteins, and potently suppressed orthotopic and subcutaneous TNBC models. Comparing to surgical resection and chemotherapy, 4-IBMs showed better efficacy of inhibiting metastasis and recurrence by inducing death of immunogenic cell, production of metastasis-relevant proteins, and facilitating the transformation from anti-inflammatory M2 macrophages to tumoricidal M1 phenotype [108].

2.1.3. Metal oxide nanoparticles in TNBC targeted therapy

Among various metal oxides NPs, iron oxide NPs (IONPs) have greatly attracted scientists' attention because of their unique characters, such as superparamagnetic (SPM) property (SPM IONPs or SPIONs), low toxicity, large surface area, biocompatibility, easy bonding to many natural biomolecules via their grafted ligands, etc [109-115]. Among various iron oxide nanomaterials, magnetite and maghemite are the top two of the most promising and popular nanomaterials for biomedical applications [116,117]. Currently, main topic of important progresses has been relying on such nanomagnets with adjustable architecture since modular designs make it possible for SPIONs to exhibit multi-functions simultaneously, such as delivery of anti-cancer drugs with real-time monitoring and imaging ability. Thanks to the combination of nanometer scale with magnetism properties, magnetic NPs have potential to serve as an attractive material for biomedical applications [118,119]. Based on their small controllable size and shape, magnetic NPs are comparable to biological entities as well as to easily interact with those entities [120]. Without a doubt, the sizes of magnetic NPs can be

prepared to be close to those of proteins (5–50 nm), cells (10–100 μm), and viruses (20–450 nm), depending on different ways of preparations [121].

Although magnetic NPs seem to be very useful for many in vivo applications, they still suffer from two primary drawbacks: removal by macrophages and an uneven bio-distribution. To resolve these two shortcomings, researchers have devoted efforts on the design and surface-functionalization of magnetic NP to render them stable and stealthy (or non-interaction) in physiological media. According to some previous studies, magnetic NPs can be surface-functionalized with a plenty of functional moieties, including some biocompatible molecules like hydrophilic molecules, silica layers, polymers, and so on [122]. Schematic representation of coating of corona or ligand layers on iron oxide nanocrystals was shown in Fig. 2.

A lot of scientific efforts were dedicated to the surface-modification of magnetic NPs aiming for improvement of targeted theranostic efficacies. Various tumor cell-specific ligands were used to decorate the magnetic nanoparticles; for example, anti-human epidermal growth factor receptor-2 (a single-chain antibody fragments) was used for targeting at breast cancer cells [123], hepatocellular carcinoma [124], and squamous cell carcinoma [125,126]. Therefore, syntheses of SPIONs and adjustments of their chemical and physical characters have been achieved, which paves a novel way for a safer and more efficient use in treating various cancers.

Moreover, by enclosing manganese-protoporphyrin (MnP) into folate-liposomes, a multifunctional nanosonosensitizer system (FA-MnPs) was designed. Facilitated by depth-responsed sonodynamic therapy, FA-MnPs exhibited promising anti-tumor efficacy in both superficial and deep tumors in the TNBC mice model, and it also induced the anti-tumor immune by re-polarizing M2 to M1 macrophages, and elicit immunogenic cell death [127,128]. Additionally, composed of hyaluronic acid (HA) / copper ion (Cu (II))-chelated dextran-aldehyde (DA)-quercetin (Q), the CuQDA/IO@HA exhibited specific cytotoxicity by precisely targeting BRCA-mutant TNBC

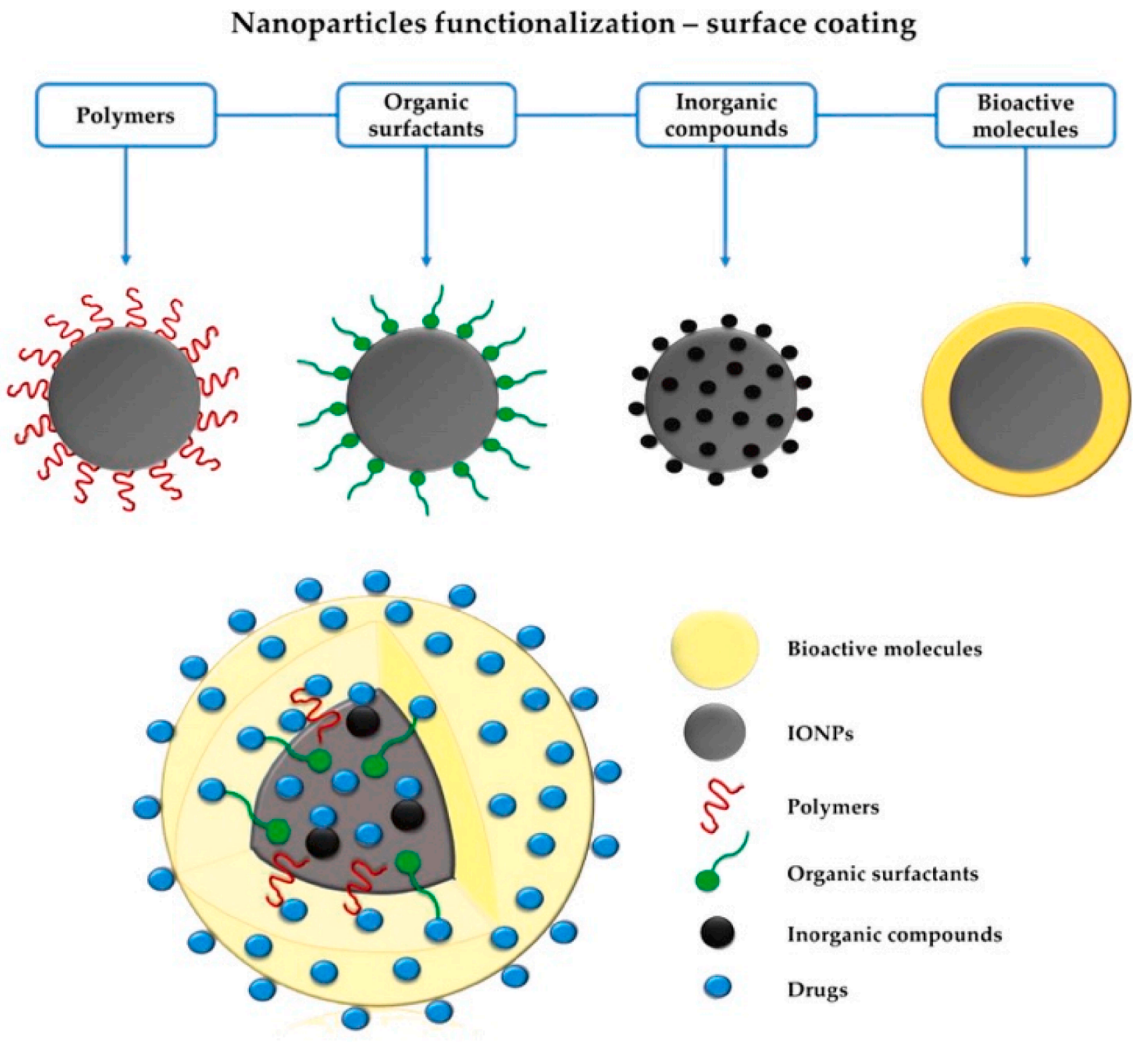


Fig. 2. Coating corona or ligand layers on iron oxide nanoparticles. (Top): Schematic representation of the main strategies used to modify the surface of iron oxide NPs (SPIONs). (Bottom): Schematic representation of complex structure based on the SPIONs surface functionalization, including drug loading. Modified and reprinted from ref. [135]. Reproduction with permission from 2018 by the authors. Licensee MDPI, open access.

Table 2
Ligands of nano drug delivery systems for targeted TNBC therapy.

Ligands	Biochemical essence	Characteristics	Key findings	Targeting efficacy	Anti-Tumor efficacy	Problems	Ref.
Aptamers	Short oligonucleotides stretch of single-stranded DNA/RNA	It can specifically bind the target molecule with high affinity and strength.	1) A newly identified LXL-1 aptamer can specifically target at surface membrane proteins on TNBC tumor.	LXL-1-A was highly specific to the corresponding tumor tissue and displayed 76% detection rate against breast cancer tissue with metastasis in regional lymph nodes.	NA	NA	[450]
			2) A platelet derived growth factor (PDGF) receptor was found to over-express in TNBC cell line. MCF7 and MDA-MB-415 breast cancer cells are known to overexpress the mammaglobin A2 and mammaglobin B1.	NA	NA	NA	[451]
			3) MAMA2 and MAMB1 aptamers could be used to detect metastatic breast cancer via using highly sensitive terahertz (THz) chemical microscopy (TCM) upon THz radiation.	NA	NA	NA	[452]
Peptides	Cell penetrating ligands as diagnostic/imaging sequences	1) Peptides are low M_w ligands with abilities to target at intracellular molecules with high specificity. 2) These target binding peptides can fuse to bacterial coat proteins, be expressed using genetic engineering, and screened by phage display library technique.	1) CK3 peptide (Cys-Leu-Lys-Ala-Asp-Lys-Ala Lys-Cys) was found able to bind to NRP-1 *trans*-membrane protein (neuropilin-1) by NIR fluorescence imaging technique.	NA	NA	There are still no ideal NRP-1-targeting peptides for direct tumor molecular imaging, as the NRP-1-targeting peptides containing exposed C-end rule motifs were not good for tumor imaging because they tended to penetrate into the first encountered organs in vivo.	[453]
			2) Activable cell-penetrating peptide (ACPPs) can target at the matrix metalloproteinase (MMP)-2 enzymes. Covalent linkage of ACPPs to cyclic-RGD peptide can enhance its in vivo uptake and contrast imaging by TNBC tumor tissues.	In vivo, dual-targeted ACPP treatment resulted in tumor contrast of 7.8 ± 1.6, a 10-fold higher tumor fluorescence compared with the negative control peptide, and increased probe penetration into the core of MDA-MB-231 tumors.	Treatment with cyclic-RGD-PLGC(Me)AG-MMAE-ACPP resulted in complete tumor regression in one quarter of MDA-MB-231 tumor-bearing mice, compared with no survival in the control groups.	The therapy experiments do not have controls to validate the proposed mechanism and primarily compare animal data for prodrug-MMAE with mice that are not receiving treatment.	[454]
			3) A pH-responsive MRI nano-probe, pHLIP-conjugated MRI-NP, can specifically target at and accumulate in TNBC cells in response to the low local pH inside cancer cells.	NA	NA	NA	[143]
Antibodies	Y-shaped protein with two epitopes	It has high selectivity and affinity toward its receptor, and is the best targeting ligand.	1) Anti-TF antibody labeled with copper-64 (anti-TF-antibo dy-64Cu) was used as PET imaging contrast agents in in-vitro TNBC model.	Serial PET imaging revealed rapid and persistent tumor uptake of (64)Cu-NOTA-ALT-836-Fab (5.1 ± 0.5 %ID/g at 24 h post-injection; n = 4) and high tumor/muscle ratio (7.0	NA	The limitation of Fab is lower binding avidity compared to the full antibody, since Fab has only one antigen-binding site. For example, the uptake in positive tumor (MDA-MB-231) was only	[455]

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Table 2 (*continued*)

Ligands	Biochemical essence	Characteristics	Key findings	Targeting efficacy	Anti-Tumor efficacy	Problems	Ref.
				± 1.2 at 24 h post-injection; n = 4), several-fold higher than that of the blocking group and tumor models that do not express significant level of TF, which was confirmed by biodistribution studies.		5.1 %ID/g in this study, which is ~ 3-fold higher than negative tumor (MDA-MB-435) and ~ 2.5-fold higher than blood. This might restrict the future application of Fabs in tumor imaging. If high absolute tumor uptake rather than high tumor contrast is required, Fab may not be very suitable.	
			2) NIR fluorophore and Indium-111 (111In) labelled uPAR antibodies were used as optical and SPECT imaging regents, respectively.	NA	NA	NA	[456]
			3) TNBC tumor could be well visualized using Iodine-124 (^{124}I) labeled B-B4 antibody (targeting at syndecan-1; CD138 antigen) and has good treatment response to I-131 (^{131}I) radio-labelled B-B4 antibody.	The tumor uptake of 125I-B-B4 peaked at 14% injected dose (ID) per gram at 24 h and was higher than that of the isotype-matched control mAb (5% ID per gram at 24 h). Immuno-PET performed with 124I-B-B4 on tumor-bearing mice confirmed the specificity of B-B4 uptake and its retention within the tumor.	All mice treated with RIT (n = 8) as a single treatment at the MTD experienced a partial (n = 3) or complete (n = 5) response, with three of them remaining tumor-free 95 days after treatment.	(1) Low number of antigen copies expressed by the triple-negative MDA-MB-468 cells low number of antigen copies expressed by the triple-negative MDA-MB-468 cell. Further studies are needed using a residual-izing agent such as that described by Goldenberg and co-workers or of radioactive metals such as lutetium-177 or yttrium-90 to increase the efficiency of RIT.	[457]
Hyaluronic-Paclitaxel nanoconjugates	Hyaluronic acid (HA)-Paclitaxel (PTX)	Hyaluronic acid (HA) has high affinity toward CD44 receptor. An ultra-small (~5 kDa) HA-PTX nanoconjugate are uptaken, via CD44 receptor-mediated endocytosis, by metastatic breast cancer (MDA-MB-231Br) cells.	1) E-selectin binding peptide modified micelle could assemble with hyaluronic acid-paclitaxel conjugate and exert good inhibition of breast cancer metastasis in a murine model.	In accordance with the fluorescence microscopy, Esbp-HA-PTX/C6 micelles demonstrated much higher cellular uptake efficiency, about 6.1-fold more than that of HA-PTX/C6 micelles in TNF-α activated HUVEC after quantitative assay. In semiquantitative analyses, Esbp-HA-PTX/DiR micelles exhibited approximately 2.2-fold higher intensity at tumor tissue than HA-PTX/DiR micelles.	(1) Esbp-HA-PTX/PTX micelles inhibited tumors most effectively (70.63%), followed by HA-PTX/PTX micelles (55.32%) and PTX solu-tion (50.64%). For PTX solution, HA-PTX/PTX micelles and Esbp-HA-PTX/PTX mi-celles groups, the number of tumor nodules in the lungs was reduced by 54.3%, 56.8% and 92.6%, respectively,	NA	[458]

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Table 2 (*continued*)

Ligands	Biochemical essence	Characteristics	Key findings	Targeting efficacy	Anti-Tumor efficacy	Problems	Ref.
					compared with saline control.		
			2) A HA-PTX-PLGA formulation could exert a sustained drug release and enhance PTX cytotoxicity to MDA-MB-231 cells as compared to cells incubated with the non-HA coated nanoparticles.	To investigate the cellular uptake of HA-coated and non-coated PLGA NPs, coumarin-6 loaded NPs were synthesised and the coumarin-6 encapsulation efficiency of these formulations were measured and were found to be (97.50 ± 1.98 for HA-PLGA NPs and 98.34 ± 0.66 for PLGA NPS.	NA	NA	[459]
			3) A small molecular weight HA-paclitaxel nanoconjugate can improve standard chemotherapeutic drug efficacy in a preclinical model of brain metastases of breast cancer.	NA	The animals administered with HA-paclitaxel nanoconjugate had significantly longer overall survival compared with the control and the paclitaxel-treated group ($P < 0.05$).	NA	[460]
Peptides-PLGA-b-PEG polymers	Peptide conjugated onto PLGA-b-PEG polymers for delivery of antisense miRNA	PEG-b-PLA micelles are a first-generation platform for systemic multi-delivery of poorly water-soluble anticancer agents.	poly (lactic-co-glycolic acid)-b-PEG polymers conjugated with Urokinase plasminogen activator receptor (uPAR) targeting peptide could carry two antisense miRNA simultaneously and exert good tumor inhibition effects.	The results demonstrate ~10-fold decrease in metastatic tumor nodules in animals injected with cells pretreated with NPs coloaded with antisense-miR-21 and antisense-miR-10b combination, compared to animals injected with cells pretreated with control NPs.	Compared the control NPs treated mice, cramble peptide conjugated NPs treated mice had a 40% reduction in tumor growth.	NA	[461]

cells in vitro. When combining with magnetic navigation, this treatment can trigger DNA damage and poly (ADP-ribose) polymerase (PARP) inhibition, and subsequently showed the excellent biocompatibility and efficacy by extending the median survival from 34 to 61 days in BRCA-mutant xenograft mice model with no obvious adverse effect in healthy organs [129].

Several studies have proved the role of Au nanoparticles (Au NPs) in the modulation of TNBC therapeutics through the inhibition of cell proliferation, progression, and metastasis [130-132]. Cu-tetra(4-carboxyphenyl) porphyrin chloride (Fe (III)) (Cu-TCPP(Fe)) metal organic framework (MOF)-based nanosheets were incorporated with Au nanoparticles (Au NPs) via in situ nucleation and loaded with RSL3 via π-π stacking, which were finally modified with polyethylene glycol (PEG) and iRGD for tumor-targeted drug delivery. Specifically, the Au NPs, which give evidence of glucose oxidase-like activities, can lead to the simultaneous inhibition of the GPX4/GSH and FSP1/CoQ10H2 pathways and cooperate with the GPX4-deactivating function of RSL3 to induce pronounced ferroptotic damage. Otherwise, coordination compound-based zinc oxide (ZnO) NPs show great promise for a future potential use in the therapy of TNBC [133,134].

2.2. Types of ligands on nanoparticles for targeting at TNBC

Ligands are the small stretch of nucleotides, oligopeptides, antibodies or small molecules themselves, which bind specifically to its receptor via ligand-receptor interactions. Ligands like Arg-Gly-Asp (RGD) peptides, antibodies, aptamers, and other small molecules (such as folic acid, BSA, etc.), are well-known ligands commonly used for targeted or probe-based diagnostic in cancer nanomedicines. The most commonly used ligands for surface-modification of nanoparticle drug delivery systems for targeting at TNBC were listed in Table 2 [136-148].

2.2.1. Arg-Gly-Asp (RGD) peptide ligands

The RGD peptide ligands have become widely used for targeting at several cancers, including TNBC. Portela et al. reported a highly sensitive analysis of c(RGDfC) by surface enhanced Raman spectroscopy (SERS) using a nanogap antennas in an aqueous environment. Good agreement between characteristic peaks of the SERS and the Raman spectra of bulk c(RGDfC) with its peptide's constituents was observed. The observed blinking of the SERS spectra and synchronization of intensity fluctuations suggest that the SERS spectrum acquired from a nanogap antennas was dominated by the spectrum of single to a few molecules [149]. Kakinoki et al. conducted the mobile RGDS. Cell culture substrates were coated with ABA-type block copolymers composed of poly (2-methacryloyloxyethyl phosphorylcholine-co-n-butyl methacrylate) segments (A) and a polyrotaxane (PRX) unit with RGDS bound to α-cyclodextrin (B). Adhesion, morphological changes and actin filament formation of human umbilical vein endothelial cells were reduced in a large extent on the nanoparticle surfaces containing mobile PRX-RGDS, as compared to the immobile RGDS surfaces constructed from random copolymers with RGDS side groups (Prop-andom-RGDS) [150].

Mesoporous silica nanoparticles (MPSNPs) were used as nanocarriers to deliver anti-cancer drugs, due to its inorganic structural nature and excellent biocompatibility features, for treatment of TNBC [151-153]. Aquib et al. have made an excellent review on MPSNPs and its clinical applications. According to this review, both breast cancer cells and angiogenic endothelial cells are over-expressed with endothelial αvβ3 integrins which are the targets of RGD peptides [154]. Various studies have reported procedures for the conjugation of MPSNPs with a variety of linear and cyclic RGD peptides having free primary amine group of lysine amino acid or free thiol groups of cysteine amino acid [155]. Surface conjugation with RGD peptides will endow MPSNPs to have abilities to target at tumor sites where the endothelial αvβ3 integrins are over-expressed. A study reported the covalent conjugation of MPSNPs with a cyclic RGDFK and a linear peptide having a sequence of seven continuous lysine residues (K7RGD). These systems were used for the assessment of the RGD conformation in an uptake by mammalian cells [156]. In comparison with MPSNPs without functionalization, the uptake of cyclic RGD-grafted MPSNPs by HeLa cells was 3.6 times higher, while its internalization was approximately two times higher in MCF-7 cells. Conversely, the uptake of linear K7RGD peptides by HeLa cells was approximately three times higher, while its internalization was 1.1 times higher in MCF-7 cells, as compared to MPSNPs without surface modification with RGD peptides. Similarly, in Huo et al.'s work, the researchers have explored the application of Arg-Gly-Asp (RGD) peptide for receptor selective targeting of the MSNPs with higher affinity, specificity and selectivity to the integrin avb3 receptors [157]. Surface grafting of the RGD-MSNPs conjugates with additional disulfide S-S bond will endue the nanocarriers to become redox responsive in tumor micro-environments, where reducing GSH level is high [158]. According to Barkat et al.'s review, despite the proven efficacy of MSNPs in majority of the preclinical studies, their applications in real world clinical treatments of tumors still require much more research efforts [159].

2.2.2. Antibodies as targeting ligands

Due to the abilities of selective targeting and controlled drug release, nanomedicines might provide a new hope for the treatment of TNBC. Antibodies and their fragments attack a lot of attention to serve as surface ligands to endow nanomedicines to be able to selectively bind to specific receptors that are overexpressed on TNBC cells. Therefore, antibody-modified nanoparticles hold great promise to achieve targeted drug delivery, enhanced therapeutic efficacy and reduced adverse effects. Several methods have been described to immobilize antibodies on the surface of nanoparticles. However, selecting the most appropriate antibody for each application is still challenging, but is also imperative to preserve antigen binding ability and to yield stable antibody-conjugated nanoparticles. Nanoparticles could be functionalized with antibodies or antibody fragments by adsorption, covalent binding or using adopter molecules. When immobilizing antibodies, conjugation should ensure a desired amount of these biomolecules (density) per nanoparticle and a correct orientation [10]. The higher the density of antibody molecules, the lower the spatial accessibility of the antigen due to steric hindrance among antibodies in proximity [160]. Moreover, the coupling method must yield a stable bond and

Table 3
Strategies for the development of antibody-nanoparticle conjugates: advantages, disadvantages, applications and mechanisms for cancer treatment.

Strategy	Explanation	Advantages	Disadvantages	Mechanism features	Ref.
Adsorption	A non-covalent immobilization strategy via physical adsorption and ionic binding.	1) Simple and less time-consuming; 2) No demand for modification of Ab or activation of NP; 3) Oriented binding (ionic adsorption)	1) Reversible binding; 2) Lack of stability; 3) Use of Ab at high concentrations; 4) Hydrophobic interactions result in poor reproducibility and possible Ab denaturation; 5) Electrostatic interactions depend on pH and ionic strength; 6) Competitive displacement of Ab by serum proteins.	1) Antibodies adsorbed to the nanoparticle surface by hydrophobic interactions (physical adsorption) or electrostatic interactions (ionic adsorption). Schematic representation of the four possible Ab orientations onto the surface of nanoparticles. 2) Works well at a pH higher or lower than the isoelectric point of the Ab to promote ionic adsorption, as well as avoid changes of pH and/or ionic strength during the assay that may be responsible for the removal of the adsorbed molecules.	[462,463]
Carbodiimide chemistry	Surface ligand and nanoparticle were chemically linked via coupling between amine groups in ligand and carboxylic acid moiety on nanoparticles.	No demand for modification of Ab	1) Lack of control over Ab orientation (random binding) 2) Antigen binding ability may decrease due to steric hindrance of the antigen-recognition site 3) Activation of NP is required 4) Usually performed in a two-step reaction to avoid undesirable cross-linking	1) During bioconjugation with the carboxylic moiety, 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide (EDC), reacts with the carboxylic acid groups on the surface of nanoparticles and an unstable amine-reactive intermediate (O-acylisourea ester). 2) If it fails to react with an amine in an aqueous solution, the O-acylisourea ester will hydrolyze and regenerate the carboxylic acid group. Then, to stabilize this intermediate, NHS or sulfo-NHS converts this amine-reactive ester into a semi-stable active ester. Both NHS and sulfo-NHS esters are reactive towards amine groups on the antibody, releasing the NHS/sulfo-NHS group and creating stable amide linkages. 3) At pH 4.5, the most efficient immobilization was obtained on carboxyl surfaces activated by EDC/sulfo-NHS, followed by EDC/NHS and then EDC with the least efficient coupling response.	[464,465]
Maleimide chemistry	At pH values between 6.5 and 7.5, a stable thioether linkage was formed via alkylation sulfhydryl reaction on the double bond of maleimide.	Oriented binding	1) Associated to a multi-step protocol 2) Reduction or thiolation of Ab is typically needed 3) Non-selectivity of maleimide toward cysteine allows exchange reactions with thiols in serum	1) Site-selective Ab conjugation based on disulfide bridging using next generation maleimides (NGM). Reduction of Ab with tris (2-carboxyethyl) phosphine (TCEP), followed by disulfide bond rebridging using the DBM-C2 reagent (dibromomaleimide, DBM, with a C-2 linker) in borate buffered s aline (BBS) solution. Generation of the DBM-C2 reagent in a two-step process: i) treatment of dibromomaleic acid with glycine at reflux in acetic acid to induce ring closure and formation of DBM-C2-acid; and ii) coupling of DBM-C2-acid with a functional amine, using N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) in acetonitrile. 2) 1C1 Fab-NP conjugates prepared with PEG chains of 7–23 units present higher conjugation efficiencies as comparison to those with a 4-unit spacer arm (PEG4).	[466,467]
"Click" chemistry	Chemical reactions with orthogonality, and site-specificity.	1) Site-specific bio-conjugation 2) High reaction rates (iEDDA and CuAAC)	1) Cu(I)-induced toxicity restricts applications of CuAAC 2) OCT-based derivatives	1) "Click" reactions include: i) *cyclo*-addition reactions, namely 1,3-dipolar (e.g., Cu(I)-catalyzed[3 + 2] azide-alkyne cycloaddition (CuAAC)	[468]

(*continued on next page*)

Table 3 (*continued*)

Strategy	Explanation	Advantages	Disadvantages	Mechanism features	Ref.
			(SPAAC) are more expensive than their alkyne counterparts 3) Moderate second order reaction rate constants (SPAAC)	reaction and strain-promoted[3 + 2] azide-alkyne cycloaddition (SPAAC) reaction) and hetero Diels-Alder (e.g., inverse electron demand[4 + 2] Diels-Alder (iEDDA) reaction); ii) Staudinger ligation; and iii) "Thiol-ene" reaction. 2) A novel strategy that combines "click chemistry" and assisted targeting of immune cells to deliver doxorubicin (DOX)-loaded NPs into poorly vascularized regions of the tumor, for breast cancer treatment. CD11b antibodies (αCD11b) were modified with *trans*-cyclooctene (TCO) using a TCO-PEG4-NHS linker, while DOX-loaded mesoporous silica NPs (DOX-MSN) were functionalized with Tz to allow conjugation through iEDDA reaction.	
Biotin-avidin	Coupling via biotin-avidin interaction, which is the strongest non-covalent interaction between a protein and a ligand.	1) Mostly oriented (Fc-specific biotinylation); 2) Highly stable and resistant under extreme conditions	1) Modification of Ab or NP (biotinylation) is required 2) Difficult to control Ab: NP stoichiometry 3) Possible immunogenicity (avidin and streptavidin) 4) Expensive technique	1) Affinity-based system rely on the strong binding between a small molecule (biotin) and a biotin-binding protein. 2) Coupling using biotin-avidin interaction requires chemical modification of the antibody with biotin (biotinylation) and functionalization of the nanoparticle with avidin or its derivatives. 3) A site-specific biotinylation at the Fc region ensures an oriented immobilization of the Ab via: i) free sulfhydryl groups, obtained after reduction of disulfide bonds, that react with maleimide-biotin; or ii) polysaccharide moieties, through oxidation of carbohydrate hydroxyls to reactive aldehydes towards hydrazide–biotin, yielding an hydrazone bond.	[469,470]

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Abbreviations: Ab - Antibody; CA - Carbonic anhydrase; CD - Cluster of differentiation; CEA - Carcinoembryonic antigen; CIC - Cancer-initiating cells; CuAAC - Copper (I)-catalyzed azide-alkyne cycloaddition; DR - Death receptor; EGFR - Epidermal growth factor receptor; EphA - Ephrin type-A receptor; Fab - Antigen-binding fragment; Fc - Fragment crystallizable; GD2 - Disialoganglioside; GPC - Glypican; hAb - Half-antibody; HER - Human epidermal growth factor receptor; iEDDA - Inverse electron demand Diels-Alder; mAb - Monoclonal antibody; Nb - Nanobody; NP - Nanoparticle; NRP - Neuropilin; OCT - Cyclooctyne; SCC - Squamous cell carcinoma; scFv - Single-chain variable fragment; SPAAC - Strain-promoted azide-alkyne cycloaddition; TEM - Tumor endothelial marker; TF - Tissue factor; TfR - Transferrin receptor; Trop2 - Trophoblast cell-surface antigen 2; VEGF - Vascular endothelial growth factor; VEGFR - Vascular endothelial growth factor receptor.

guarantee that the biological activity of the antibody is reserved [10,161]. Some commonly used methods for covalent bonding of antibodies onto nanoparticles were listed in Table 3**.** Antibodies could also be grafted onto the surface of nanoparticles via noncovalent interactions based on biotin-avidin system, which is presented in Fig. 3.

2.3. Nanoparticles with ligands responsive to tumor microenvironment

According to prior research, cancer cells proliferate and live, including secreted active factors, etc. in a particular area of cancer microenvironments in cancer tissues. The interaction of cancer cells with the microenvironment is like a relationship between the seeds and soil. A tumor microenvironment could promote cancer formation, proliferation and metastasis, induce angiogenesis, inhibit immune response, breed cancer stem cells, and stimulate over-expression of multidrug resistance (MDR) genes, leading to drug tolerance. Considering the support and promotional effect of the TNBC microenvironment to cancer cells and cancer tissues, researchers have tried to change the "soil" microenvironment to inhibit tumor growth and achieve effective cancer treatment. The TNBC microenvironment has some characteristics different from normal cell physiological environments, such as low pH value, low oxygen level, high temperature, high concentration of glutathione (GSH) and high expression enzyme, etc.[162,163]. Therefore, with the

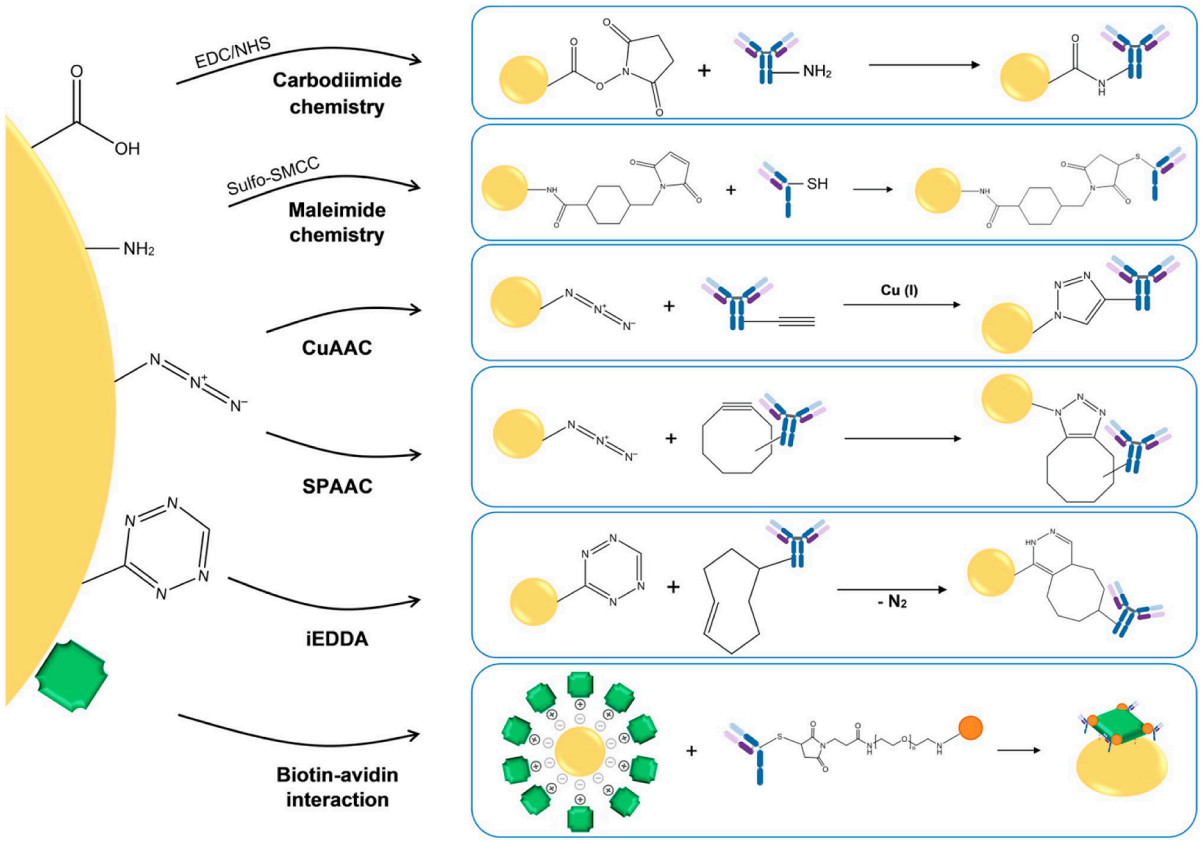

Fig. 3. Covalent coupling and non-covalent interaction of antibodies and nanoparticles. Chemical bond formation for the covalent coupling methods could be achieved by the use of coupling reagents, such as carbodiimide, maleimide, and "click" chemistry reagent. The non-covalent conjugation between antibodies and nanoparticles could be achieved by the use of biotin-avidin interaction. Modified and reprinted from ref. [10]. Reproduction with permission from Royal Society of Chemistry. Copyright © 2020, Royal Society of Chemistry.

above-mentioned characteristics of TNBC microenvironment as stimulation factors, it is possible to significantly improve the therapeutic effect of anti-cancer drugs based on the design of tumor microenvironment-responsive nano drug delivery systems.

2.3.1. Temperature responsive nano drug delivery systems

In general, temperature-responsive nanomaterials are composed of both hydrophilic and hydrophobic moieties in their molecular structures. The molecules as a whole may show hydrophilicity and volume swelling at low temperatures since there is a strong intermolecular hydrogen bonding interactions between the hydrophilic groups and the water solvent molecules. Upon increasing the temperature, the hydrogen bonds will be weakened or destroyed gradually, and the hydrophilicity of the molecule will also be weakened gradually, resulting in the change of the whole molecule from hydrophilicity to hydrophobicity (via formation of intramolecular hydrogen bonding), as well as shrinkage of the volume. Hence, the structure, molecular size, and physicochemical properties of the temperature-responsive nano drug delivery system will change correspondingly with changes of the environmental temperature. Consequently, the payload drugs release rate will also change or increase at a higher temperature tumor microenvironment. In this regard, temperature can be used to control the drug release rate. According to prior research, the local temperatures of many tumor tissues are in general slightly higher than that of normal tissues by 5 ~ 10 °C. There may be an accelerated blood flow and higher permeability in the tumor blood vessels when the local temperature is high. Accordingly, diffusive release of the payload drugs becomes more rapidly in local tumor tissues with high temperatures. In such a way, temperature-responsive nano drug delivery systems could be used to selectively release payload drugs at tumor sites for killing cancer cells. Temperature responsive nanocarriers (e.g., temperature responsive micelles, liposomes and polymeric nanoparticles, etc.) have attracted much attention for controlled delivery ad release of anti-cancer drugs [164].

Poly (N-isopropylacrylamide) (PNIPAM) is one of the temperature-responsive materials attracting a great attention [165,166]. It displays a low critical solution temperature (LCST) of about 32 °C, close to physiological temperatures [167]. When the ambient temperature is higher than its LCST, the PNIPAM shows strong hydrophobicity. Decreasing the temperature to be below the LCST will change PNIPAM from hydrophobic to strongly hydrophilic [168]. Through reversible addition-fragmentation chain transfer (RAFT) polymerization and free radical polymerization, a NPAM oligomer (NOS) with low molecular weight could be synthesized, which was further used for preparation of temperature-responsive liposomes, with better controlled and improved drug release property [169].

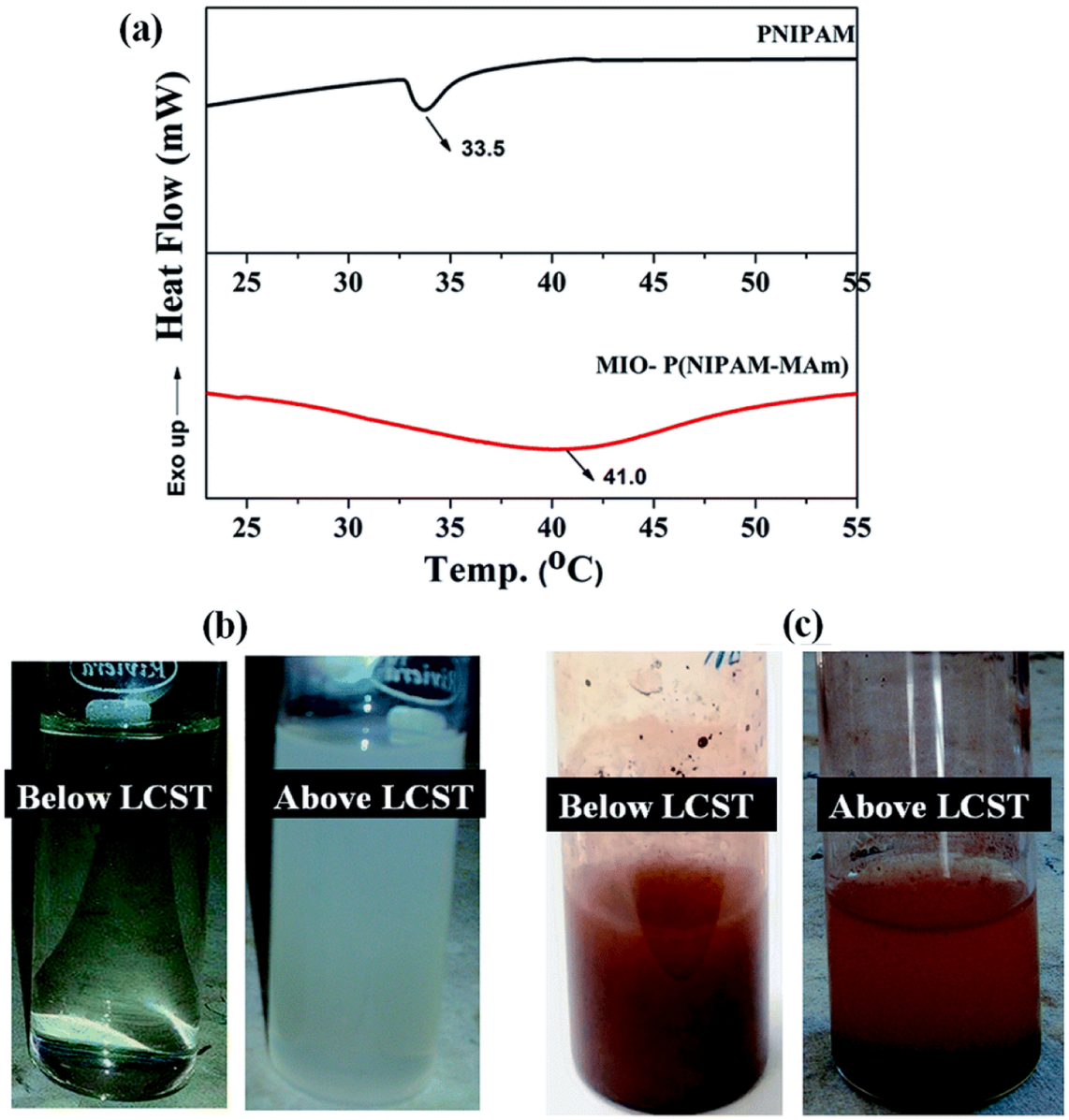

Fig. 4. Differential scanning calorimeter (DSC) thermograms of aqueous solutions of (a) PNIPAM and MIO-P(NIPAM-MAm) nanocomposites. Digital images of aqueous dispersion of (b) PNIPAM and (c) MIO-P(NIPAM-MAm) nanocomposite below and above LCST, respectively. Modified and reprinted from ref. [171]. Reproduction with permission from Royal Society of Chemistry. Copyright © 2017, Royal Society of Chemistry. LCST represents low critical solution temperature.

Star-shaped porphyrin-cored poly(L-lactide)-block-poly(N-isopropylacrylamide) (SPPLA-PNIPAM) block copolymers were successfully synthesized via the ring-opening polymerization (ROP) and RAFT polymerization[170], and were shown to be temperature responsive. Upon decreasing the PNIPAM block monomer chain length, the morphology of SPPLA-PNIPAM copolymer in an aqueous solution was changed from spherical micelle to vesicle through wormlike micelle transition, with the corresponding LCSTs being 37.9, 37.2 and 35.9 ℃, respectively. The SPPLA-PNIPAM block copolymers were shown to have good application prospect in tumor treatment. Meanwhile, the temperature responsive PNIPAM was introduced to the surface of mesoporous magnetic nanoparticles by Asghar et al. for combined delivery of both hydrophilic doxorubicin (DOX) and hydrophobic curcumin (CUR) [171]. Their results showed that the in vitro release of the two payload drugs behaves in a temperature dependent manner with a slow drug release rate below LCST and sustained drug release above LCST. In vitro cellular experiments showed that the nanocarrier alone had no cytotoxicity, and the anti-cancer activity was significantly improved after drug loading. Different LCSTs of pure PNIPAM and MIO-P (NIPAM-MAm) nanocomposites were estimated by DSC (Fig. 4).

In addition to PNIPAM, other nanocarrier materials possessing temperature-responsive property also play an important role in the

treatment of tumors. For example, in the research by Sudhakar et al., a series of temperature-responsive nanomaterials were prepared by polymerization of N-vinylcaprolactam (NVCL). And then CUR was loaded as an anti-cancer drug. Drug release experiments showed that PNVCL had practical potential to be used a nanocarrier for delivery of anti-cancer drugs [172,173]. Furthermore, Enaam et al. introduced temperature responsive poly(ethylene glycol) (PEG) polymer P(MEO2MA-co-OEGMA) onto the surface of Fe_3O_4 magnetic nanoparticles, which were used to deliver Adriamycin (an anti-cancer model drug) [174]. It was found that the composite magnetic nanoparticles could response to the local temperature changes and release anti-cancer drugs gradually at physiological temperatures. Meanwhile, temperature responsive nanogel polymers were prepared by Seo et al. by grafting poly(L-lactide) onto pullulan [175]. The authors also discovered that the release of DOX model drug could be controlled by changing medium temperature, which was expected to be a sustained drug delivery/release system for tumor treatment. Considering its good biocompatibility, low toxicity, and the adjustability of thermo-sensitivity for controlling the payload drug release rate, temperature responsive nano drug delivery systems have a very important prospect in applications for the treatment of tumors. However, it shall be noted that there are some limitations in the temperature responsive nano drug delivery systems, such as high cost, poor thermo-sensitivity and unclear bio-degradation mechanisms, which should be taken into account in the follow-up research.

2.3.2. pH-responsive nano drug delivery systems

The pH value of normal tissues and blood is about 7.4, while the intercellular substance of tumor tissues and the interior of tumor cells are weakly acidic. The pH value in endosome of tumor cells can be as low as 5.5, and that in lysosomal body is about 5.0. On the basis of the significant decrease of pH values in tumor tissues and cells, the design of pH responsive nano drug delivery systems has become a hot research topic in tumor therapy [176-178]. The molecular structure of pH responsive materials contains some acid-base groups in general, such as carboxylic acid group, amino group, imine linkage, hydrazone, etc. When the anti-cancer drugs are delivered to a tumor site with these pH-sensitive groups on the surface of nanocarriers, the extent of ionization of these acid-base groups will change along with the local pH values. Subsequently, the charge, swelling degree and osmotic pressure of naoncarriers will change according to the local pH values, leading to local environment-stimulated release of the payload drugs so as to effectively kill cancer cells.

Polymeric micelles have attracted increasingly more attention owing to their ability to accommodate hydrophobic drugs, easy preparation and ability to exert controlled drug release. There has been extensive design, use, and development of pH-responsive micelles for the delivery of anti-cancer drugs at present [179,180]. For instance, Li et al. linked DOX, an anti-cancer drug, to PEG via pH responsive benzoic acid imine bond, which could self-assemble into stable spherical micelles under neutral conditions [181]. It was observed that under acidic microenvironments in tumor tissues (pH $\sim$ 6.8) and lysosome (pH $\sim$ 5.0), the micelle would disintegrate to release the payload DOX drug gradually. Zhang et al. prepared a pH-responsive block copolymer micelle from PEG, glyoxylated dextran and DOX [182]. Their results indicated that 90% of the encapsulated DOX drug could be released rapidly in the acidic condition of pH = 5.5, while only a small fraction of drugs was released in the neutral condition [183]. In addition, in order to overcome the multidrug resistance of paclitaxel, Liu et al. developed a low pH-responsive hyaluronic acid-deoxycholic acid-histidine micelle able to target at both endosome and CD44 receptor **(**Fig. 5**)** [184]. The micelle could effectively inhibit the growth of tumor cells in MCF-7/Adr tumor-bearing mice, and exhibit a good ability to overcome multidrug resistance.

Other types of pH-responsive nano drug delivery systems have also been developed for tumor treatment. Ali Pourjavadi et al. designed and synthesized novel mesoporous silica nanoparticles (MCM-41) with a double layer coating of pH-responsive poly (acrylic

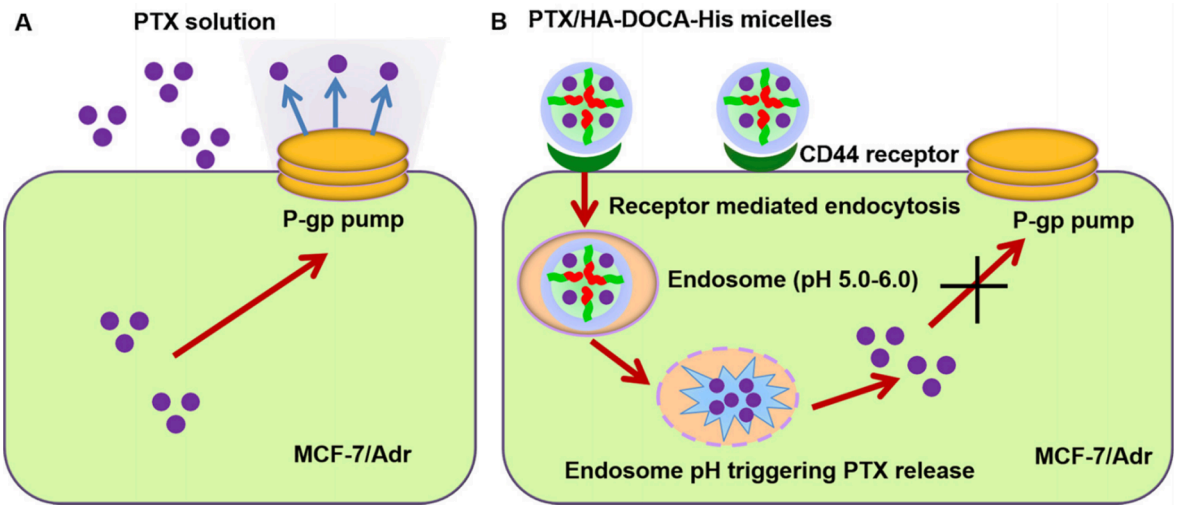

Fig. 5. Schematic illustration on proposed mechanism for multidrug resistance (MDR) reversion of PTX/HA-DOCA-His micelles in MCF-7/Adr cells. (A) P-gp mediates PTX efflux out of cellular membrane in MCF-7/Adr cells, (B) CD44 receptor-mediated endocytosis for internalization of micelles. The low pH in the endosome triggers PTX release from PTX/HA-DOCA-His micelles to conquer the MDR reversion. Modified and reprinted from the ref. [187]. Copyright © 2018, Elsevier B.V. Reproduction with permission from Elsevier.

acid-co-itaconic acid) and human serum albumin (HSA) for the delivery of Gemcitabine. According to their results, MCM-41 reaches the highest drug release rate at pH 5.5 (pH of the endosome) due to the shrinkage of outer layer at pH 5.5[185]. Meanwhile, in an experiment carried out by Gu et al., a NGR-modified docetaxel-loaded pH-responsive liposomes (DTX/NGR-PLL) was prepared for targeted delivery of docetaxel [186]. The drug encapsulation efficiency was about 70%, and the drug release rate is pH value dependent. Simultaneously, both in vitro and in vivo experiments verified that the DTX/NGR-PLL liposome has specific targeting ability and enhanced anti-cancer activity toward human fibrosarcoma cells. Tyagi et al. reported a simple and easy method for preparation of graphene nanostrip-poly(vinylpyrrolidone) nanoparticles [188]. The graphene GRP-PVP-NP has dual functions of pH responsivity and anti-cancer drug delivery. The DOX was loaded by supramolecular interaction, and could be effectively released under the conditions of low pH values and low oxygen concentration in tumor microenvironments.

pH-responsive nano drug delivery system is attractive for drug delivery system in cancer treatment, and it is also a hot topic in cancer research and treatment. However, its pH response is dependent on many factors, such as the particle size, morphology, zeta potential, surface properties, drugs loaded, etc. Therefore, further systematic investigation is required for each pH responsive nano drug delivery system so that a better control in the drug release can be achieved.

2.3.3. Redox-responsive nanoparticle drug delivery systems

Reactive oxygen species (ROS) are involved in the regulation of many physiological and pathological processes of human bodies. The balance of redox states inside tumor cells is dependent on the oxidation and reduction states of NADPH/$NADP^+$ and glutathione (GSH, GSH/GSSG), where under a reducing condition, the GSH concentration is higher than that of NADPH, and the former then regulates the redox microenvironments of tumor cells [189-191]. At the molecular level, GSH controls the reducing conditions via the

Table 4
Key features of the synthetic processes for redox-responsive nanogels fabrication.

Nanocarriers	Method	Concrete operations and mechanisms	Characteristics & problems	Ref.
Polymer NPs	Living radical polymerization	Incorporation of redox-responsive cross-linkers via radical polymerization, including nitroxide-mediated polymerization (NMP), atom transfer radical polymerization (ATRP), reversible addition–fragmentation chain transfer (RAFT) polymerization, and reverse iodine transfer polymerization (RITP)	(1) The resulting NPs have low size polydispersity. The NPs dispersed in water showed the 4.5-fold increase in the quantum efficiency when compared with the free dye mol- ecules in water.	[471]
Polymer NPs	Michael addition polymerization	Michael addition reaction between secondary (2°) amines and electron deficient olefins, using disulfide cross-linker as redox responsive moiety	(1) The NPs can realize precise ratiometric control of drugs being loaded, increase cellular uptake of the drugs, induce mitochondrial dysfunction and augment tumor treatment efficiency by inducing apoptosis. the NPs exhibited satisfactory performance in promoting apoptosis of tumor cells and achieved high therapeutic outcomes for multi-drug resistance tumors.	[472]
Polymer nanogel	Self-cross-linking of thiol groups	Simple thiol–disulfide exchange reaction between two polymer chains leads to formation of redox responsive nanogels, 2-(pyridin-2-yl disulfanyl) ethyl acrylate (PDSA) plays a vital role; molecules of biological interests can be attached.	These robust nanowires could be reduced to the fully solvated polymer, representing a novel, reversible cross-linking procedure for functional P3HT-based nanowire fibrils.	[473]
Dendrimeric nanogel	Branched armed cross-linking	Dendrimeric disulfide cross-linked branched nanogels have been synthesized from branched multi-armed PEG derivatives.	(1) The bioreducible nanogels improve antitumor drug internalization, contribute to endosomal escape, and realize intracellular drug-controlled release. The doxorubicin-loaded nanogels afford high anti-tumor efficiency and reduce the side effects to BALB/c mice bearing 4 T1 tumor.	[474]

Table 5
Reported important studies with redox-responsive drug carriers.

Entry	Nanocarrier	Loading-drugs	Drug release rate	Methods	Characteristics	Ref.
1	F68@SS-COFs for loading of DOX	Doxorubicin (DOX)	The DOX release achieves a cumulative release of about 23% of total encapsulated drug in 1 h and about 90% in 24 h when incubated with PBS pH 5.0 with 10 mm glutathione (GSH).	PEGylation of redox-responsive covalent organic frameworks (COFs)	High DOX-loading, rapid response to release DOX	[231]
2	MTX-FTC NPs	Methotrexate (MTX)	In the presence of 10 mM of GSH, a faster drug release took place owing to the breakage of the crosslinking points in the NP structure, exhibiting a release equal to 59.85% in the first 30 min and up to 88.4% in 24 h.	l-Cysteine and folic acid molecules were linked to chitosan to form FTC NPs.	Tumor specificity Tumor specific targeting and redox responsive MTX drug release	[475]
3	Xyl-SS-Cur-5-FUSA	Curcumin and 5-FU	More than 80% of curcumin and 74% 5-FUSA drug were released at pH 5.0 over 48 h	A disulphide (-S-S-) linkage was used to render Xyl-SS-Cur-5-FUSA redox responsive.	High loading of curcumin and 5-FUSA, high cytotoxicity to human colorectal cancer cells (HT-29, HCT-15).	[476]
4	Liposomes	Hydrophilic and hydrophobic drugs	NA	Self-assembly of tetraphenyl ethylene (TPE) into liposome-like vesicles, able to deliver both hydrophilic and hydrophobic drugs.	Good targeting, high drug loading	[477]
5	Organosilica-micelles	Chemotherapy drugs	NA	disulfide-doped organosilica-micellar hybrid nanoparticles, PEG and PEI modified,	Two-stages redox-responsive, long blood circulation duration, high tumor accumulation, improved antitumor efficacy	[223]
6	PEG-dendrimer-camptothecin	Camptothecin	Be able to release ~ 70% of camptothecin	PEGylation of dendrimer with a –S-S- linkage for loading of camptothecin	Glutathione redox responsive, able to release ~ 70% of camptothecin, high level gene transfection	[478]
7	(PEI-oxliPt(IV) @RNBC/GOD	RNase A protein (i.e., RNase A nitrophenylboronic conjugate, RNBC) and glucose oxidase (GOD)	The release of RNBC in the absence of sodium ascorbate was negligible, and only 6.2% of protein release was attained within 56 h. In comparison, a 4-fold increase in the accumulative release of RNBC was obtained in the presence of 10 mM sodium ascorbate within the same incubation time.	Cross-link of polyethylenimine with oxaliplatin (IV)) for delivery of ROS-cleavable, caged RNase A/ glucose oxidase.	Dissociate in reducing environment, release active oxaliplatin drug/protein, high tumor cell killing efficacy	[477]
8	Celecoxib-DOX-SiO_2 NPs	DOX and celecoxib	The addition of DTT (10 × 10–3 m) that can cleave disulfide bonds drastically promoted the release of DOX and celecoxib at pH 7.4 (greater than50%, greater than70%), and even more effectively at pH 5.0 (greater than80%, greater than80%).	Celecoxib-modified mesoporous silica nanoparticles with poly (β-cyclodextrin) wrapping (MSCPs) for delivery of doxorubicin (DOX)	Co-deliver DOX & celecoxib, block COX-2/PGE_2 signaling, enhance DOX's antitumor activity, inhibition of tumor repopulation, eliminate expansion of cancer cells, metastasis, and drug resistance.	[227]
9	MMC@BSA	Hydrophobic drugs	NA	Magnetic microcapsules (MMCs) were coated with albumin shell for delivery of hydrophobic drugs.	Excellent magnetism-mediated shifting ability and targeted hydrophobic drug delivery	[225]
10	NCssGEM NPs.	Camptothecin and gemcitabine	NA	AIEgens (NPAPF) was coupled with camptothecin-gemcitabine (CPT-ss-GEM) to form NCssGEM NPs.	NIR light and redox responsive, high tumor penetration and anticancer efficacies	[230]

Abbreviation: COFs: covalent organic frameworks; DOX: doxorubicin; MTX: methotrexate; FTC: folate redox-responsive chitosan; 5-FUSA: 5-fluorouracil-stearic acid; TPE: tetraphenyl ethylene; PEG: polyethylene glycol; PEI: amido-bonded polyethylenimine; MSCPS: mesoporous silica nanoparticles with poly(β-cyclodextrin) wrapping; MMCs: magnetic microcapsules; GSH: glutathione;

formation and fragmentation of disulfide bonds, and scavenges excess reactive oxygen species (ROS), thereby getting oxidized itself to GSSG. The GSSG was then again reduced to GSH by glutathione reductase using NADPH as a sacrificial electron donor substrate. The GSH concentration is higher (2–10 mM) than the extracellular compartment (2–20 μM) [192,193]. Especially, the tumor tissues have been reported to exhibit 4-fold higher GSH concentration than those in normal tissues [194]. This significant difference in the GSH level makes redox-responsive nanogels a most attractive platform for tumor-targeted drug delivery.

In general, redox-responsive disulfide S-S bonds were introduced into nano materials by various physical or chemical methods to endow them become redox response. Upon uptake through endocytosis, the disulfide S-S bonds on nanocarriers break and the nanocarrier structure was destroyed owing to the reduction of high concentration of GSH in the cell, which leads to a rapid release of the payload drugs. A number of chemodrugs such as doxorubicin (DOX) [195,196], paclitaxel (PTX) [197-200], indomethacin [201,202], cisplatin [203], 5-fluorouracil [204-206], etoposide [207], irinotecan [208], curcumin [209-212], protein [213], peptides [214], and nucleic acids [215-217] (e.g., siRNA, antisense oligodeoxynucleotide, and DNA) have been delivered to cancer cells in a targeted, controlled release manner. The basic principle for the fabrication of these systems is to incorporate redox-sensitive units, such as disulfide, ditellurium, and diselenide bonds onto nanocarriers. Cleavage of these redox-sensitive bonds was achieved in the presence of reducing agents. For example, the oxidized S-S bond will be reductively cleaved upon receiving an electron from a reducing reagent. The selection of a suitable synthetic strategy and design as well as fabrication of nanogel matrix with redox-responsive units are the most critical issues, which require an extensive and more in-depth understanding of the concepts of chemical and biomedical science. Cross-linkers are the principal ingredient for the fabrication of redox-responsive nanogels. They are the functional redox-active units containing disulfide, ditellurium, and diselenide bonds, forming 3D cross-linked redox-responsive networks to hold the therapeutics and to break in response to a redox trigger to release the payload drugs, and undergo biodegradation. The critical techniques and key points of the synthetic process are shown in Table 4 [218,219].

Development of redox-responsive drug delivery nanocarriers has recently become an emerging area of research. ROS is an important cellular signal species, which can trigger activation of oxidative stress response mechanisms in cells [76,220]. ROS-responsive drug delivery carriers currently being developed mostly involve organochalcogens (selenium, tellurium, diselenium, and ditellurium), organoboron compounds (aryl boronic ester), sulfur containing compounds (thioether, thioketal, vinyl dithioether), aryl oxalates, and ferrocenes, either as cross-linkers or as important constituent of polymeric backbone [221,222]. These redox responsive moieties in nanocarriers could utilize the ROS in cancer cells to trigger the release of payload drugs. Table 5 summarizes published studies with redox-responsive drug nanocarriers [223-233].

2.3.4. *Dual and triple stimuli-responsive nanoparticle drug delivery systems*

The characteristics and development trend of temperature responsive, pH responsive and redox responsive nanoparticle drug delivery systems are summarized in the Table 6. However, temperature, pH, the GSH concentration and other factors in tumor microenvironments do not change independently actually, but are correlated to each other. Therefore, there is of great significance to integrate the mechanisms of multiple tumor microenvironment stimulated responses into the same nanocarrier to establish a multi-stimuli responsive nano drug delivery system to control the release of payload drugs more efficiently and to exert the optimal anti-cancer effect [234]. Such multiple stimuli-responsive nanogels possess dual advantages of tumor microenvironment-triggered drug release and enhanced therapeutic efficacy.

At present, there is extensive and broad research on dual-stimuli responsive nano drug delivery system. Temperature- and redox-responsive nanogels generally involve a redox-responsive cross-linker and temperature-responsive polymer matrix. Some examples of temperature-responsive polymers are poly(N-isopropylacrylamide) (PNIPAAm) [235], poly(N,N′-diethyl acrylamide) [227], poly(N-(l)-(1-hydroxymethyl) propylmethacrylamide) [225], and poly(oligo(ethylene oxide)monomethyl ether methacrylate) (POEOMA). Fundueanu et al. prepared poly(vinyl alcohol) (PVA) microspheres with glutaraldehyde as a crosslinking agent [236]. In their study,

Table 6
Characteristics and development trends of several tumor microenvironment sensitive nano drug delivery systems.

Drug delivery system	Composition	Stimuli	Sensitivity principle	Defects and development direction	Ref.
Temperature responsive nano drug delivery system	Thermosensitive polymeric assemblies/liposome assemblies/nanocrystal assemblies/metal organic frameworks	Temperature	Hydrophilic-hydrophobic transition	High cost, temperature sensitivity, and difficulty in degradation	[479]
pH responsive drug delivery system	pH-sensitive organic and inorganic materials, including polymers, lipids (liposomes, nanoemulsions, and solid-lipid NPs), metal, and ceramic NPs	pH value	Ionization or hydrolysis of acid-base groups	pH sensitivity, poor stability	[480]
Redox-responsive nano drug delivery system	Representative molecular motifs including ferrocene/viologen/tetrathiafulvalene/ naphthalene diimide/oligothiophene/disulfide/ tris(bipyridine)ruthenium	GSH concentration	Cleavage of disulfide bond	Less types of carriers, limited application scope	[481]
Multi-stimuli responsive nano drug delivery system	Combination of multi-stimuli-responsive nanomaterials mentioned above	Multiple factors	Joint influence of multiple factors	Complex design and preparation, mutual interference of multiple stimuli	[482]

the temperature responsive PNIPAM polymer was grafted on the surface of PVA microspheres to endow thermo-sensitivity [237]. Through the reaction of the non-grafted PVA hydroxyl with succinic anhydride, pH responsive carboxyl group was introduced to obtain dual pH- and temperature responsive microspheres. The as-prepared PVA microspheres showed good drug loading performance, and the corresponding drug release could be controlled by temperature. Furthermore, dual stimuli-responsive nanogels generally involve a combination of redox-responsive cross-linkers and pH-responsive polymeric moieties as important nanogel constituents. Some of the important examples of pH-responsive polymers are poly(acrylamide (PAAm) [238], poly(acrylic acid) (PAA) [239,240], PMAA [241], poly(2-diethylaminoethyl methacrylate) (PDEAEMA) [242,243], polyethyleneimine [244,245], poly(l-lysine) [246,247], poly(2-vinyl pyridine) (P2VP) [248], poly(Nvinylamine) (PVAm) [249], poly(4-vinyl pyridine) (P4VP) [250], and chitosan [251,252]. The pH- and redox-responsive nanogels hold excellent potential and play a diverse role in tumor-targeted drug delivery and release thanks to their multidimensional role in response to variation in GSH concentration and pH inside the tumor cellular compartments. Teo et al. synthesized polymeric micelles with dual pH- and redox-responses by ring opening polymerization of functional cyclic carbonate and the adoption of disulfide S-S bond with PEG of different molecular weight as an initiator [253]. DOX was loaded via electrostatic interactions. The DOX release rate could be enhanced at least twice under pH 5.0 as compared to a neutral condition [254]. Further animal experiment showed that the drug-loaded micelles had high DOX release rate under tumor microenvironments, resulting in high cytotoxicity and excellent anti-cancer effect. The proposed pH and redox dual responsive micelles exhibit good potential as carriers for delivery of anti-cancer drugs. Curcio et al. synthesized pH and redox dual-responsive dextran nanogels (DEX-SS) for enhanced intracellular drug delivery via precipitative co-polymerization of methacrylated dextran (DEXMA), 2-aminoethylmethacrylate (AEMA) and N, N'-bis (acryloyl) cystamine (BAC). The DEX-SS nanogels were then loaded with methotrexate (MTX) [255]. The DEX-SS nanogel was sensitive to the variations of pH and redox environment. Incubation of nanogels in buffer pH 5.0 containing 10 mM glutathione (GSH) could synergistically increase the mean diameter and the PDI to 750 nm and 0.42, respectively [256].

Triple-stimuli responsive nanoparticle drug delivery system has gained increasingly more attention due to its multi-stimuli responsive, controlled-drug release means and better anti-tumor responses. Triple stimuli-responsive nanogels generally involve a combination of a redox-responsive cross-linker along with temperature- and pH-responsive polymer matrix as important nanogel

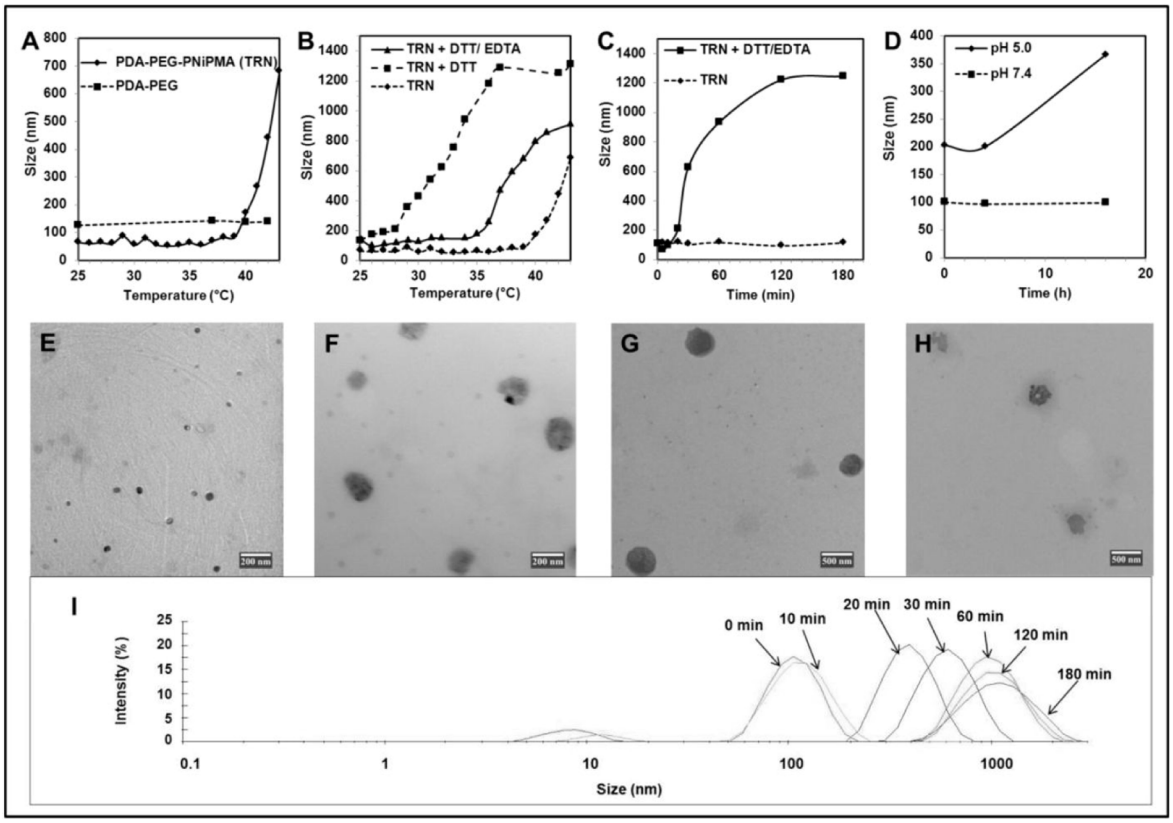

Fig. 6. The size distribution and images of TRN in response to different physical and chemical conditions. The z-average size of TRN in response to the change of temperature (A, B), the addition of 10 mM DTT (C), and the change of pH from 7.4 to 5.0 (D) acquired by DLS. All the size measurements were carried out at 37 °C unless otherwise specified. TEM images of control TRN at room temperature (E), heated at 42 °C (F), treated with 10 mM DTT for 2 h at 37 °C (G), and incubated in pH 5.0 buffer (H). Images were taken with a Hitachi H8000 TEM. Scale bars are 200 nm in (E) and (F), and 500 nm in (G) and (H). The size distribution of TRN in response to the addition of 10 mM DTT over time (I). Modified and reprinted from ref. [259]. Copyright © 2014, Elsevier Ltd. Reproduction with permission from Elsevier.

constituents [257,258]. He et al. developed a pH, thermal, and redox potential triple-responsive expansile nanogel system (TRN), which swells at acidic pH, temperatures higher than its transition temperature, and redox reducing environments [259]. The size of the TRN quickly expands from 108 to ~ 1200 nm (in diameter), achieving more than 1000-fold size enlargement (in volume), within 2 h in a redox reducing environment at body temperature, which could be seen from Fig. 6. Sigma-2 receptor targeting ligand-functionalized TRN can selectively accumulate at head and neck tumor, and deliver Pc 4 to target at mitochondria inside cancer cells to achieve enhanced photodynamic therapy efficacy.

In a study reported by Yang et al, poly (N-isopropylacrylamide)-ss-acrylic acid (P(NIPAM-ss-AA)) nanogels based on NIPAM and AA cross-linked by N,N'-bis (acryloyl) cystamine (BAC) were constructed to have a property of triple responses toward temperature, pH and redox [260]. The nanogels exhibit pH and redox dual responsive-initiated DOX release in vitro and in tumor cells, in which DOX release from nanogels was accelerated by low lysosomal pH (pH 4.5) and by highly redox reducing cytosolic environment (10 mM GSH). MTT analysis showed that DOX-loaded nanogels could efficiently inhibit the proliferation of HepG2 cells. In vivo animal studies demonstrated that DOX-loaded nanogels could accumulate in tumor tissues more efficiently than free DOX, leading to higher tumor inhibition activity and fewer side effects. In the presence of BAC crosslinker, Li et al. prepared folic acid (FA)-conjugated pH/temperature/redox multi-stimuli responsive poly(methacrylic acid-co-N, N-bis (acryloyl) cystamine/poly (N-isopropylacrylamide-co-glycidyl methacrylate-co-N, N-bis (acryloyl) cystamine) microspheres by a two-stage distillation-precipitation-polymerization process with subsequent surface modification with FA [261]. The microsphere loaded with DOX exhibits a high loading capacity of 208.0% and an encapsulation efficiency of 85.4%. The resultant microsphere was a promising vector for delivery of anti-cancer drugs in view of its advantages of low cytotoxicity and degradability, precise molecular targeting property and multi-stimuli responsive, and controlled drug release. So far, the interactions among several stimuli sometimes lead to weakening or disappearance of another factor. Besides, multi-stimuli responsive nanocarrier materials are more complex in design and preparation process, resulting in limited applications in practice.

2.4. Nano-Pharmacokinetics in treating TNBC

The fact that the bioavailability of the free anti-tumor agent was restrained by poor water solubility hampered the development in this field. To solve this problem, nanomedicines were designed and improved to enhance the biodistribution of the systematically-administered drugs from 1959 [262]. Modified with nanomaterials, the solubility and chemical stability of the free chemotherapeutic agents are improved, which helps to regulate their pharmacokinetic pattern and protect them from being biodegraded [263]. Pharmacokinetic (PK) is defined as the time course of the drug concentrations that reaches different parts of our body after its administration. It is the study of the absorption, distribution, metabolism, and excretion of the drug. When compared to free drugs, nanomedicines have many pharmacokinetic advantages, such as improved pharmacokinetics profiles, selectivity and specificity, controlled drug release, and site-specific multidrug delivery. Apart from offering more advantages in biodistribution and clearance aspects, nanomedicines also alleviate the cytotoxicity [264]. Shape, size, surface pattern, and administration route are the significant physicochemical features that affect their PK properties.

2.4.1. Role of nanomaterials in pharmacokinetics

Nanomaterial conjugation can solve many limitations of conventional drugs and greatly improve the PK profiles. Nanomedicines can reach to previously unreachable sites smoothly, extend systemic circulation time and subsequently improve accumulation chance, control and delivery drugs specifically by targeting the site to facilitate the availability as well as minimize the toxicity [265].

The selectivity and specificity stand as a key feature of nanomedicines. After modifications, nanocarriers can reach the targeting action site through active or passive targeting mechanisms. Through enhanced permeability and retention (EPR) effect, nanomedicines can be accumulated passively in leaky blood vasculature [266]. By directly interacting with different surface ligands, the active targeting can be achieved in various tumor-specific sites in different selective attachments [267]. Besides, the stimuli-response system also showed promising effect to control the drug to release at specified sites. The dual-stimuli types, for example, external and internal types, were testified to trigger changes of nanomedicines [268]. Internal stimuli includes some changes in the target tissue, such as pH, redox, ionic strength, and stress [269], while the external stimuli (also known as physical stimuli) includes temperature, light, electric fields, ultrasound, and magnetic force [270]. Nanomaterials can also control the release of drugs to provide sustained drug-release with reduced dosing frequency. According to the drug-release mechanisms, controlled-drug-release is divided into four types: diffusion-controlled, stimuli-controlled, chemical-reaction-based controlled and solvent-controlled release [271]. Based on the approaches discussed above, nanomaterials make it possible to delivery multidrug in a site-specific way. All these pharmacokinetic benefits will finally benefit the patients by providing a high therapeutic efficacy with lower systemic adverse effects.

From the biodistribution and clearance aspects, nanomedicines also have its properties. Biodistribution is defined as the reversible transfer of drugs or chemicals from one location to another in a biological system. Nanoparticle properties, exposed physiological environment, and route of administration are the critical factors that affect the biodistribution. When the nanoparticles are modified<8 nm of diameter, they will pass the glomerular capillary membrane of kidneys, and subsequently be filtered into renal tubes and cleared by urine [272]. However, though nanomedicines will alleviate the cytotoxicity through plenty of PK benefits, nanomedicines also have the potential to cause adverse effects either on human health or the environment, and one of the critical factors is their small size. With a hydrophobic surface, several airborne nanoparticles may accumulate in the liver and spleen for a longer period to cause toxicity. Also, gut and bone marrow can be organs that may have more materials accumulation when compared to the brain [273].

2.4.2. Problems of nano-pharmacokinetics in TNBC

Because each dynamic process of absorption, distribution, metabolism and excretion (ADME) of nanomedicines in vivo after administration has a complex dynamic process of different forms of nanoparticles and free drugs, coupled with limited understanding of the in vivo disposal process of nanomedicines, unclear release mechanism, uncertain potential toxicity and incomplete pharmacokinetic behavior, all the factors mentioned above may be some of the critical reasons for the low rate of successful clinical practice of nanomedicines applied in TNBC [268,274]. In addition, since there may be many different forms of nanomedicines in the body (such as free drugs, loaded drugs, nanoparticles, carrier materials, etc.), how to establish appropriate analytical methods for different forms of nanomedicines to truly and accurately reflect the concentration of different forms of nano drugs in biological samples in the body is also a problem that needs to be solved urgently to truly describe the pharmacokinetics process of nanomedicines in vivo. On this basis, it will further contribute to the targeting research of nanomedicines, evaluate their effectiveness and safety, and improve the rate of successful clinical practice of nanomedicines, so as to promote the application and development of nanomedicine delivery systems in TNBC [275].

2.4.3. Advances in PIT mediated SUPR effect

A paper published in Nature Reviews Materials analyzed the nanomedicine delivery efficiency after reviewing the relative literature published between 2005 and 2015 and reported that only 0.7% of the administered nanomedicine was delivered successfully to a solid tumor site [276,277]. Though this paper was considered controversial for the view that the efficiencies for antitumor nanomedicines were low and not improving, it indeed caused a storm in this field, which encouraged scientists to make further efforts to solve this problem and improve efficiency [278]. The reason responsible for the very low efficiencies of nanomedicines' accumulation at a tumor site is most probably due to the fact that those nanomedicines are lack of tumor-targeting abilities, and the accumulation of nanomedicines at a tumor site solely relies on the passive accumulation via the "enhanced permeability and retention" (EPR) effect. Such a problem can be conquered by introducing tumor-targeting abilities to nanomedicines via surface chelating of nanomedicines/nanocarriers by tumor-targeting antibodies (vide infra).

Photoimmunotherapy (PIT) mediated super-enhanced permeability and retention (SUPR) effect can be one promising treatment to bring the dawn for such a complicated problem [279]. PIT is a novel cancer treatment which can cause specific cell killing and increase the vascular permeability rapidly by being exposed to 690 nm light through the conjugation of IR-700 photosensitizer and a targeted monoclonal antibody. By using various of imaging methods with labeled nanoparticles, the effect that remarkable increase in permeability for nanomedicines and the clear retention in the tumor site was visualized, and this effect was named as super-enhanced permeability and retention (SUPR). Sano et al. also reported that the best administration time to achieve the highest SUPR effect is immediate administration after the PIT. Compared with the conventional enhanced permeability and retention (EPR) effect of nanomedicines which can only moderately increase the tumor transmission of nanomedicines, Sano et al. found that PIT mediated SUPR effect can cause a 24-fold increase in the distribution of nanomedicines in the treatment of tumors compared with the control tumors [279]. In addition, the PIT mediated SUPR effect has no special requirements on the properties of nanomaterials. It can not only promote the transmission of non-targeted nanoparticles, such as PEGylated quantum dot (Qdot800; mean diameter 50 nm)[279], paramagnetic iron oxide (SPIO) (mean diameter ~ 200 nm) [280], ultra-small paramagnetic iron oxide contrast agent (USPIO, mean diameter 20 nm) [281], gadolinium labeled polyamidoamine dendrimer (mean diameter 10 nm) [282] in tumor bed, but it can also facilitate the transmission of other antibodies or antigen presenting cells towards tumor bed [283-285]. The key feature of the SUPR effect is the use of antibody to introduce the tumor-targeting ability. It was also experimentally observed that upon surface modification with a tumor specific antibody or biomarkers-specific probe, the percentage of nanomaterial accumulation at a tumor site could be drastically increased to be within 10 ~ 20% of the total amounts of nanomaterials [318-322]. Moreover, with the gradual deepening of research in this field, together with several promising combination therapies emerging in this field, such as PIT combined with PIT [286-288], PIT combined with chemotherapy [289-292], PIT combined with immunotherapy [293-296], it has great potential to be widely used in tumor treatment in the future.

3. Interactions of nanoparticles with TNBC

3.1. Characteristic features of TNBC

As a heterogeneous group of tumors, TNBC is characterized by aggressive behavior, high risk of distant tumor metastasis, recurrence and poor survival. Several promising surface receptors, genes, and corresponding ligands were reported as potential targets for the treatments of TNBC [297], including Breast Cancer type 1 and type 2 (BRCA1/2), Homologous Recombination Repair (HRR) genes involved in DNA-double strand break repair, and DNA homologous recombination repair, respectively. Poly ADP-ribose polymerase (PARP), Ataxia Telangiectasia Rad3 (ATR) and WEE1 inhibitors were also discovered as potential targeted therapy agents [298-301]. PD-L1 protein was involved in the tumor immune evasion process, making anti-[immune checkpoint inhibitors] antibodies possible as immunotherapy agents [302-304]. Phosphatidylinositol 3-kinase (PI3K) pathway was found to be a key regulator in cell proliferation, driving the discovery of PI3K and AKT inhibitors [305,306]. Besides, some other biomarkers were currently under investigation, like Glycoprotein non-metastatic b (GPNMB), Trophoblast cell-surface antigen 2 (Trop-2), LIV-1 (a zinc transporter protein downstream target of STAT3), CA6 (a biomarker selectively expressed on solid tumors), and so on [307-310]. These biomarkers may also provide possible targets for the treatment of TNBC using nanoparticles targeted therapies.

Table 7
Reported targeted signaling pathways by nano drug delivery systems in cancer treatment.

Entry	Targeted signaling pathway	Nanocarrier	Research aim	Key findings	Ref.
1	Methanol oxidation reaction pathway	Pt-Ru bimetallic nanoparticle	To explore manipulating the Surface Composition of Pt-Ru Bimetallic Nanoparticles to Control the Methanol Oxidation Reaction Pathway	Using in situ Fourier transform infrared-diffuse reflection (FTIR) analysis, the researchers report that the methanol oxidation reaction (MOR) intermediates can be controlled by precisely tuning the location and content of Ru on the Pt-Ru alloy surface.	[483]
2	Lysosomal pathway of apoptosis	DOX-loaded peptide dendritic copolymer nanoparticle	To to investigate the performance and possible mechanisms of enzyme-sensitive mPEGylated dendron-GFLG-DOX conjugate based nanoparticles for blockading the MDR phenotype of MCF-7/ADR.	1) mPEGylated dendron-GFLG-DOX conjugate based nanoparticles could induce cathepsin B in the cytoplasm and enhance lysosomal-mediated cell death compared to free DOX. 2) mPEGylated dendron-GFLG-DOX conjugate based nanoparticles enhanced the drug's penetration, toxicity, and growth inhibition compared to free DOX in the three-dimensional multicellular tumor spheroid model.	[483]
3	PD-1/PD-L1 pathway	Dual-locking nanoparticle (DLNP)	To describe a dual-locking nanoparticle (DLNP) that can restrict CRISPR/Cas13a activation to tumor tissues.	1) DLNP has a core–shell structure, in which the CRISPR/Cas13a system (plasmid DNA, pDNA) is encapsulated inside the core with a dual-responsive polymer layer. 2) After carefully screening and optimizing the CRISPR RNA (crRNA) sequence that targets programmed death-ligand 1 (PD-L1), DLNP demonstrates the effective activation of T-cell-mediated antitumor immunity and the reshaping of immunosuppressive tumor microenvironment (TME) in B16F10-bearing mice, resulting in significantly enhanced antitumor effect and improved survival rate.	[484]
4	Nrf-2-Keap1 and NF-kB and mTOR/Maf-1/ PTEN pathway	Solid lipid nano-formulation of astraxanthin	To scrutinize the chemoprotective effect of astraxanthin against the 7,12-dimethylbenz (a)anthracene (DMBA)-induced breast cancer	1) AX-SLN reduced the p-AKT which is accountable for the reduction in the NF-kB expression and also reduced the expression of Keap1 and NF-kB along with increasing the expression of HO-1 and Nrf-2. Further, 2) AX-SLN significantly altered the mRNA of LXR (α,β), HMG-CoAR, PTEN, Maf1, PI3K, mTOR, Akt, FASN, and ACC1. 3) AX-SLN inhibits the mammary gland carcinogenesis via Nrf-2-Keap1, NF-kB, and mTOR/Maf-1/PTEN pathway.	[485]
5	cGAS-STING pathway	Radiotherapy-activated hafnium oxide nanoparticles	To explore the impact of hafnium oxide nanoparticles (NBTXR3) activated by radiotherapy on cell death, DNA damage, and activation of the cGAS-STING pathway	Compared to radiotherapy alone, NBTXR3 activated by radiotherapy enhances cell destruction, DNA double strand breaks, micronuclei formation and cGAS-STING pathway activation in a human colorectal cancer model.	[485]
6	HER2 signaling pathway	HER2-glycan-imprinted nanoparticles	To introduce an effective strategy by blocking the HER2 signaling pathway in the treatment of HER2-positive breast cancer	1) The nano molecularly imprinted polymer (nanoMIP), imprinted using HER2 N-glycans, could bind almost all HER2 glycans and suppress the dimerization of HER2 with other HER family members, blocking the downstream signaling pathways, thereby inhibiting HER2 + breast cancer growth. Invitro experiments demonstrated that the nanoMIPs specifically targeted HER2 + cells and inhibited cell proliferation by 30 %. 2) Invivo experiments indicated that the mean tumor volume of the nanoMIP-treated group was only about half of that of the non-treated groups.	[486]

(*continued on next page*)

Table 7 (*continued*)

Entry	Targeted signaling pathway	Nanocarrier	Research aim	Key findings	Ref.
7	DNA repair pathway	Demethoxycurcumin-loaded chitosan nanoparticle	To understand whether Demethoxycurcumin-carbomethyl-hexanoyl chitosan (DMC-CHC) NPs efficiently potentiate cisplatin-induced apoptosis through downregulation of excision repair cross-complementary 1 (ERCC1) in non-small cell lung carcinoma cells (NSCLC)	1) A sulforhodamine B (SRB) assay indicated that DMC-CHC NPs significantly increased cisplatin-induced cytotoxicity by highly efficient intracellular delivery of the encapsulated DMC. 2) A combination of DMC-CHC NPs and cisplatin significantly inhibited on-target cisplatin resistance protein, ERCC1, via the PI3K-Akt pathway. 3) This combination treatment markedly increased the post-target cisplatin resistance pathway including bax, and cytochrome *c* expressions.	[487]
8	JAK2/STAT3 signaling pathway	Biodegradable Nanoparticles	To develop a new delivery system for the co-delivery of Erlotinib (ELTN) and fedratinib (FDTN, a small-molecular, highly selective JAK2 inhibitor)	1) Mechanistic study showed that FDTN notably down-regulated the expression levels of proteins in the JAK2/STAT3 signaling pathway, including p-EGFR, p-JAK2, p-STAT3 and Survivin, therefore reversing the ELTN resistance. 2) Synergistic anti-cancer effect was achieved by PEG-PLA NPs encapsulating both ELTN and FDTN in ELTN-resistant NSCLC tumors. Lower systemic side effect was noted for the co-delivery NPs compared to free drugs.	[488]
9	JNK apoptotic pathway	Cerium Oxide Nanoparticles	To describe how cerium oxide nanoparticles, sensitize pancreatic cancer to radiation therapy through oxidative activation of the JNK apoptotic pathway	1) The increase in activation of apoptosis signaling kinase 1 (ASK1) activation following the co-treatment with cerium oxide nanoparticles (CONPs) followed by radiation therapy (RT) suggests that the increased JNK activation is the result of increased thioredoxin 1 (TRX1) oxidation. 2) The ability of CONPs to sensitize pancreatic cancer cells to RT was mitigated when the TRX1 oxidation was prevented by mutagenesis of a cysteine residue or when the JNK activation was blocked by an inhibitor.	[489]
10	Fas apoptosis pathway	Magnetic nanoparticle	To investigate the expression of c-FLIP and caspase-8 and effect of monoclonal antibody CD95L (FasL) for apoptosis stimulation	1) Caspase-8 apoptosis pathway was activated on transfected cells. 2) Magnetic nanoparticle-mediated gene transfer is a successful non-viral method for transfection, and it does not affect the expression of other cell proteins. 3) The raised c-FLIP concentration in cytosol inhibits apoptosis. Transfection of CD95-GFP-tagged pDNA significantly increases apoptosis by activating caspase-8 pathway.	[490]
11	EGFR/ERK pathway	Paclitaxel nanoparticles co-delivered with microRNA-7	To sensitize Paclitaxel (PTX) chemotherapy for ovarian cancer	1) The resulting PTX/miR-7 nanoparticles (P/MNPs) protect miRNA from degradation, possess a sequential and controlled release of drugs, improve the transfection efficiency of miRNA, decrease the half-maximal inhibitory concentration of PTX, and increase the apoptosis of ovarian cancer cells. 2) The chemotherapeutic efficacy of PTX is prominently enhanced in vitro and in vivo via the inhibition of PTX-induced EGFR/ERK pathway activation by miR-7.	[491]
12	P53/PRC1 pathway	Chitosan-coated doxorubicin nanoparticles	To evaluate the effect of chitosan coated doxorubicin nano-particles drug delivery system in liver cancer	1) The FA-CS-DOX nanoparticles were irregular and spherical particles around 30–40 nm, with uniform size and no adhesion. 2) No significant difference was noted in doxorubicin release rate between CS-DOX and FA-CS-DOX.	[492]

(*continued on next page*)

Table 7 (*continued*)

Entry	Targeted signaling pathway	Nanocarrier	Research aim	Key findings	Ref.
				3) FA-CS-DOX nanoparticles showed stronger cytotoxicity than CS-DOX. 4) FA-CS-DOX nanoparticles promoted the apoptosis and arrested cell cycle at G2/M phase, and they up-regulated p53, inhibiting cell survival through p53/PRC1 pathway.	
13	EGFR/PI3K/Akt-mediated pathway	Gold nanoparticles-conjugated quercetin	To evaluate the effects of gold nanoparticles-conjugated quercetin (AuNPs-Qu-5) in MCF-7 and MDA-MB-231 breast cancer cell lines	1) The pro-apoptotic proteins (Bax, Caspase-3) were found to be up regulated and anti-apoptotic protein (Bcl-2) was down regulated on treatment with AuNPs-Qu-5. 2) AuNPs-Qu-5 treatment inhibited the EGFR and its downstream signaling molecules PI3K/Akt/mTOR/GSK-3β. 3) Administration of AuNPs-Qu-5 in breast cancer cell lines curtails cell proliferation through induction of apoptosis and also suppresses EGFR signaling.	[493]

3.2. General mechanisms and signal pathways involved in the interactions of nanoparticles with TNBC

The application of nanomaterials in disease diagnosis and treatment covers co-delivery of drugs and genes, imaging and diagnosis, detection of biomacromolecule, comprehensive treatment of tumor, etc.[311,312]. Nanomaterials having sizes in the range of 1 ~ 100 nm show unique physical and chemical properties. Many metal nanoparticles have been shown to be able to absorb and convert ultrasonic wave, electromagnetic wave, and near-infrared light to thermal heat or chemical excitation energy, and exert hyperthermia or generate ROS for killing cancer cells [313]. Nanoparticle-based nanocarriers can realize multi-functions simultaneously, including controllable targeted drug delivery, sustained release of payload drugs, diagnostic imaging and therapeutic photothermal ablation [314-317].

In the cancer treatment, nano delivery systems have been reported to directly deliver doxorubicin (DOX), docetaxel (docetaxel), cyclophosphamide, 5-fluorouracil and cisplatin to tumor cells. Furthermore, nano delivery systems can increase the drug uptake by tumor cells via targeted drug delivery, and also accurately target at tumor tissues through overexpressed biomarker receptors on tumor cellular membrane (such as folate receptor, transferrin receptor, CD44 transmembrane proteins, etc.). In addition, the photothermal and photodynamic therapeutic effects mediated by metal nanoparticle nanocarriers themselves, such as graphene nanocomposites, gold nanoparticles, Fe_3O_4 nanoparticles and polymer nanocomposites, provide additional means to kill tumor cells and tumor stem cells. As for the specific process, the nanocarriers that reside between and within tumor cells, could absorb incident near-infrared light and convert it into heat energy or ROS locally to kill tumor cells [318-326]. Meanwhile, it can mediate long-lasting and controlled release of high-dose chemotherapeutic drugs to effectively inhibit and kill tumor cells [327].

The main targeted signaling pathways of nano drug delivery system include methanol oxidation reaction pathway, lysosomal pathway of apoptosis, PD-1/PD-L1 pathway, Nrf-2-Keap1 and NF-kB and mTOR/Maf-1/PTEN pathway, cGAS-STING pathway, HER2 signaling pathway, DNA repair pathway, JAK2/STAT3 signaling pathway, JNK apoptotic pathway, Fas apoptosis pathway, EGFR/ERK pathway, P53/PRC1 pathway, and EGFR/PI3K/Akt-mediated pathway. Studies regarding targeted signaling pathways involved in nano drug delivery to cancers were summarized in Table 7 in detail [324,328-339].

3.3. Nano-therapeutic modalities developed for treating TNBC

3.3.1. Photothermal therapy (PTT)

Many metal nanoparticles have been shown to be able to absorb and convert near-infrared light to heat, which can be utilized to trigger release of payload drugs as well as exert local hyperthermia or generation of ROS to killing cancer cells [340-344]. Normal tissue around tumor has less accumulation of nanocarriers and thus suffer less damages under near-infrared light irradiation, which significantly improves the safety and effectiveness of photothermal and photodynamic therapies. Due to their strong localized surface plasmon resonance (LSPR) absorption, metal nanoparticles could absorb visible-near infrared light very efficiently and transform photon energy to heat and local hyperthermia with temperatures beyond 42 ℃ to kill tumor cells. In addition, temperature sensitive liposomes (LTSL) will release payload DOX above 42 °C to exert chemotherapy effect on killing tumor cells. According to the fluorescence confocal Z-stack imaging and transmission electron microscopy, the uptake of multifunctional gold nanoparticles (MGN) by TNBC cells was increased significantly. Furthermore, cell viability test and fluorescence cell imaging results indicated that as compared to free DOX and single DOX loaded liposomes, MGN-DOX-LTSL has superior therapeutic effect on killing tumor cells. It was worth noting that even at low concentration (0.5 $mg{\cdot}L^{-1}$) of DOX, MGN-DOX-LTSL causes a higher percentage of cancer cell deaths (33%) than free DOX (17%). MGN-DOX-LTSL integrates the photothermal effect from MGN and delivery of chemotherapeutic drugs from LTSL to maximize the cytotoxicity and achieve complete eradication of invasive breast cancer stem cells [345].

Different nanomaterials have very different properties. Graphene quantum dot (GQD)-based nanomaterials are environmentally friendly without containing highly toxic heavy metals. Due to its chemical structures, it is easy to realize surface functionalization of GQDs on the basis of its C=C double bonds. In addition, GQD has unique optical properties. Upon photo excitation, GQDs are able to absorb and convert photon energy to heat, emit luminescence in the NIR region for tumor bioimaging, and sensitize formation of singlet oxygen to exert photodynamic therapy effect on killing cancer cells [346]. Hollow mesoporous silica nanoparticles (HMSN) could be coated onto GQDs to form GQD@HMSN-PEG by poly(ethylene glycol) (PEG) modification. The composite nano drug delivery system could exert simultaneously multi-functions, including bioimaging, photothermal therapy effect and photodynamic therapy effects on killing cancer cells. Meanwhile, GQD@HMSN-PEG has high DOX drug loading rate, longer tumor retention time and better curative effect in the treatment of TNBC [347].

Binding of integrin α antibody to PEGylated nano-micelles could promote the internalization of the composite micelles by TNBC cancer cells. For example, the metastatic migration of drug-resistant MDA-MB-231 TNBC and 4T1 cancer cells was delayed after 24 h of treatment, while the mitochondrial membrane potentials of these MDA-MB-231 TNBC and 4T1 cancer cells was significantly reduced under high temperature. In the 4T1 spontaneous metastasis model, intratumoral nano-micelle administration results in anti-tumor and fibrogenic blocking effects [331]. In another report, DOX@HAPPγ composed of hyaluronic acid (HA), polypyrrole (PPγ) nanoparticles and DOX was used for bioimaging and treatment of TNBC. DOX@HAPPγ has been reported to have multi-functions, including fluorescence imaging, stimulator-induced response for drug release, and photothermal-induced heating, visual tracking of treatment process, high penetration of tumor tissue, etc [348]. The nano-vesicle composed of a cell membrane shell and a composed methylene blue-cisplatin-gelatin nanogel core, can exert contrast-enhanced photoacoustic tumor imaging, generation of photothermal hyperthermia, and luminescence imaging under laser irradiation. Such a composite nano-vesicle was demonstrated to be able to release of methylene blue and anti-cancer drug cisplatin, effectively kill 4 T1 cells, and shrink the primary tumor, achieving an inhibition rate of lung metastasis of up to 97% without having obvious dark toxicity to animals [349].

Lip (PTQ/GA/AIPH) is a second near infrared (NIR-II) light excitation multimodal phototheranostics nanomedicine formed by integrating the targeting aptamer, azo compound, HSP inhibitor, and semiconducting polymer. It can provide dual-modal imaging (photoacoustic and NIR-II fluorescence) and NIR-II PTT, producing cytotoxic free radicals and resulting in oxygen-irrelevant photonic thermodynamic therapy effects. With little adverse effects, this delivery system has promising potential of accurate diagnosis and effective inhibition of deep TNBC lesion [350]. By combining miR-34a and photoresponsive gold nanoshells (NS), miR-34a/NS was designed for releasing tethered miR-34a through excitation with either nanosecond pulsed near-infrared light or continuous wave. This system showed promising efficacy of suppressing the proliferation, viability, and migration of TNBC cells by precise gene regulation [351,352]. Besides, Bumpy Au triangular nanoprisms (BATrisms) has the advantages of high cell penetration, absorption peak within NIR region, increased surface area, and enhanced photothermal conversion efficiency. By integrating BATrisms and LK peptides (leucine and lysine rich cell-penetrating peptides), their cellular uptake efficiency has been largely developed. In TNBC xenograft mice model, LK-BATrisms showed a significant anti-tumor efficacy even under a very small dose and very low laser power (2.5 μg Au and 808 nm, 0.25 W/cm^2) [353].

3.3.2. Gene therapy

Gene therapy is an important modality for the treatment of TNBC. Small interfering RNA (siRNA) is a double stranded RNA composed of 20–25 nucleotides, which precisely participate in specific RNA interference to regulate the expression of target genes. GNR@LPMO is composed of mesoporous organosilica-coated gold nanorod (GNR@LPMO), which is characterized by uniform size of 175 nm, large pore size on the silica shell, high photothermal conversion efficiency and good biocompatibility. As compared to traditional liposomes and GNR, GNR@LPMO has higher siRNA loading capacity. Ni et al. reported in their study that functional siRNA could be effectively delivered to TNBC cells by GNR@LPMO, which induces tumor cell apoptosis by knockout of polo-likekinase1 (PLK1) [354]. By combining effective gene transfer with photothermal ablation, GNR@LPMO could induce tumor inhibition rate 15 times higher than that of the single treatment mode, and enhance the killing effect on both drug-resistant tumor cells and tumor stem cells. siRNA interference is an optimal practice to knock down gene expression and for studying protein function in various cell types. By alternately depositing siRNA and poly-L-arginine on nanoparticles to form layer-by-layer films, a single bilayer on the surface of nanoparticles could effectively load up to 3,500 siRNA molecules [355]. The resulting nanoparticles exhibit an extended serum half-life of 28 h. Moreover, one dose of intravenous drug administration could significantly reduce the target gene expression in the tumors by almost 80%. By generating siRNA-loaded film on top of a DOX-loaded liposome, a combined chemo-gene therapy could be realized with effective inhibition of the expression of the multidrug resistance protein 1. In in-vivo experiments, it was demonstrated that the tumor volume was suppressed by 87.5% and cancer cell counts decreased dramatically after treatment with the siRNA-polymer NP delivery system [356].

MicroRNAs (miRNAs) are short noncoding RNAs that act as a regulator for the expression of multiple genes and are themselves a therapeutic target. Using the three-way junction motifs of thermo-kinetics and chemical stability as scaffolds, a RNA aptamer able to bind to CD133 receptor and a locked nucleic acid sequence, was used to inhibit the expression of miRNA-21 in cancer cells. Functional analysis shows that the use of a RNA aptamer is able to inhibit both the migration of cancer cells and the expression of miRNA-21, while the expressions of downstream tumor gene suppressors PTEN and pDD4 were up-regulated [357]. Another research indicates that both the miRNA-205 and miRNA-34a have a significant inhibitory effect on the proliferation of TNBC cells, in which the miRNA-205 could negatively regulate the expression of epithelial mesenchymal transitions (EMT) related transcription factor ZEB1, and down-regulates the HER-3 expression, thus affecting the tumor development of HER-3-positive cells. Simultaneously, inhibition of TNBC cell cycle progression, proliferation and tumor growth could be realized by using targeting factors such as E2F1, a main regulator of cell cycle progression [358]. By using metal organic framework (MOF) nanoparticles (ZIF-8) as nanocarriers for combined gene/chemodynamic

therapies, the miR-34a-m@ZIF-8 complex demonstrated excellent efficacy in inhibiting tumor growth in a TNBC mice model via enhanced cell uptake and lysosomal stimuli-controlled release of miRNA, leading to an obvious decrease in BCL-2 expression and an enhancement of cancer cell apoptosis [359].

In addition to inhibition of proliferation of TNBC cells, nanocarriers containing the miRNA-34a could also exert an important role in inhibiting cancer cell migration. It was suggested that miRNA-34a might further inhibit the growth and the migration of breast cancer cells by down-regulation of the expression of Bcl-2 gene and the silencing information regulator 1 [360].

Coating the negatively charged nanocarriers with positively charged poly(lysine) and miRNA-34a alternately may help the nanocomposite to enter cancer cells and protect the payload miRNA-34a. The uptake of the nanocomposite particles by MDA-MB-231 TNBC cells was detected and confirmed by confocal microscopy, Western blotting, and EdU cell proliferation flow cytometry. According to these results, the nano delivery system with miRNA-34a could inhibit the expression of SIRT1 and Bcl-2 with inhibition rates of (46 ± 3) % and (35 ± 3) %, respectively. Inhibition of the expression of SIRT1 and Bcl-2 could reduce the proliferation rate of TNBC tumor cells by 33% [361]. Meanwhile, the gene expression profile analysis of miRNA microarray in TNBC patients showed that the miRNA-374a-5p was up-regulated. Functional studies in vitro and in vivo showed that up-regulation of miR-374a-5p could promote tumor progression in TNBC [362]. miRNA-374a-5p could directly target at arrb1, of which the expression was specifically down-regulated in TNBC patients. The overexpression of arrb1 could suppress the growth and migration of tumor necrosis cells, and its expression level was negatively correlated with the histological grade of breast cancer, but positively correlated with the survival of tumor necrosis cells. Moreover, the up-regulated expression of arrb1 could activate adenine monophosphate as well as protein kinase in TNBC cells, which was related to the expression of miR-374a-5p [363]. Furthermore, HA-PEI-PLGA, a HA nanocomposite being modified by poly(ethylene imine) (PEI) and poly(lactic acid) (PLGA), was loaded with DOX and miRNA-52-3P. The composite HA-PEI-PLGA-DOX nanoparticle have an average particle size of 131.7 nm. It had a high drug encapsulation rate, which could prevent the enzymatic degradation of miRNA-52-3P in serum. The in vitro cellular experiments revealed that the HA-PEI-PLGA-DOX nanoparticles could increase the uptake of DOX by MDA-MB-231 TNBC cells, as compared to uptake of free DOX. In addition, miRNA-52-3P loaded in the HA-PEI-PLGA nanoparticle could promote the apoptosis of TNBC cells by targeting at the tumor suppressor gene p53 and apoptosis inhibitory factor Survivin [364].

3.3.3. Immunotherapy enhanced by nanoparticle delivery system in TNBC treatment

3.3.3.1. Mechanisms of immunotherapy enhanced by nano delivery system. Nanoparticles have been widely used as nanocarriers in tumor immunotherapy, including the delivery of vaccines, antibodies, and immune-modulators to specific immune cells, to improve the tumor inhibition efficacies [365-367]. The cyto-biological and molecular biological mechanisms responsible for the immunotherapy enhancement by nanoparticle delivery system in TNBC were summarized in the Table 8 [368-378].

Based on previous studies, lung metastasis of breast cancer is the main cause responsible for deaths of TNBC patients. Anti-metastasis is one of the major challenges in TNBC treatment. Activation of immune system is of great significance in the treatment of metastatic cancers, especially in the TNBC. DOX@HIMSN, a nano drug delivery system composed of mesoporous silica nanoparticles (HIMSN) and payload drug DOX, was constructed for the treatment of TNBC. It was found that DOX@HIMSN could promote the maturation of dendritic cells and the release of anti-tumor cytokines, improve the cytotoxicity of tumor cells, and stimulate the anti-TNBC immune response [379].

It was reported that Arg-Gly-Asp (RGD) peptide could be coupled with DOX and mitomycin C via amide bond linkage to form a nano drug delivery system RGD-PLN. The RGD-PLN nanoparticle could induce morphological changes of tumor cells in in vitro experiments, enhance the toxicity to tumor cells, target at tumor mesenchymal blood vessels and solid cancer cells, and show high concentration aggregation in lung metastasis. From bioimaging experiments, it was observed that intravenous administration of RGD-PLN at a dose of 10 $mg{\cdot}kg^{-1}$ could dramatically decrease the number of pulmonary metastases by 31%, which is significantly higher than 4.7% observed in the control group. Similarly, the area index of pulmonary metastases was reduced by 4.0% upon intravenous administration of RGD-PLN at a dose of 10 $mg{\cdot}kg^{-1}$, which is slightly higher than 2.4% observed in the control group. The results unambiguously showed that RGD-PLN nanoparticle could significantly inhibit pulmonary metastasis and prolong the survival time of the host [380].

There was an increase in the expression of interleukin 6 (IL-6) in TNBC as compared to that in healthy breast tissue. Confocal microscopic images showed that DOX-HA conjugated super-paramagnetic Fe_2O_3 nanoparticles could deliver higher dose of DOX to TNBC tumor cells than administration of DOX in its free from. In addition, the morphological changes observed under electron microscope showed a significant effect of enhanced apoptosis. ELISA results showed that the expression of IL-6 and NF-κB decreased significantly upon administration of DOX-HA-Fe_2O_3 NPs [381]. In addition, 4 T1 mouse breast cancer cells were implanted into the lateral part of BALB/c female mice in another research, followed by different treatments with either tumor necrosis factor-α (TNF-α) alone, or DOX alone, or combination of both. Experimental results showed that nanomicelles loaded with DOX and TNF-α could significantly increase the amount of chemotherapeutic drugs uptake by 4 T1 tumor cells in mice [382]. Many research reports have demonstrated that nanoparticle drug delivery systems could simultaneously load and deliver cytokines and chemotherapeutic drugs to activate the immune system and achieve synergistic anti-tumor effects. Moreover, tumor growth in tumor-bearing mice could be inhibited noticeably by intravenous injection of nanovesicles loaded with both cytokine IL-2 and DOX. Interferon γ could significantly inhibit the growth and metastasis of TNBC primary tumor, further promote the maturation of dendritic cells, stimulate the infiltration and activation of CD8 + T lymphocytes and natural killer cells, increase the recruitment of CD45 + immune cells and Ly6G + neutrophils, and effectively inhibit TNBC tumor cells[383]. Unique modes of immune-activation by nanomedicines were schematically

Table 8
Cyto-biological and molecular biological mechanisms of immunotherapy enhanced by nano delivery system in TNBC treatment.

Mechanism	Research level	Key research findings	Ref.
Promoting immunogenic cancer cell death	Cellular level	1) Nanomedicine formulations are an attractive modality to promote immune genic cell death (ICD) because they can concentrate cytotoxic agents in tumor cells. 2) Nanomaterials can be designed to directly interact with external energy sources, allowing amplification of ICD induced by treatments such as radiotherapy and magnetic hyperthermia. 3) ZnP@pyro PDT treatment (Zn-pyrophosphate nanoparticles loaded with the photosensitizer pyrolipid photodynamic therapy) significantly inhibited 4 T1 tumor growth with a 68% reduction in tumor volume and a 75% reduction in tumor weight compared to the PBS control group.	[494]
Ligand presentation to immune cells	Cellular level	1) Many key immunoregulatory receptors engagements, especially costimulatory signals provided to T cells and natural killer cells, occur at cell–cell junctions. Nanomedicines can present multiple ligands, either to co-engage multiple receptors on target immune cells or to engage multiple cell types simultaneously. 2) Precise spatiotemporal codelivery of aPD1 and aOX40 using nanoparticles (NP) (dual immunotherapy nanoparticles, DINP) results in improved T-cell activation, enhanced therapeutic efficacy, and increased immunological memory. DINP elicits higher rates of T-cell activation in vitro than free antibodies. 3) DINP demonstrated the highest response rate (100%) and significantly better than aOX40-NP plus free aPD1 in tumor inhibition. The survival curve showed that the tumor-free survival rate after DINPs treatment was 30%, compared to 10% after the treatment by aPD1-NP plus free aOX40 or by aOX40-NP plus free aPD1.	[495]
Linking therapeutics to immune cells	Cellular level	1) In an approach of linking supporting drugs to adoptively transferred cells, supporting drugs are encapsulated in or otherwise formulated into nanoparticles that are chemically attached to the plasma membrane of the donor cells. These nanoparticle 'backpacks' are designed to release the drug at a prescribed rate or under selected microenvironmental conditions. 2) Cell conjugated nanoparticles have also been used to backpack lymphocytes with small molecule supporting drugs. This approach of backpacking T cells with cytokines has recently entered clinical trials for a variety of solid tumor types. 3) Attaching nanoparticle formulations to immune cells substantially alters the biodistribution of the nanomedicine, providing greatly enhanced accumulation of particles in tumors when attached to tumor reactive T cells. 4) The same cytokine dose loaded in cell-bound NPs elicited markedly amplified proliferation by Pmel-1 cells (81-fold higher peak photon count relative to unmodified Pmel-1 T-cells on day 6, $P < 0.0001$). Cytokine NP-carrying T-cells displayed enhanced long-term persistence (14.8-fold and 4.7-fold higher photon counts than Pmel-1 T-cells alone at 16 and 30 days after T-cell infusion, respectively, $P < 0.0001$).	[496]
Targeting drugs to circulating lymphocytes	Cellular level	1) To use nanomaterials to directly target drugs to lymphocytes in vivo through chemically conjugated antibodies or other targeting moieties that will bind to target cell surface receptors, this strategy can be used to target either endogenous immune cells or adoptively transferred cells, but it may be particularly efficient in the case of adoptive cell therapy (ACT). 2) Another approach to delivering nanomaterials to cells in the blood is to target compounds to lymph nodes, with the goal of engaging lymphocytes as they recirculate through these secondary lymphoid organs. Nanoparticles can efficiently pass from parenteral injection sites into lymphatic vessels, and hence to lymph nodes. 3) The approach to target stimulation to CAR T cells was demonstrated, whereby an albumin-binding lipid tail was linked via a PEG spacer to a small molecule or peptide ligand for a CAR. This lipid–PEG–CAR ligand construct was efficiently shuttled to lymph nodes following parenteral injection and decorated the surfaces of macrophages and DCs through insertion of the lipid tail into antigen presenting cell plasma membranes. 4) Boosting of CAR T cells by DCs coated with the CAR ligand led to enhanced CAR T cell expansion, increased effector functions and enhanced tumor rejection in several syngeneic mouse tumor models.	[497]
Intracellular delivery of danger signals and nucleic acids	Molecular level	1) Nanomaterials can serve as surrogates of natural viruses to promote access of nucleic acids and other drugs to the cytosol. In the setting of cancer immunotherapy, this is particularly of interest for delivering compounds to activate cytosolic danger sensor proteins or to deliver RNA or DNA that encodes immunomodulatory proteins. 2) Another intriguing approach is the use of synthetic polymers that directly engage danger signal pathways. Immunostimulatory spherical nucleic acids (IS-LSNAs) comprised of RNA selective for toll-like receptors (TLRs) 7/8 are synthesized. 3) IS-LSNAs potently activate TLR7/8 via NF-κB signaling in reporter cell lines and in primary immune cells as evidenced by cytokine production and the upregulation of costimulatory receptors. These immune-stimulators are taken up by myeloid cells and antigen presenting cells more efficiently than free TLR ligands, leading to enhanced immune-stimulation. 4) IS-LSNAs induced higher levels of these molecules (by 25 times for IL-6, 30 times for IL-10, 3 times for IL-12p40, and 10 times for IP-10, and 20 times for TNFα) when compared to free RNA.	[498] [327]

(*continued on next page*)

Table 8 (*continued*)

Mechanism	Research level	Key research findings	Ref.
Temporal control of immune-stimulation	Molecular level	1) Nanomedicine formulations can be designed to interact with external energy sources such as light or heat to permit precisely controlled timing of drug release. 2) In the approach of near infrared light activatable nanoparticles complexed with TLR9 agonist CpG containing DNA, photolabile DNA strands complementary to CpG DNA were linked to the surface of near infrared light sensitive upconversion nanoparticles. 3) The immune device is composed of a rationally designed UV light-activatable immunostimulatory agent and upconversion nanoparticle, which acts as a transducer to shift the light sensitivity of the device to the NIR window. 4) This device derived immune infiltration of tumors and enhanced survival of the mice, illustrating the potential of the remote-controlled immune device for triggering of immunoactivity at the right time and site. The TNF-α and IL-6 production elicited by PCpG/UCs and NIR irradiation were still 3.3- and 6.0-fold higher than that elicited by nonirradiated PCpG/UCs, respectively. The live tumor cells in the groups treated with PCpG/UCs + NIR and CpG/UCs were significantly decreased (with a tumor cell density of 26.3 and 19.1%, respectively) in comparison with other groups.	
Altering pharmacokinetics of immunotherapy agents	Molecular level	1) Nanomedicine formulations are also being pursued as a means to allow safe systemic administration of innate immune stimulators such as TLR agonists, STING agonists and ligands for other danger sensors. 2) Liposomal nanoparticle-delivered cGAMP (cGAMP-NP) activates STING more effectively than soluble cGAMP. Within the tumor microenvironment, cGAMP-NPs direct both mouse and human macrophages (M), reprograming from protumorigenic M2-like phenotype toward M1-like phenotype; enhance MHC and costimulatory molecule expression; reduce M2 biomarkers; increase IFN-γ-producing T cells; augment tumor apoptosis; and increase CD4 + and CD8 + T cell infiltration. 3) Activated T cells are required for tumor suppression, as their depletion reduces antitumor activity. Importantly, cGAMP-NPs prevent the formation of secondary tumors, and a single dose is sufficient to inhibit TNBC. 4) cGAMP-NP treatment significantly inhibited tumor growth, leading to 100% survival at day 20 when compared with significant death among control mice receiving either blank-NP or soluble cGAMP.	[499]
Promoting immunotherapy retention in cancer tissues	Tissue level	1) Nanoparticles can be physically trapped in the TME following injection because the interstitial space in tumors is filled by a collagen rich extracellular matrix. The collagen fibres form a meshwork with irregular spacings ranging from 20 to 130 nm that traps particles of a similar or larger size. 2) Intratumoral injection of immune-stimuli chemically conjugated to liposomes 100–200 nm in diameter leads to their distribution through the local lesion and some accumulation in tumor draining lymph nodes, but no detectable dissemination into the blood. 3) Such alterations in biodistribution have allowed the safe administration of combination treatments that were lethally toxic as free drugs, with concomitant enhancements in antitumor activity. 4) Treated tumors were either completely cured (89%) or showed significantly delayed progression, while contralateral untreated tumors were also strongly inhibited, with 22% of dual-tumor-bearing animals achieving rejection of the distal simultaneously-established tumor.	[500]
Targeting lymphoid tissues	Tissue level	1) Particles with sizes ranging from 5 to 50 nm injected into tissues are too large to efficiently enter the blood vasculature, and instead preferentially enter lymphatic vessels, and are thus targeted to downstream lymph node. 2) TLR agonists conjugated to 30nmdiameter polymer nanoparticles injected intradermally near melanomas led to an accumulation of the TLR agonists in tumor draining lymph nodes. 3) Activation of DCs in these sites and induction of T cell priming that slowed tumor progression and enhanced survival.	[501]
Targeting myeloid cells	Systemic level	1) An alternative to depleting suppressive myeloid cells is to reprogramme them to a phenotype that promotes antitumor immunity. Innate immunostimulants that mimic danger signals produced by pathogens induce proinflammatory cytokine production and polarize macrophages from an immunosuppressive state towards a tumoricidal phenotype. 2) R848, an agonist of the toll-like receptors TLR7 and TLR8 identified in a morphometric-based screen, is a potent driver of the M1 phenotype in vitro and that R848-loaded β-cyclodextrin nanoparticles (CDNP-R848) lead to efficient drug delivery to tumor-associated macrophages in vivo. 3) As a monotherapy, the administration of CDNP-R848 in multiple tumor models in mice altered the functional orientation of the tumor immune microenvironment towards an M1 phenotype, leading to controlled tumor growth and protecting the animals against tumor rechallenge. When used in combination with the immune checkpoint inhibitor anti-PD-1, improved immunotherapy response rates were observed. 4) Complete tumour regression was observed in 2/7 tumors, and animals cured in the course of treatment resisted secondary tumour challenge, further indicating that the treatment had triggered anti-tumour memory.	[502]

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Table 8 (*continued*)

Mechanism	Research level	Key research findings	Ref.
Targeting non-immune stromal cells	Systemic level	1) Polymer nanoparticles designed to dissolve rapidly under the slightly acidic conditions found in tumors allowed selective delivery of angiotensin receptor blockers to CAFs within the TME as measured by the levels of active drug in the tumor in comparison with treatment with the free drug. 2) This nanomedicine therapy, when combined with checkpoint blockade, increased survival and reduced metastasis following primary tumor resection in multiple breast tumor models. Delivery of docetaxel to CAFs using these particles led to enhanced survival in models of breast. 3) Acetylated carboxymethylcellulose nanoparticles were discovered to preferentially accumulate in α smooth muscle actin positive CAFs in breast and pancreatic tumors, mediated in part by opsonization of the particles with albumin and subsequent interaction with the albumin receptor SPARC (secreted protein acidic and rich in cysteine) expressed by these cells.	[463]

shown in Fig. 7.

3.3.3.2. Delivery of tumor vaccines by nanocarriers. Researchers have developed various nanoparticle delivery systems to stimulate or activate the immune system to fight against tumors. Tumor vaccines utilize tumor-associated antigen (TAA) to activate the human body's immune system to response against tumor cells, which plays an important role in early prevention and treatment of cancers. At present, cervical cancer vaccine has been successfully marketed. In general, tumor vaccines are composed of TAA and adjuvants. As compared to direct injection, the delivery of TAA by nanocarriers can protect antigen from enzymatic degradation in serum, target the drug at dendritic cells (DCs) or T cells, and produce cross-presentation effect of antigens. As a result, the cytotoxic lymphocyte (CTL) is effectively stimulated to promote anti-tumor immunity [385,386].

DC is an important antigen presenting cell (APC) in vivo, and it is the key cell type that induces immune response. Zhuang, et al. [387] co-loaded the melanoma-specific antigen peptides TRP2180-188 and HGP10025-33 on the surface of zinc phosphate nanoparticles, and internally encapsulated the Toll-like receptor 4 agonist monophosphoryl lipid A (MPLA) as an adjuvant. DC targeting was achieved via surface modification of mannose. Both in vitro and in vivo experimental results showed that the co-presence of dual antigen peptides could stimulate a stronger immune response than a single antigen alone. The nano delivery system makes it possible

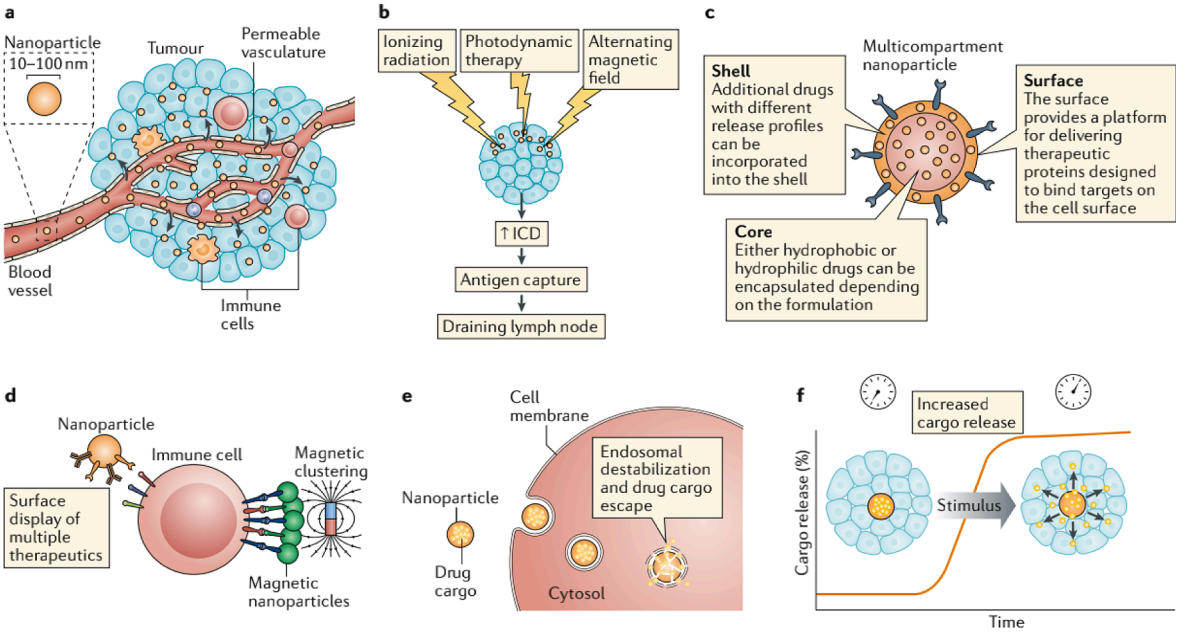

Fig. 7. Nanomedicines could promote unique modes of immuno-activation. (a) Nanomedicines can accumulate within tumor tissues via the enhanced permeation and retention (EPR) effect, concentrating the drug at tumor sites. (b) Nanoparticles could be designed to interact with external energy sources, such as ionizing or non-ionizing radiation or magnetic fields to enhance immunogenic cell death (ICD). (c) Nanomedicines allow co-delivery of therapeutic drugs with very different properties to tumor sites. (d) Multiple ligands could be arrayed on the surface of polymeric nanoparticles to enhance engagement of immune-stimulatory receptors. (e) Nanoparticles could be formulated to destabilize endosomal membranes and promote drug delivery into the cytosol. (f) Nanoparticles allow control of the kinetics of drug release, either preprogrammed through the particle chemistry or through responsiveness to an external stimulus, such as light or heat. Modified and reprinted from ref. [384]. Reproduction with permission from Springer Nature. Copyright © 2020, Springer Nature.

the targeted delivery at DC and the continuous release of antigens, leading to inhibition of the growth of melanoma. The prediction of new epitope by tumor exon sequencing technology makes it possible to produce individualized vaccines, which could be used for the synthesis of tumor specific antigen (TSA) for various tumors, and achieve precise treatment of tumors. Kuai, et al. [388] established a new nano-vaccine system for individualized neo-epitope vaccination. Phospholipids and apolipo-protein-like polypeptides were used to produce high-density lipoprotein like nano-disc. These nano-discs could be loaded with antigenic peptides and adjuvants to improve the efficiency of their delivery to lymphoid organs, achieve continuous antigen presentation of DC, produce a large number of CTL, and realize further specific recognition and killing of tumor cells. Researchers loaded the multi-epitope antigen peptide of sequenced

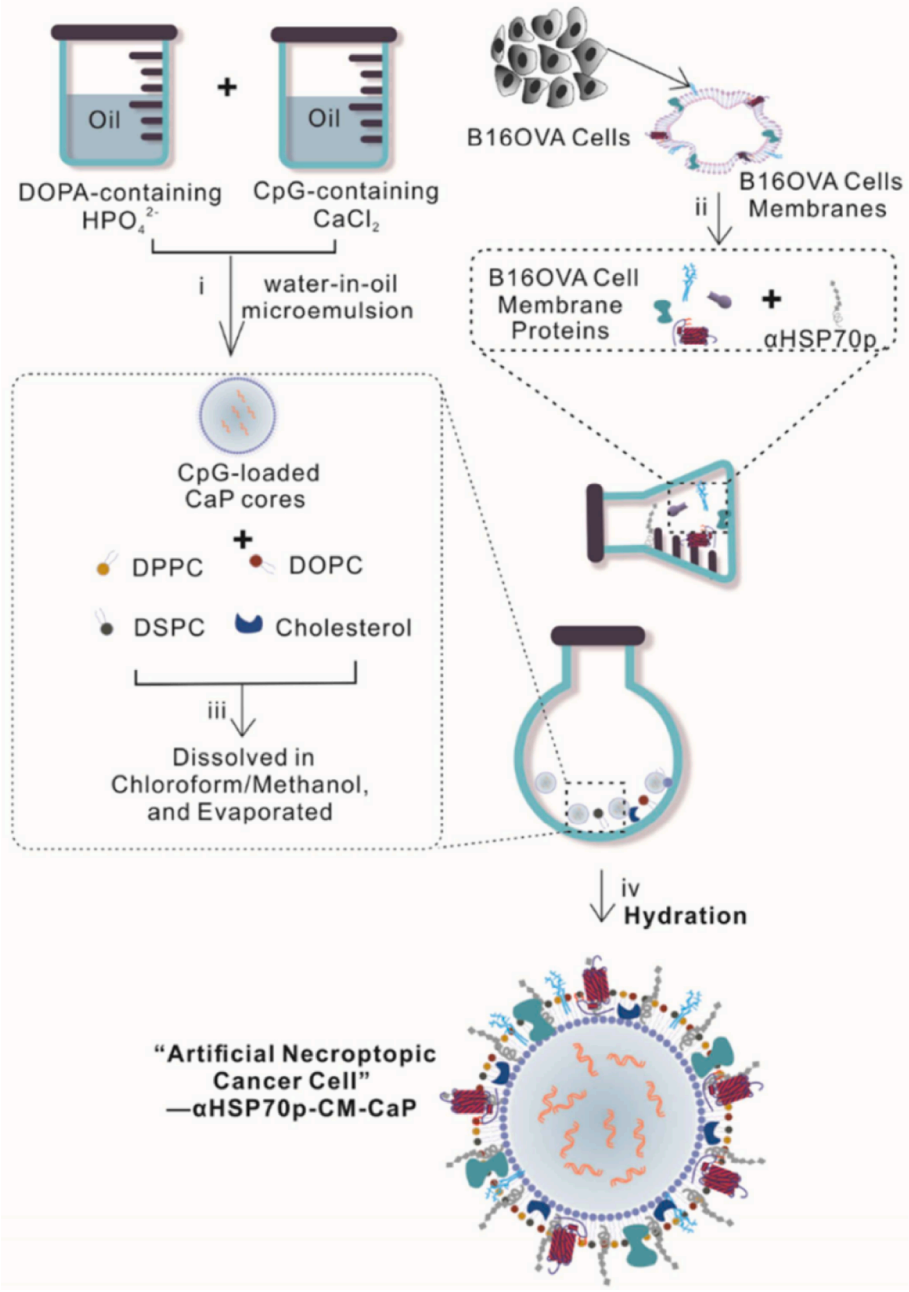

Fig. 8. Preparation of the αHSP70p-CM-CaP nano vaccine, which enables the co-delivery of three components, B16OVA cells membrane proteins (CM), adjuvant CpG and an α-helix peptide modified HSP70p. (i) Preparation of the CpG-containing CaP core using a water-in-oil microemulsion method. (ii) Isolation of B16OVA cancer cells membrane proteins (CM) from the cultured B16OVA cells by detergent. (iii) Lipids and the CaP core were mixed and evaporated to form a thin film. (iv) The film was hydrated with αHSP70p- and CM- containing solution to form the αHSP70p-CM-CaP, which was further processed by centrifugation and purification. Modified and reprinted from ref. [393]. Reproduction with permission from Elsevier. Copyright © 2018, Elsevier Ltd.

melanoma on the nano-disc. In a mouse model, the immune checkpoint blocker, programmed cell death protein 1 (PD-1) antibody and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody, were used in combination with the vaccine to enhance the anti-TNBC tumor efficacy. Such a combined therapy eventually completely eliminates the TNBC tumor. Two studies published in Nature confirmed the possibility of the implementation of personalized vaccines and showed good safety in small-scale human trials, bringing positive clinical responses to high-risk melanoma patients. Among 13 patients, 8 cases showed no signs of recurrence within 23 months after the vaccination, and 5 cases with proliferation of cancer at the time of vaccination. 2 cases of them had tumor regression, and a case had complete remission after vaccination and using PD-1 antibody drug [389]. In another study, 4 of the 6 patients had no recurrence within 25 months after vaccination, and 2 patients with recurrent disease subsequently received PD-1 antibody drug for treatment, and the tumor was completely eliminated [390].

Some studies showed that adjuvants can greatly improve the immune activities of DC, lymphoid cells and macrophages to specific antigens. Cytosine-phosphate-guanine oligonucleotide (CpG)) is a classical immune adjuvant. Duan, et al. [391] prepared a pH responsive nano-delivery system, which could be degraded to release antigens and adjuvants CpG, TAA and CpG in the acidic environments of cytoplasm and inclusion body. This could enhance the cross-presentation of antigens, and stimulate the activation of T cells and the generation of cytokines. Kang, et al [392] designed a nano-delivery system that could deliver TAA to natural killer cell (NK cell) and APC. The process of synthesis of the nano-delivery system was shown in Fig. 8. In the preparation process, the TAA, aHSP70p protein and adjuvant CpG of melanoma were wrapped inside the calcium phosphate nucleus of a nano delivery system. The calcium nucleus was coated with bilayer lipid membranes. Effective lymphocyte transfer and multi-epitope T cell reaction could be observed by injecting the nanoparticles into mice. The composite nano delivery system could also induce the amplification of CD8 + T cells and NKG2D + NK cell subsets. The nanoparticles also had synergistic effect on the antigen presentation and maturation of bone marrow derived DC.

3.3.3.3. Delivery of immune antibodies by nanocarriers. Immunotherapy based on immune antibodies has become an effective modality for anti-cancer treatment. Monoclonal antibody is provided with strong specific binding ability toward a specific antigen, which could reduce the adverse reactions at non-targeted sites, and improve the efficacy of immunotherapy of tumors. Immunotherapy, however, suffers from many limitations, such as poor pharmacokinetics, limited tumor penetrability, and difficulty to cross the biological barriers [394,395]. To avoid occurrence of these problems, the antibody could be wrapped in a nanocarrier and delivered directly to tumor sites. Kim, et al. [396] used polyion complex micelle to load and deliver an antibody to the cytoplasm. Their results showed that the antibody delivered by nano-micelles could avoid lysosome degradation, and thus enhance the recognition ability of APC for intracellular antigen.

As a tumor necrosis factor receptor, OX40 monoclonal antibody showed good antitumor effect in an animal model. However, it did not show similar antitumor effect in a phase I clinical trial [397]. Chen, et al. [398] constructed biodegradable PLGA nanoparticles to carry the OX40 monoclonal antibody. Their results showed that the PLGA-OX40 nanoparticles could better induce the proliferation of CTL, and enhance the specific cytotoxicity of tumor antigen and the production of cytokines as compared to administration of free anti-OX40 antibody. It was confirmed that the delivery of OX40 monoclonal antibody by PLGA nanoparticles could produce a prolonged, enhanced antigenic specificity immune response. In addition to the use of nanocarriers for the delivery of antibody, nanobody (Nb) has also become a hot research topic in recent years. Traditional antibody plays an important role in the tumor treatment, but the tumor penetration ability is poor. Sometimes, it is difficult for a large-sized antibody to reach a specific target site. Nb contains only a variable region of antibody heavy chains, and thus the relative molecular mass is small. It is relatively easier for Nb to infiltrate into some cancer tissues, where it is otherwise difficult for large antibody molecules to reach. In addition to directly using Nb as immune blockers in tumor treatment, it could also be delivered by using nano-delivery systems [399]. van Driel, et al. [400] co-loaded epidermal growth factor receptor's Nb and a photosensitizer in the same nanocarrier for photodynamic therapeutic treatment of head and neck cancer, and achieved a very good outcome.

3.3.3.4. Delivery of interfering genes by nanocarriers. The delivery of small interfering RNA (siRNA) by nanocarriers provides a method for intracellular antigen synthesis, which has great application values in antitumor immunotherapy [401,402]. Kranz, et al. [403] developed a RNA-lipoplex (LPX) complex, loaded with siRNA of encoding tumor antigens, by controlling the positive and negative charge ratio, to control the spleen targeting and transfection efficiencies of RNA. The fatty-acid layer in the outer layer of liposomes protects RNA from enzymatic degradation by ribonuclease. The RNA-LPX nanocomposite could achieve targeted delivery of RNA to DCs. The RNA-LPX could achieve effective uptake of RNA by DC and macrophages, stimulate high expression level of coding antigens, and induce plasmocyte-like DC and macrophages to release interferon α (IFNα). It was also found that the RNA-LPX could promote synthesis of new antigens and induce strong responses of memory T cells and effective T cells. Li, et al. [404] constructed a cationic nanoparticle, NPsiCTLA-4, for the delivery of CTLA-4 siRNA, which could effectively transfer siRNA to T cells in in vitro experiments, and decrease the level of CTLA-4 mRNA and protein after activation of T cells. In vivo experiments showed that the nanoparticles could introduce CTLA-4 siRNA into CD4 + and CD8 + T cell subsets at tumor sites, increase the proportion of anti-tumor CD8 + T cells, and decrease the proportion of inhibitory regulatory T cell (Treg) in tumor infiltrating lymphocytes (TIL). NPsiCTLA-4 could effectively inhibit the tumor growth, and prolong the average survival lifespan of mice bearing melanoma.

Tumor-associated macrophage (TAM) is the ideal target for tumor immunotherapy [405]. The M2 macrophage is a leukocyte with large quantity in tumor microenvironments; and it can induce immunosuppression through multiple mechanisms. Qian, et al. [406] constructed a polypeptide lipid nanoparticle (M2NP) for targeting at the M2-like TAM to resolve the problem of the immunosuppressive effect induced by M2 cells. The M2NP could load simultaneously both polypeptides for targeting at M2 cells and siRNA that

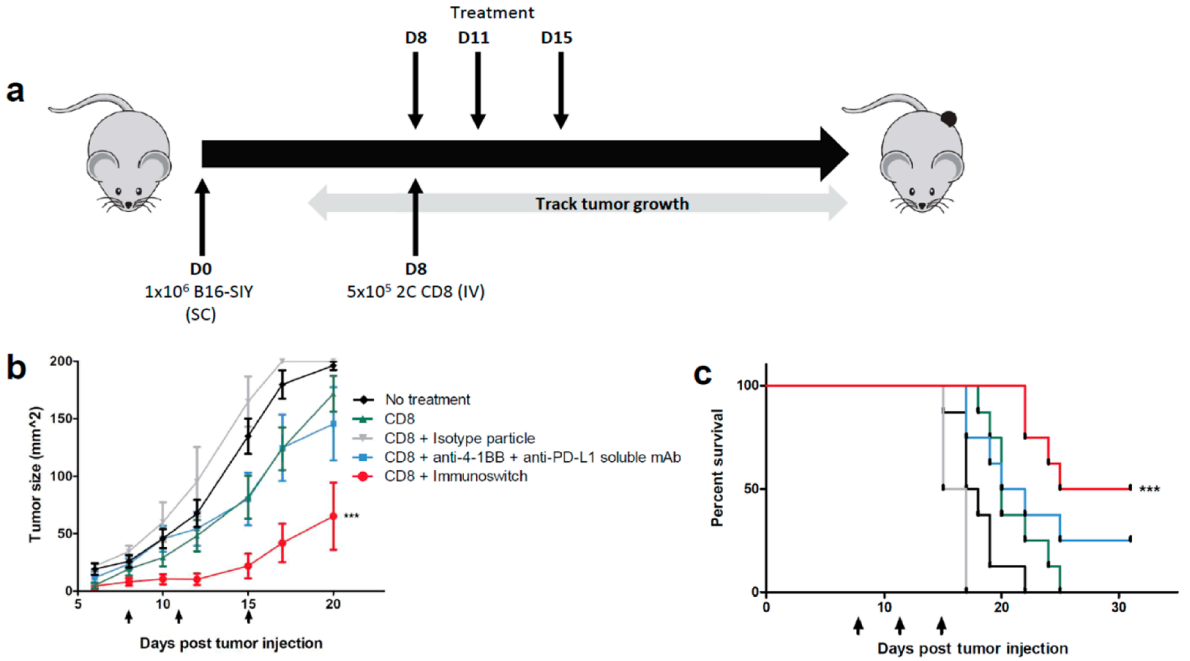

Fig. 9. Immuno-switch nanoparticles could inhibit tumor growth in vivo. (a) Schematic time line in the in vivo mice model. C57BL/6 mice (n = 4 isotype, n = 8 all other groups) were injected with 1×10^6 B16-SIY cancer cells subcutaneously (SC) on day 0. 2C CD8 cells were isolated on day 0, stimulated with anti-CD3/anti-CD28 expander beads on days 0 and 4 as previously described, and isolated from the beads and injected intravenously (IV) on day 8. Nanoparticle and antibody treatments were given intratumorally (IT) on days 8, 11, and 15, respectively. (b) Tumor growth curves show that immune-switch treatment could significantly delay the tumor growth as compared to no treatment and all other controls. Black arrows indicate the time (day) points for treatment. Significance of data was evaluated by two-way ANOVA with Bonferroni post-test ($p < 0.001$). (c) Immuno-switch treatment could significantly extend the average survival lifespans of treated mice groups as compared to the control group without treatment. Significance of data was determined by log-rank test ($p = 0.0002$). Combined results from two independent experiments are shown with ***$p < 0.001$. Modified and reprinted from ref. [407]. Reproduction with permission from American Chemical Society open access. Copyright © 2017, American Chemical Society.

interferes with the expression of colony stimulating factor 1 receptor. As compared to the control group, the M2NP loaded with siRNA could eliminate the M2-like TAM by 52%, reduce 87% of the tumor size, and prolong the average survival lifespan of mice (Fig. 9). In addition, the molecular targeting strategy could also inhibit the production of immunosuppressive factor interleukin (IL-10) and transforming growth factor β, increase the expressions of immunomodulatory factors IL-12 and IFNγ, and increase CD8 + T cell infiltration in tumor microenvironments by 2.9 times. The M2NP carrying siRNA could also lower the expressions of T cell immunoglobulin, mucin protein 3 (Tim-3) and CD8 + T cell, and stimulate the secretion of IFN γ by 6.2 times.

3.3.3.5. Nanocarriers rebuilding tumor immune microenvironments. Tumor microenvironments have many unique physiological characteristics, including hypoxia, micro-acidity, vascular irregularity, etc. In addition, tumor microenvironment can produce immunosuppressive micro-domains by releasing cytokine mediators and aggregating immunosuppressive cells, which is an important cause leading to chemodrug tolerance and poor prognosis [408]. Therefore, rebuilding the tumor immunosuppressive microenvironments is of great importance to the success of tumor immunotherapy. Some studies have showed that a low dose of paclitaxel can inhibit Treg activity, and enhance cytokine's anti-tumor effect [409]. Song, et al. [410] constructed a nanogel coated with erythrocyte membrane which is sensitive to tumor microenvironments. The nanogel was loaded with chemotherapy drug paclitaxel and cytokine IL-2, wherein the paclitaxel had immune-modulatory effect. Paclitaxel in a low dose could regulate immune activity, activate DC, reduce the number of Treg, and further enhance the immune effect and IL-2 induced cell activation. This new nanogel has good tumor targeting and micro-acid environmental response abilities, could enhance the tumor penetration of chemodrugs, and mediate combined immunotherapy and chemotherapy with synergistic anti-tumor effect. Chiang, et al. [411] designed a method to co-load immune checkpoint blocking inhibitor PD-L1 antibody and T cell activator CD3, CD28 antibodies onto iron oxide nanoparticles (IO@FuDex3). The IO@FuDex3 could effectively enhance the proliferation of TIL, and rebuild the immunosuppressive tumor microenvironment. Furthermore, it can effectively target at tumor cells under the guidance of a magnetic field (by an external magnet), achieve accurate anti-tumor treatment to the greatest extent, and reduce the adverse effects on normal cells. Kosmides et al. [412] prepared an "immuno-switch particle", which were loaded with both PD-L1 antibody and 4-1BB antibody. 4-1BB is a costimulatory molecule of T cell, and can stimulate the activation and proliferation of T cells after combining with its ligands. The nano delivery system not only could block the immunosuppressive PD-L1 pathway of NK cells, but also could activate the 4-1BB costimulatory pathway in CD8 + T cells. Their results showed that the nano "immune-switch" nanoparticles could exert significant antitumor effects on mouse melanoma

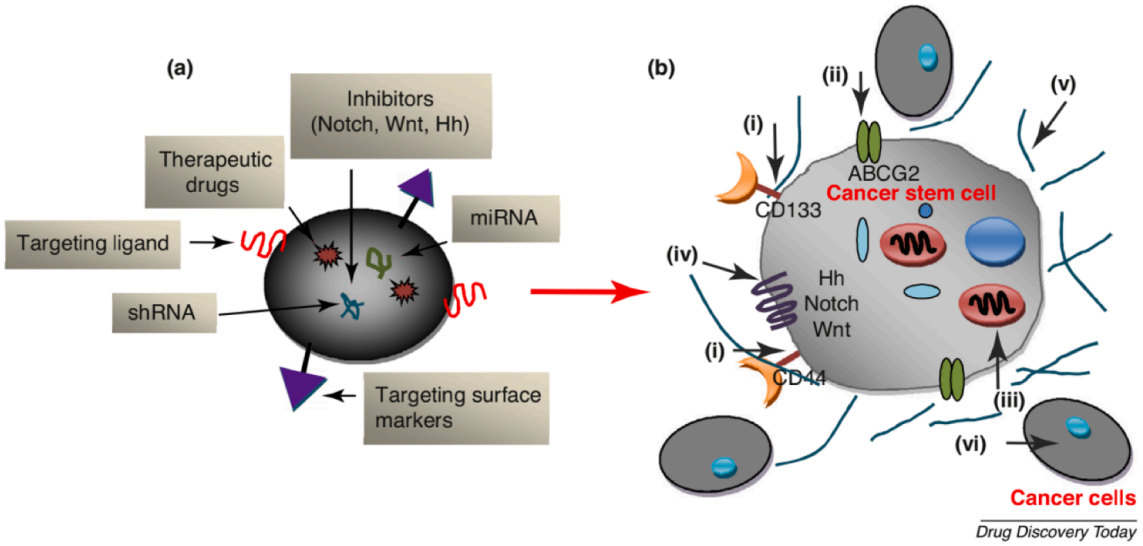

Fig. 10. (a) Targeting of cancer stem cells (CSCs) by functionalized nanoparticles. (**b**) Cellular targets: (i) cell surface biomarkers, (ii) drug efflux pumps, (iii) metabolism, (iv) cell signaling pathways, (v) tumor niche, and (vi) bulk cancer cells. Abbreviation: shRNA, short hairpin RNA. Modified and reprinted from ref. [90]. Reproduction with permission from Elsevier. Copyright © 2017, Elsevier Ltd.

and colon cancer models, and also relieved the immunosuppressive state of tumor microenvironments.

3.3.4. Nanoparticles for targeting at breast cancer stem cells (BCSCs)

Emerging evidences suggested that breast cancer stem cells (BCSCs) having tumor-initiation and self-renewal abilities are able to create chemotherapy resistance, and promote tumor metastasis and recurrence. BCSCs have unique growth and recovery abilities, including self-renewal ability, differentiation potential, and resistance to most of anti-cancer treatments, such as radiotherapy, chemotherapy, etc. [413,414]. Self-renewal ability is essential for the maintenance and propagation of BCSCs. To escape from strict regulation, BCSCs rely on key dysregulated SRSPs, such as signal transducer and activator of transcription (STAT) signaling, Proto-oncogene tyrosine-protein kinase Src (SRC) signaling, and Wnt/β-catenin signaling, which lead to extensive cell propagation [415]. This aberrantly activated self-renewal ability of CSCs is considered as an early event in the tumorigenesis, which enables these cancer stem cells to resist against conventional chemotherapeutic agents, and results in tumor recurrence [416].

TNBC tumors have been consistently reported to display cancer stem cell (CSC) signatures at functional, molecular, and transcriptional levels. In recent decades, CSCs-targeting strategies have achieved good therapeutic effects on anti-tumor treatment of TNBC in multiple preclinical studies. Some of these strategies are currently being evaluated in clinical trials. In general, their clinical applications are not successful due to the poor water solubility of chemodrugs, short blood circulation time, instability and off-target effect [416]. The concepts for targeting at cancer stem cells (CSCs) by functionalized nanoparticles were schematically presented in Fig. 10. A nano drug delivery system targeting at BCSCs could specifically carry anti-BCSCs drugs to BCSCs without having off-target effect. At present, polymeric nanoparticles (PNPs), liposomes and micelles have attracted great attention from researchers [417,418]. A nano drug delivery system usually consists of three parts, namely, core materials, therapeutic drugs and surface ligands.

Table 9
Clinical trials related to applications of nanoparticle delivery systems for targeted TNBC treatment.

Entry	NCT number	Title	Drug with nanoparticle	Status	Study type	Phase	Ref.
1	NCT03719326	A Study to Evaluate Safety/Tolerability of Immunotherapy Combinations in Participants with Triple-Negative Breast Cancer and Gynecologic Malignancies	Albumin/ paclitaxel bound NP	Recruiting	Interventional	Phase 1	[503]
2	NCT01525966	Carboplatin and Paclitaxel Albumin- Stabilized Nanoparticle Formulation Before Surgery in Treating Patients with Locally Advanced or Inflammatory Triple Negative Breast Cancer	Paclitaxel/ albumin-stabilized NP formulation	Active, not recruiting	Interventional	Phase 2	[504]
3	NCT00733408	Nab-Paclitaxel and Bevacizumab Followed by Bevacizumab and Erlotinib in Metastatic Breast Cancer	Paclitaxel/ albumin-stabilized NP formulation	Completed	Interventional	Phase 2	[505]

4. Clinical trials using nanoparticles to treat TNBC

In the targeted therapy of TNBC, many clinical trials have been reported to adopt nanoparticles to deliver genes/drugs to treat TNBC. Some reports have already made initial progress. Recent clinical trials related to clinical applications of nanoparticle delivery systems for targeted TNBC treatment were summarized in the Table 9.

Albumin-bound paclitaxel (nab-PTX) nanoparticle has been reported to be highly effective and toxic towards TNBC cancer cells as compared to free Cremophor-based Taxol, and achieved high pathological complete response (pCR) rates in patients with TNBCs [419-421]. Futamura et al. conducted a phase II clinical trial, evaluating the safety and efficacy of preoperative neoadjuvant chemotherapy (NAC) with nab-PTX, followed by an epirubicin plus cyclophosphamide (EC)-based regimen for operable breast cancer [422]. Four cycles of every-3-week (q3w) nab-PTX [plus q3w trastuzumab in cases of human epidermal growth factor 2 (HER2) positivity, followed by four cycles of q3w EC, were administered to patients with operable breast cancer (stage IC–IIIA). The primary endpoint was the pCR rate (ypT0/TisypN0). A total of 55 patients were enrolled, all of them underwent NAC plus radical surgery. The overall pCR rate was 22.2% ($p = 0.006$). The pCR rates for patients with TNBC, HER2-rich, luminal/HER2, and luminal B breast cancer molecular subtypes, were 15.4%, 60%, 29.4%, and 10.5%, respectively [423]. The expression of secreted proteins being acidic and rich in cysteine, showed no association with pCR. The clinical response rate was 70.4% (38/54), and the safety profile was tolerable. Although sensory neuropathy, arthralgia, and myalgia were common AEs after nab-PTX therapy, they were tolerable and could be resolved by the end of NAC [423]. This clinical trial demonstrated the necessity of a novel pre-operative NAC regimen before sequential treatments by nab-PTX (plus TZ in HER2-positive patients) and then EC. This regimen using nanoparticle delivery system appears to be an effective alternative for NAC in TNBC patients. Similarly, in an earlier study, Mrózek et al. conducted a Phase II trial of neoadjuvant adopting weekly drug administration of albumin-bound paclitaxel nanoparticle, carboplatin, and biweekly bevacizumab therapy in women with clinical stage II or III HER2-negative breast cancer [424]. A total of 33 female patients were enrolled. Six patients (18%) achieved pCR. All pCRs occurred in TNBC (pCR = 50% for TNBC). At the end of the cycle 2, the changes in relative angiogenic volumes were significantly different between responders and non-responders ($P = 0.001$) [425]. The major toxicity of this NCT was myelosuppression. So, we could see from this trail that NCT with weekly drug administration of nab-PTX, carboplatin, and biweekly bevacizumab resulted in a pCR rate that was neither superior to the historical data with anthracycline- or taxane-containing NCT, nor to carboplatin and taxane combinations in patients with TNBC [425]. Apart from that, Symonds L et al. conducted a Phase II clinical trial of nab-paclitaxel and bevacizumab, followed by maintenance therapy with erlotinib and bevacizumab for patients with metastatic TNBC. A total of 55 evaluable patients were enrolled. The median PFS and OS for the cohort was 9.1 months (95% CI, 7.2–11.1) and 18.1 months (95% CI, 15.6–21.7), respectively. Among the 53 patients with measurable disease, 39 (74%) had experienced a partial response; and 10 (19%) had stable disease. The most common toxicity of this trial was uncomplicated neutropenia. In another words, this clinical trial resulted in PFS similar to that of other trials, providing a promising break from cytotoxic chemotherapy for TNBC patients [426]. Additionally, Gluz O and his colleague conducted a randomized WSG-ADAPT-TN trial to compare carboplatin vs. gemcitabine with a nab-paclitaxel backbone with a focus on early response. A total of 336 patients were enrolled. pCR favored nab-paclitaxel/carboplatin group (28.7% vs 45.9%, 95% CI (dBA) = 6.2% to 27.9%, $P = 0.002$), and was lower in non-responders than in early responders (19.5% vs 44.4%, $P < 0.001$). This randomized trial suggested an excellent tolerability, high efficacy, and a

Table 10
Applications of nanoparticle delivery systems in the treatment of TNBC.

Therapeutic drug	Drug delivery system	Mechanism	Therapeutic outcome	Ref.
Dual receptor tyrosine kinase inhibitor ZD6474	ZD6474-AuNP	Inhibit tumor cell proliferation, migration, invasion and induce apoptosis	Reduced tumor volume	[506]
Cisplatin and docetaxel	NACLAT1-AuNP	Kill tumor cells by photothermal ablation	Reduced tumor recurrence and metastasis	[507]
5-Fu	5-Fu-AuNP	Increase the expression of mitogen activated protein kinase phosphatase 1 and histone H3, and decrease the expression of thymidylate synthetase	Increase the sensitivity of tumor cells to 5-FU and induce tumor cell death	[508]
Pd[DMBil1]-PEG750	Photosensitizer-silica core-NP	Produce strong active oxygen, oxidize and damage tumor cells	Induce TNBC cell death non-invasively	[509]
DOX	DOX-LDGI-NP	Enhance the penetration ability of drugs in tumor area and promote the apoptosis of tumor cells	Superior effect of synergistic therapy than that of drug therapy alone	[510]
miRNA-34a	miRNA34a-LBL-AuNP	Inhibit the expression of tumor proliferation genes SIRT1 and Bcl-2, and effectively inhibit the proliferation of tumor cells	Tumor cell proliferation decreased by 33%	[511]
miRNA-708	miRNA708-AuNP	Target at tumor cell clone with miRNA 708 low expression, inhibit tumor metastasis	Decreased lung metastasis of TNBC	[433]

Abbreviations: 5-FU: 5-fluorouracil; Pd[DMBil1]-PEG750: palladium 10,10-dimethyl-5,15-bis (pentafluorophenyl) biladiene-based photosensitizer; ZD6474-AuNP: dual receptor tyrosine kinase inhibitor-amphiphilic copolymer-gold nanoparticles; NACLAT1-AuNP: neutral amino acid transporter 1-gold nanoparticles; Fu-AUNP: fluorouracil-gold nanoparticles; DOX-LDGI-NP: doxorubicin-gold nanoparticles-iron oxide plasma magnetic hybrid nanoparticles; miR34a-LBL-AuNP: microRNA34a layer assembled gold nanoparticles; miR708-AuNP: microRNA708 layer-by-layer assembled gold nanoparticles.

neoadjuvant nab-paclitaxel/carboplatin regimen, superior to nab-paclitaxel/gemcitabine in patients with TNBC [427].

5. Conclusion and perspective

TNBC is considered highly aggressive because of its strong diversity, the difficulty to classify the aggressiveness, and the poor prognosis. For the detection of TNBC, Véronique Baud et, al. found a new biomarker for diagnosing TNBC: a new antibody which can specifically target RelB phosphorylation through the NF-κB signaling pathway to facilitate the diagnosis of TNBC and predict its aggressiveness [428]. For the treatment of TNBC, nanoparticles could be surface-modified with TNBC-targeting probe and used to co-deliver various kinds of chemodrugs and biologically active species, such as proliferation signaling pathway key enzyme inhibitor ZD6474 [429], cisplatin/docetaxel [430], 5-fluorouracil [431], Pd[DMBil1]-PEG750 photosensitizer [432], tumor proliferation inhibiting genes miRNA-708 and miRNA-34a [433,434], etc, and achieve synergistic TNBC-targeting and therapeutic effects, which are difficult to achieve using individual payload component alone. By using nanoparticle delivery systems, it becomes possible to effectively inhibit tumor proliferation and metastasis via various approaches and mechanisms (see Table 10), and effectively suppress the growth, metastasis and recurrence of tumor cells and their drug-resistant clone cells. The significance of using nanoparticle delivery systems to exert tumor-targeting therapy for the treatment of TNBC is mainly reflected in the following aspects: 1) when combined with chemotherapy drugs, photothermal therapy could inhibit and kill TNBC cells in many ways, especially the removal of tumor stem cells, which is expected to mitigate or solve the problem of tumor proliferation, metastasis and recurrence. 2) The combination of gene therapy and nanotechnology promotes the precision and intelligence of TNBC treatment significantly. 3) A nano delivery system can make it possible to combine immunotherapy and chemotherapy, which can effectively control tumor angiogenesis and inhibit infiltration of normal tissue. 4) With the abilities to target at tumor sites, nanoparticle delivery systems could achieve high selectivity, good histocompatibility and low cytotoxicity to normal tissues/organs.

The key features of nanoparticle delivery systems distinctly different from molecular drugs are their tumor-targeting ability and massive multidrug/gene co-delivery ability. The development of nano delivery systems presents a completely different way of drug designs and usages. In conventional molecular drug design and discovery, the main focus is to search for molecular drugs with structures to achieve large affinity differences between normal human enzymes/proteins and those of bacteria/virus/cancer cells, so as to reduce the unwanted adverse effects. The extent of adverse effects in molecular drugs is significantly determined by how large the affinity differences between the to-be-treated species and the normal tissues. The larger the affinity differences, the smaller the unwanted side effects. Whereas in the nanoparticle delivery systems, the main challenge switches from searching drugs with large affinity differences to the precision of tumor site- (or to-be treated species-) targeting. In general, cancer cells (as well as bacteria/virus) have some specific overexpressed receptors on the surface of their cellular membranes, whereas normal human cells have very few the same types of receptors on their membrane surface. With precise targeting using the cancer cell receptor-specific binding probes, a nano delivery system can carry multi-toxic drugs to diseased sites with very low off-target adverse effects to normal tissues. By using nanoparticle delivery carriers with precise tumor-targeting, those otherwise “bad” chemodrugs with poor water solubility or strong adverse effects now can be re-used to treat diseases and cancers. Currently, it was not yet observed or reported that cancer cells (and bacteria) are able to pump nanomedicines out of cancer cells and create resistance to nanomedicines. Therefore, nano delivery systems provide an alternative route to overcome the tough drug resistance problem commonly encountered in clinic treatment of TNBC and other cancers using conventional molecular chemodrugs alone.

5.1. *The future development of nanoparticle-based nanomedicines*

Although having the above-mentioned unique features, nanoparticle delivery systems, however, have their own problems and shortcomings, which are awaiting to be conquered in the future. Firstly, in the aspect of drug release from nanocarriers, there is a need to overcome the interference of tumor microenvironments, and other problems, such as limited tumor tissue permeation, local osmotic pressure barrier of tumor tissues, charge barrier from cancer cell membranes, and the increasingly serious drug-resistant clone of heterogeneous tumor cells for nano delivery systems to play a role [435,436]. Secondly, nanomaterials are featured by low and unclear metabolism pathways in vivo, nonlinear drug metabolism, unwanted distribution in some major organs (via splenic and hepatic macrophage clearance), etc., which bring new challenges to the study of pharmacokinetics and toxicokinetic of nanomedicines. How to avoid splenic and hepatic macrophage clearance, accumulation and thus cytotoxicity of nanomedicines to major organs is one of the major challenges in the future development and clinical applications of nano delivery systems. Thirdly, the interactions with biological species (such as, blood, proteins, immune cells, tissues, etc), the long-term cytotoxicities and metabolism pathways of nanomaterials reported up-to-date were rarely investigated and evaluated. These issues have to be resolved before nanomedicines can be widely and safely applied in real world clinical treatments of TNBC and other human cancers. Despite many the above-mentioned issues have not been resolved, some patients may still benefit from the use of nanomedicines, especially those suffering from severe adverse side effects of conventional chemodrugs, and the absence of effective treatment modalities, and are facing the threat of immediate or short-term deaths. Being able to extend life span and kill cancer cells effectively has a higher priority than considering the long term cytotoxicities of nanomedicines. With continuous improvement and further research on the in vivo metabolisms of nanomaterials and in-depth research on targeting at TNBC, a comprehensive targeted nano delivery system integrating diagnosis probes, imaging contrast reagents, and multi-therapies (such as gene therapy, photothermal therapy, medicinal chemotherapy and immunotherapy), will be able to provide more diverse, more efficient, more accurate and more intelligent strategies for the clinical treatment of TNBC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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