

Review Article

Nanobiotherapeutic strategies to target immune microenvironment of triple-negative breast cancer

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Abstract: Triple-negative breast cancer (TNBC) is the subtype with the least favourable outcomes in breast cancer. Besides chemotherapy, there is a chronic lack of other effective treatments. Advances in omic technologies have liberated us from the ambiguity of TNBC heterogeneity in terms of cancer cell and immune microenvironment in recent years. This new understanding of TNBC pathology has already led to the exploitation of novel nanoparticle systems, including tumor vaccines, oncolytic viruses, and antibody derivatives. The revolutionary ideas in the therapeutic landscape provide new opportunities for TNBC patients. Translating these experimental medicines into clinical benefit is both appreciated and challenging. In this review, we describe the prospective nanobiotherapy of TNBC that has been developed to overcome clinical obstacles, and provide our vision for this booming field at the overlap of cancer biotherapy and nanomaterial design.

Keywords: Triple-negative breast cancer, nanotechnology, biotherapy strategies, tumor immune microenvironment

Introduction

Triple-negative breast cancer (TNBC) is the most aggressive, metastatic, and refractory subtype of breast cancer. TNBC has no response to endocrine therapy and anti-HER-2 targeted therapy because of few expressions of estrogen receptor and progesterone receptor and few amplifications of ERBB2 (commonly referred to as human epidermal growth factor receptor 2 [HER2]) [1, 2]. Compared to other solid tumors, TNBC is more heterogeneous, which lead to poor prognosis, high risk of relapse, short progression-free survival and low overall survival. Currently, the TNBC is treated with anticancer agents alone or in combination with surgery or radiation therapy. Chemotherapy supplies a major part of the therapeutic modality [3, 4]. In the last few decades, effective alternatives for biotherapy have improved the therapeutic outcome, prognostic value, and diagnostic value of TNBC [5-7]. Patients with BRCA1/2 gene mutations can be

treated with poly (ADP-ribose) polymerase inhibitors such as olaparib (Lynparza) and talazoparib (Talzenna) [8-10]. To date, pembrolizumab (Keytruda), an immune checkpoint inhibitor, is the only anti-PD-1 monoclonal antibody that the FDA has approved for TNBC [11, 12]. Furthermore, the TROP2 antibody-drug conjugate sacituzumab (Trodelvy), conjugated to the chemotherapeutic SN-38, has already been FDA-approved for TNBC [13, 14].

Targeted delivery to TNBC is a hot topic among researchers. In this context, nanoparticle delivery systems have proven to be effective in providing considerable tumor delivery via active- and passive-targeting mechanisms [15-17]. The shortcomings and limits of nanomaterial-based biotherapy approaches are currently being addressed in the landscape of product development for nanomaterial-based biotherapy approaches. An expanding landscape of innovation approaches for nanomaterial-based biotherapy management is currently address-

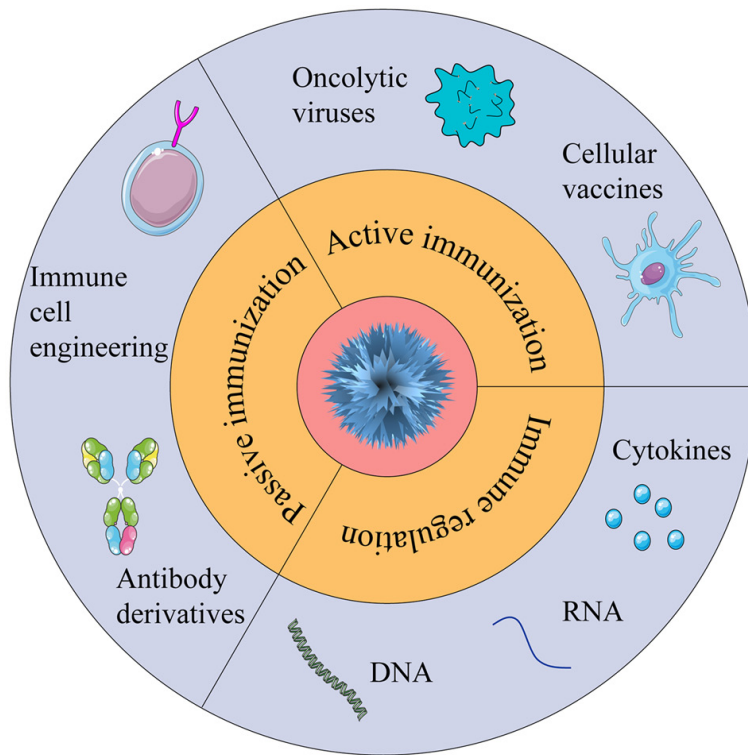


Figure 1. Graphical abstract. Triple-negative breast cancer (TNBC) exhibits poor prognosis, high risk of relapse, short progression-free survival and low overall survival. The review expounds on the heterogeneity of TNBC and antitumor mechanism of nanobio-drug delivery system. The review also critically discusses the nanobiotherapeutic strategies to target immune microenvironment for managing TNBC from three aspects: active immunization, passive immunization and immune regulation.

ing the shortcomings and limitations, including increasing biodistribution and therapeutic window with intravenous administration [18], specific tumor targeting [19], reducing treatment-related adverse events [20]. Here, we discuss the currently heterogeneous entirety of the TNBC ecosystem and its immune-related characteristics, as well as expanding nanobiotherapeutic options (**Figure 1**). Since this review concentrates on nano-delivery systems relevant to TNBC cells and immune microenvironment, the nanomedicines that respond to tumor microenvironment (TME) characteristics and matrix components will not be extensively discussed, such as stromal cells [21], hypoxia [22], low pH [23], and redox status [24].

Heterogeneity of triple negative breast cancer in tumor microenvironment

The TME of TNBC is a heterogeneous and complex organization composed of cancer cells,

stroma and endothelial cells, innate and adaptive immune cells, and transformed extracellular matrix [25]. Over the last decade, it has become increasingly clear that the components in the TME hamper antitumor response and help the progression and metastasis of TNBC [26]. The immune TME is modified by the pathogenic mechanisms of cancer cells and carcinogens [5]. The TNBC landscape is the entirety of a coordinated ecosystem that relates to intrinsic characteristics caused by immune editing. Currently, the intrinsic and extrinsic features of TNBC cells have been evaluated separately due to complementary biological features [27, 28]. Among various techniques deployed to assess gene expression, RNA sequencing (RNA-seq) can provide qualitative (RNA sequence) and quantitative (RNA abundance) analyses of either targeted mRNA transcripts or the complete transcriptome of a particular tissue. Two methods of

RNA-seq are henceforth commonly considered for onco-immunology studies: standard bulk RNA-seq and single-cell RNA-seq [29]. Technological improvements in single-cell analyses are offering unprecedented prospects for the reinterpretation of TNBC heterogeneity. As a surrogate of what scRNA-seq analysis can produce, more than 50 deconvolution algorithms for bulk RNA-seq data are published, such as TIMER (<https://cistrome.shinyapps.io/timer/>), CIBERSORT (<https://cibersort.stanford.edu/>), ABIS (<https://giannimonaco.shinyapps.io/ABIS/>), EPIC (https://gfellerlab.shinyapps.io/EPIC_1-1/) and so on.

Previously, heterogeneity studies primarily provided more explanations for the genomic, transcriptomic, and proteomic properties of intrinsic TNBC cells [30, 31]. As is widely accepted, TNBC is classified into four transcriptome-based subtypes relied on analyses of bulk mRNA profiles: basal-like 1 and 2, luminal

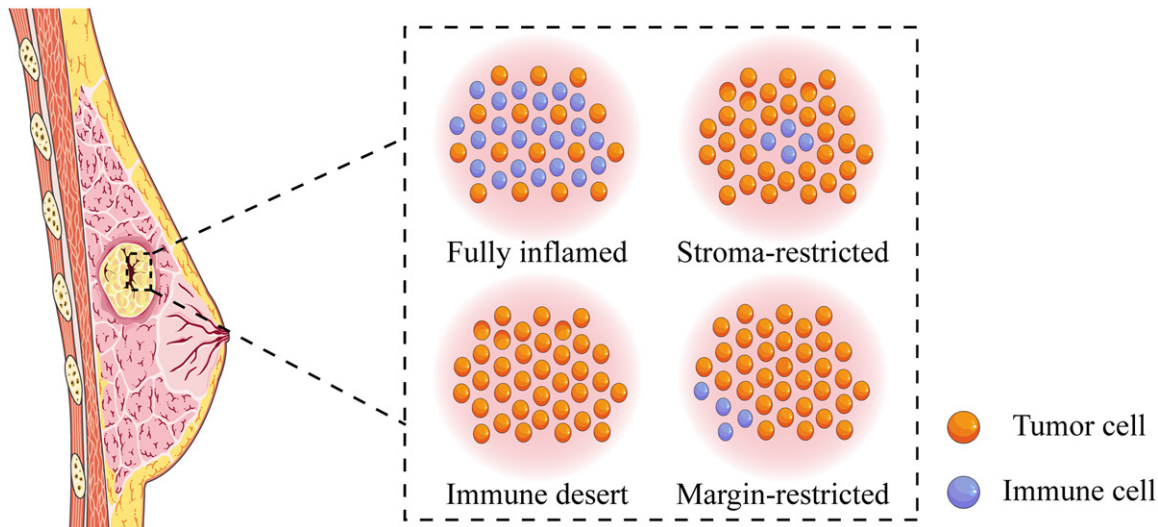


Figure 2. Four subtypes of TNBC immune TME. Fully inflamed (FI): a uniformly high number of CD8+ tumor-infiltrating lymphocytes in tumors. Immune desert (ID): Tumors have a uniformly low number of CD8+ tumor-infiltrating lymphocytes. Stroma-restricted (SR): low number of TILs limited to tumor stroma. Margin-restricted (MR): low number of TILs limited to tumor margin.

androgen receptor (LAR), and mesenchymal [28]. Basal-like 1 has significant proliferative activity (expressed Ki67 genes) and proliferation gene drivers. The phenotype of basal-like 2 is basal-myoepithelial. The LAR subtype is associated with malignancies that demonstrate apocrine differentiation on histologic inspection and express high quantities of androgen receptor hormones. The mesenchymal subtype shows epithelial/mesenchymal transition and PIK3CA mutation, and have extracellular matrix interaction genes. Indeed, a genomic and transcriptomic investigation verified these subtypes in a large cohort of Chinese patients, confirming basal-like, LAR, and mesenchymal as TNBC cell-intrinsic subtypes [32]. Recently, the same team conducted integrative clustering analysis to build a subtype set that included both the sample proteome and the phosphoproteome [33]. They stratified tumor samples into four proteomic subgroups (named iP-1-4) that differed in prognosis significantly. Their study also revealed subtype-specific signaling networks, metabolic reprogramming, and signature regulators that highlighted subtype-specific biological traits. It is expected to be employed in the clinic as a reference framework for targeted therapy of TNBC.

During the past two decades, the complicated nature of the TME has been increasingly apparent to researchers [34, 35]. Four subtypes of

immune TME subtypes (Figure 2), respectively, margin-restricted (MR), immune desert (ID), fully inflamed (FI) and stroma-restricted (SR), were proposed on the basis of immune cell numbers and their spatial distribution within whole sections of TNBC tumors and gene expression profiling [27]. Tumors defined as immune desert or fully inflamed have a uniformly low or high number of CD8+ tumor-infiltrating lymphocytes (TILs). Margin restricted and stroma restricted, respectively, refer to CD8+ TILs limited to the tumor margins or stroma, and both have low numbers of TILs [36]. Keren et al. [37] revealed that lineage enrichment of immunoregulatory proteins was associated with tumor construction. Immune desert tumors present few immune cell infiltrates, which primarily consist of PD-L1⁺ tumor-associated macrophages and exhausted T cells. Fully inflamed tumors have PD-1 expressed on CD8 T cells and IDO and PD-L1 mainly on tumor cells. Compartmentalized tumors have PD-1 expressed on CD4 T cells, whereas IDO and PD-L1 are predominantly expressed on other immune cells. A subset of compartmentalized tumors had a gradient of HLA-DR and H3K9ac/H3K27me3 from the boundary to the tumor center, indicating that the tumor-immune boundary is a particularly special region of immune suppression with changed expression profiles by both tumor and immune cells.

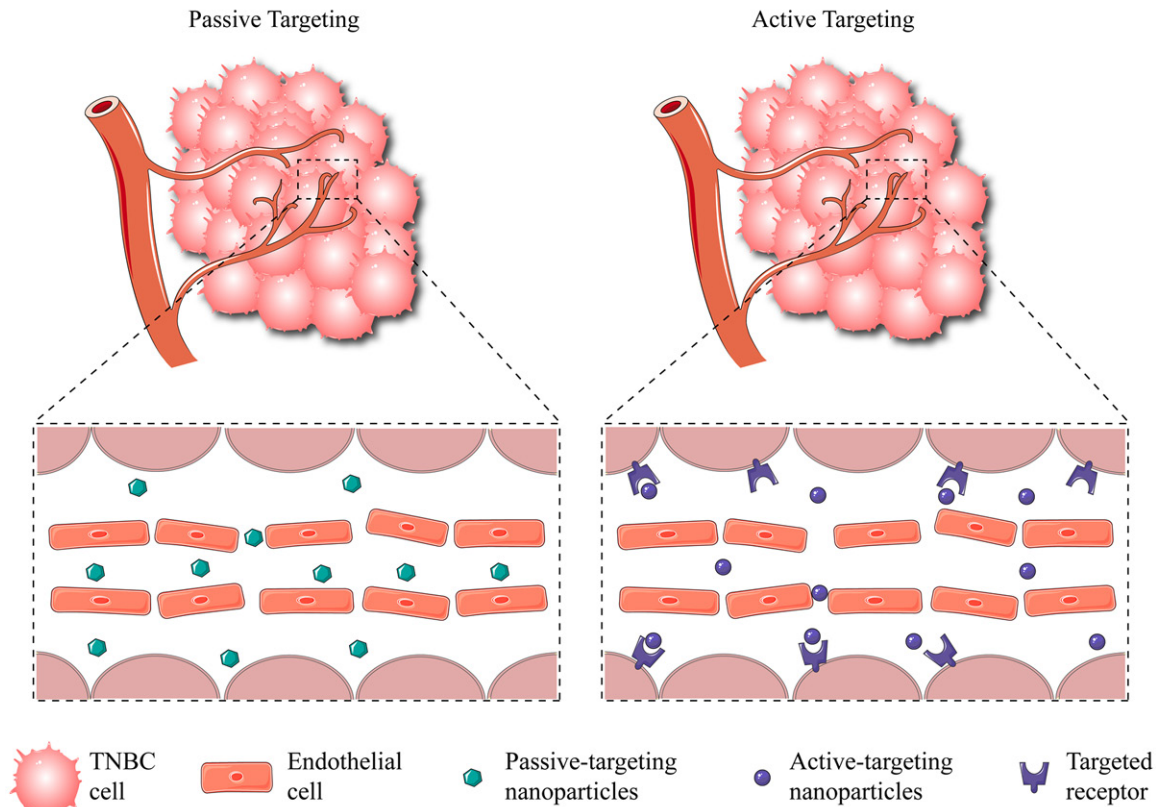


Figure 3. Mechanism of passive targeting and active targeting. Passive targeting: a manifestation identified as the enhanced permeability and retention (EPR) effect. This phenomenon arises as a result of the disordered tumor vascular structure, enhanced vascular permeability, and lymphatic obstruction, resulting in fluid retention and drug accumulation in the tumor at a high level. Active targeting: linking the exterior of nanoparticles to specific targeting payloads like aptamers, antibodies, and peptides that are responsive to antigens or receptors on the tumor cell. This is in pursuit of maximum payload transport, improved half-life and systemic circulation, and minimal systemic or non-specific toxicity.

Furthermore, another study improves on the work of Keren et al. by profiling the proteins involved in cell-to-cell crosstalk and setting up a connection between the spatial architecture of cells with different expression patterns and clinical outcomes [38]. It demonstrated that the co-expression pair of functional proteins in patients' cells was a trademark of a complex TIME, pointing to highly specific cellular phenotypes. The four most important co-expression profiles were CD45RO + H3K27me3, CD45RO + H3K9ac, CD45RO + HLA Class 1, and HLA-DR + IDO, which were associated with recurrence and survival.

Antitumor mechanism of nanobio-drug delivery system

Drug delivery to TNBC tumors is difficult due to the lack of specific cellular receptors (ER, PR,

and HER2) [39]. Some of the typically utilized nanocarriers that have been evaluated for the therapeutics delivery are polymeric nanoparticles, micelles, liposomes, dendrimers, nanoconjugates, albumin nanoparticles, and carbon nanotubes [40, 41]. Furthermore, nanobiology-based delivery systems have proven to be effective in tumor delivery via active- and passive-targeting mechanisms [42, 43] (**Figure 3**). All these strategies are further modified to deliver not only chemotherapeutics but also oligonucleotides or proteins.

Passive targeting happens due to a manifestation identified as the enhanced permeability and retention (EPR) effect. This phenomenon arises as a result of the disordered tumor vascular structure, enhanced vascular permeability, and lymphatic obstruction, resulting in fluid retention and drug accumulation in the tumor

at a high level [44]. The EPR effect increases the efficacy and antitumor effects while reducing the toxic and side effects on normal tissues, which provided a great impetus for development and studies of nanomedicines. Recently, Cui and colleagues presented a mitochondrion-targeted copper-depleting nanoparticle (CDN) [45]. The positively charged exterior of CDN can facilitate the accumulation of particles as well as the selective robbery of copper in the mitochondrion. Oxidative phosphorylation (OXPHOS) activity was suppressed and ATP generation was decreased, eventually leading to cell death. A follow-up animal experiment confirmed that by targeting mitochondrion, CDN considerably decreased adverse effects when compared to conventional copper chelating medicines. Hence, reasonable nanoparticle design that takes advantage of the mitochondrion microenvironment can enhance specific mitochondrion targeting and improve treatment outcomes. In addition, the therapeutic window of passive targeting nanoparticles is usually compromised for safety application, ultimately leading to limited concentration in the tumor center [46]. Targeting tumors with EPR effects alone remains controversial [47-49]. Some people have proposed that EPR effects can only be observed in mouse and cannot be duplicated in humans, and that heterogeneous and dynamic TME may invalidate EPR effects [47]. Surprisingly, the latest research even reverses EPR effects. Only 26 gaps were discovered in 313 detected blood capillaries from all experimental models, and the entire gap percentage is only 0.048 percent of the blood capillary surface area, while the number of inter-endothelial gaps is 60 times lower than the accumulated nanomaterials [47, 50]. In a follow-up study, Sun et al. investigated the design criteria for nanomedicine in three preclinical cancer models using five clinically used nanomedicine drugs. The EPR effect in tumors and normal tissues has been observed not only in nanomedicines but also in small compounds with a high affinity for protein. Drug concentration in tumors is determined by the EPR effect and binding capacity to plasma proteins and tumors [51]. Overvaluation of EPR effects would result in inadequate anti-tumor activity, prompting additional study to exploit nanoparticles with the active targeting capability detailed below.

Active targeting depends on linking the exterior of nanoparticles to specific targeting payloads like aptamers, antibodies, and peptides that are responsive to antigens or receptors on the tumor cell [52, 53]. This mechanism has several benefits over passive targeting, including precise targeted delivery, decreased immunogenic reaction, increased circulation time, and an improved therapeutic window with injection administration [40]. This is in pursuit of maximum payload transport, improved half-life and systemic circulation, and minimal systemic or non-specific toxicity. Pang et al. [54] developed a MoS₂-BSA-Apt nanosheet with strong specific recognition by incorporating NAA with bovine serum albumin (BSA) and MoS₂. Accordingly, superb targeting, optimal biological distribution, and an evident suppressive effect on TNBC could be examined. Du et al. [52] coupled 18 nm iron oxide nanoparticles (IOs) with a tumor-targeting peptide called CREKA (Cys-Arg-Glu-Lys-Ala), since CREKA could selectively link to fibrin-fibronectin compounds that are abundantly expressed in TNBC cells. According to MRI and MPI evidence the targeting molecule increases the intratumoral distribution homogeneity of nanoparticles. Here, we supply several information about bionano-delivery works in **Table 1**. However, NPs are still subjected to “protein corona” throughout systemic distribution, leading to off-target orientation, decreased effectiveness, and unfavorable toxicity [55, 56]. Rational matched design, in vitro and in vivo evaluation, and intelligence analysis tools should be explored to acquire an considerable insight of the challenges upon mutual effect of biosubstance-NP, involving particles size, charge, surface chemistry, temperature, and pH [57]. For example, prior research discovered that the hydroxyl group availability of graphene affects the biosorption of typical plasma proteins, and secondary structural variations also have a contribution to biosorption occurrence [58]. According to this phenomenon, hydrophilicity modification could be an approach to prevent protein corona. Enhancing EPR efficacy or generating active tumor binding capacity can both improve the targeting properties of nanoparticles.

Nanobiological therapy for triple negative breast cancer

Cancer nanobiological therapy is an innovative method medium for therapeutic drug adminis-

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Table 1. The summary of different nano-delivery works

Reference	Nano delivery system	Payload	Animal model	Effect
[64]	spherical nucleic acids (SNAs)	The SNAs comprise immunostimulatory oligonucleotides (CpG-1826) as adjuvants and encapsulate lysates derived from TNBC cell lines as antigens	EMT6 mouse mammary carcinoma model	Tumor cell lysate-loaded SNAs vaccines enhanced the co-delivery of the adjuvant and antigen to immune cells in comparison to non-SNA conjugated mixtures of lysates and oligonucleotides. Oxidized TNBC lysates increased anti-tumor effects of SNAs through enhanced activation of dendritic cells and the induction of long-term immunological memory.
[65]	a hybrid ultrasound responsive self-healing nanocomposite hydrogel (NC gel) system	membrane-coated R837-PLGA	4T1 orthotopic breast tumor model with spontaneous metastases	Significant anti-tumor immune efficiency was confirmed after multiple rounds of ultrasonic stimulation in animals inoculated with such nanovaccines encased in hydrogel.
[67]	α -lactalbumin (α -LA)-engineered breast cancer-derived exosomes	human neutrophil elastase (ELANE) and Hiltonol (TLR3 agonist)	MDA-MB-231 mouse model and patient-derived tumor organoids	HELA-Exos had substantial anticancer effects in organoid and animal models of TNBC, promoting cDC1 activation in situ and eventually triggering strong tumor-specific immune responses of CD8 T cells.
[68]	self-assembled by a near-infrared (NIR)-absorbing semiconducting polymer and an amphipathic polymer	conjugated with a Toll-like receptor 7 (TLR7) agonist via an acid-labile linker	4T1 bilateral tumor model	Experimental animals establish immunological memory with high infiltration and proportion of various T cell subsets.
[72]	iRGD-liposome	recombinant NDV that expressed the DC chemokine MIP-3	4T1 tumor model	iNDV3 α -LP enhanced tumor ICD effect as a result of increased viral replication. The immunosuppressive TME was reversed when OVts triggered significantly suppressed tumor angiogenesis and intense tumor-specific cellular and humoral immunity.
[79]	polymer nanoparticles named P/PEAL _{siCD155}	PD-L1 and siCD155	4T1 tumor model	P/PEAL _{siCD155} NPs can efficiently target the tumor and trigger a significant intra-tumor anti-tumor response of CD8 TILs in the 4T1 TNBC tumor model. In addition to achieving spatiotemporal targeting of the surface receptor and intracellular mRNA, P/PEAL _{siCD155} NPs may enhance CD155-mediated immune surveillance in the early stages while inhibiting CD155-mediated immunological escape in the later stages.
[84]	an epigenetic nanoinducer OPEN, decorated by a T lymphocyte membrane that is engineered with programmed cell death protein 1 (PD1)	IFN inducer ORY-1001	4T1 mammary tumor model	OPEN enhances IFNs expression while hampering IFN-induced immune checkpoint upregulation, leading to an 8- and 29-fold increase, respectively, in intratumoral infiltration of total and active cytotoxic T cells, as well as a substantial suppression of xenograft tumor progression. OPEN's unique shell generally expresses other ICRs, providing the ability to recognize and block various ICLs, enabling OPEN to overcome multigenic resistance to ICB induced by IFN.
[90]	E64-DNA, a lysosome-targeted DNA nanodevice	E64	E0771 mammary tumor model	E64-DNA selectively targeting TAMs with organelle-level specificity. Reprogramming the lysosome endows the nanoparticles with a novel, therapeutically effective property. Reduced cysteine protease activity in M2-like TAM lysosomes activates CD8 T lymphocytes and slows cancer progression. As a result, enhancing antigen presentation in M2-like TAMs improves adaptive immune response even in suppressive TME.

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[99]	Fe ₃ O ₄ magnetic nanoparticles that were decorated with 3-aminopropyltriethoxysilane	CpG (FeNP/CpG)	4T1 tumor model	FeNP/CpG suppressed tumor growth and lung metastasis by increasing CpG absorption of bone marrow derived DCs (BMDCs). It also inhibits adverse reactions of free CpG as a single agent therapy, such as systemic inflammation that is out-of-control.
[100]	a unique gene-delivery nanoparticle named FDMCA	plasmid-encoded MIP-3	4T1 mammary tumor model	The expression of CD80, CD86, and MHCII in DCs was upregulated, substantially boosting DC maturation and suppressing macrophage M2 polarization. a considerably lower incidence of CD31 vasculature in vivo. Lung metastases were considerably suppressed.
[109]	chitosan-lactate nanocomposites	CD73 siRNA	4T1 tumor model	In 4T1 breast cancer-bearing mice, application of CD73 siRNA-loaded chitosan-lactate nanocomposites in combination with tumor lysate pulsed DCs vaccination resulted in significant antitumor activity [110].
[116]	Poly (b-amino esters)	CRISPR-Cas9 genome engineering system	4T1 tumor model	In TME, knockout of Cdk5 drives PD-L1 to be downregulated, which results in significant T cell-mediated immunological effects. This effect inhibits tumor proliferation and invasion.
[121]	hyaluronic acid-based nanoparticles called TCiGNPs	granzyme B	MDA-MB-231 mammary tumor model	TCiGNPs are destroyed by hyaluronidase in TME, and granzyme B is released to provide antitumor activity.
[123]	lipid-protamine-DNA nanocomposite	a recombinant plasmid	4T1 tumor model	lipid-protamine-DNA nanocomposite with a recombinant plasmid expresses proteins to snare IL-10. the utilization of these nanocomponents improves CTL infiltration and suppresses tumor progression.
[124]	lipid nanocarriers	agonists of the CSF-1 receptor and MAPK pathways	4T1 mammary tumor model	improve the anti-tumor M1-like phenotype at TME and tremendously decrease cancer progression.
[125]	Pluronic F127	PTX and IL-12	4T1 tumor model	significantly enhancing CTL-mediated immune activity and inducing M1 polarization of macrophages, inhibiting immunosuppressive TME.
[126]	DC2.4-derived nanovesicles	doxorubicin (DOX) and pro-inflammatory cytokines (IL-2 and IFN- γ)	4T1 tumor model	biomimetic nanovesicles propelled CD45 leucocytes and Ly6G neutrophils into the TME.

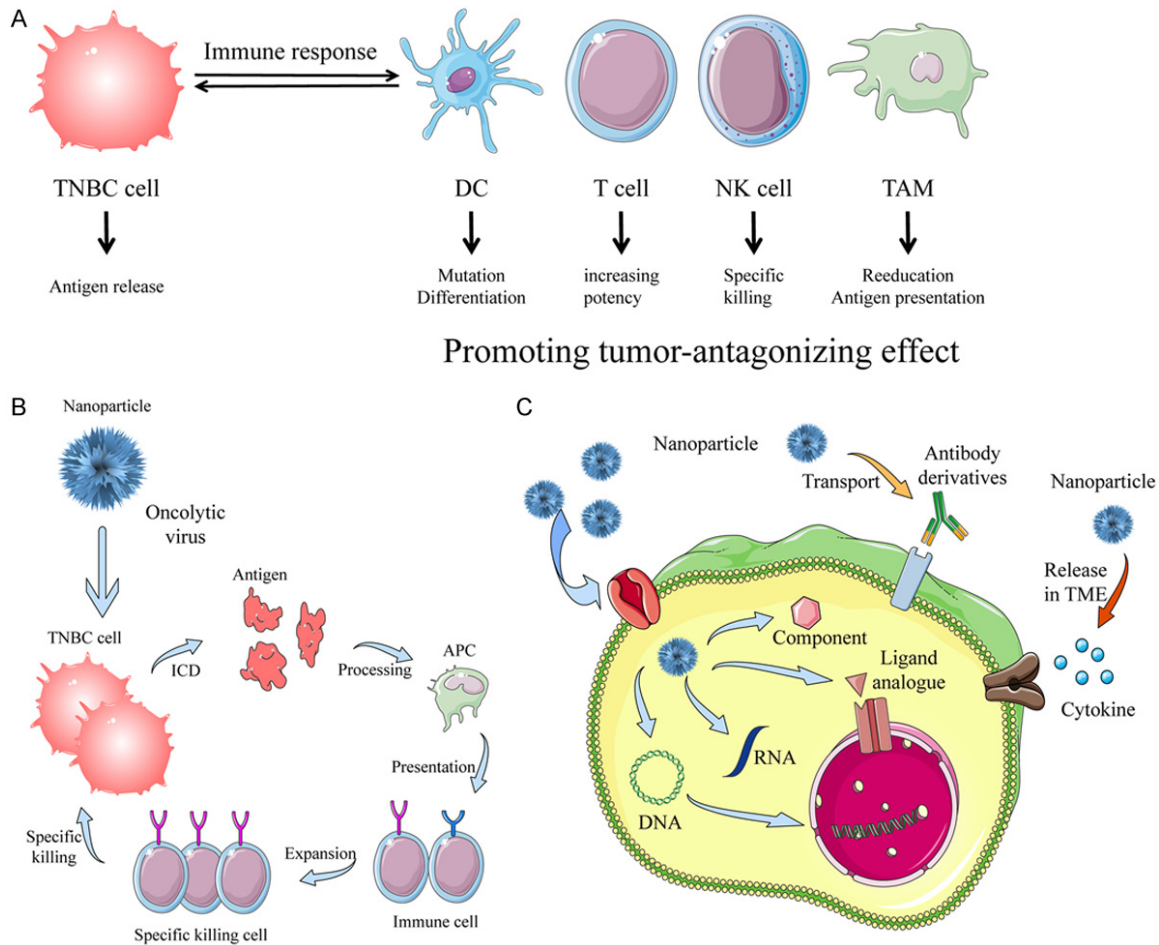


Figure 4. Several nano-biotherapeutic methods to target immune microenvironment of TNBC. A. Summary of the functional effects underlying TME cells regulation by bio-nanoparticles. B. The involvement of immune cells in the immune response to tumor cells' ICD induced by nanoparticles. C. Nanoparticles release their payloads and exert functional effects in the tumor microenvironment and inside the cells.

tration that has a significant effect on the TME [59]. The integration of nanotechnology with biotherapy is one of the most promising areas in anticancer therapy. Nanoparticle-based biotherapy enables the specific targeting of certain immune cells and signalling basis of the immunosuppressive TME, preventing tumor immune escape and increasing therapy efficacy and anti-tumor activities [60, 61] (**Figure 4**). Bio-nanoparticles can kill the tumor cells directly. Currently, the guidelines of tumor biotherapy is transforming, and there is growing awareness of improving the autoimmunity of tumor patients. In this regard, three strategies are mainly adopted: active immunization, passive immunization and immune regulation.

Active immunization

Active immunization mainly depends on the mobilization of organic immunity. It is closely

related to the individual's immune traits, which determine whether the recovery can be successful or not. Here, we address the involvement of several biomaterials in the formulation of cellular vaccines and oncolytic viruses to restore immunity via activating and expanding tumor-specific activities of the host immune system.

Cellular vaccines

Cellular vaccines generally target dendritic cells (DCs), the most important antigen-presenting cells, to promote anti-tumor immunity. Succeeding applications in sequence-based bioinformatics have improved our capability to recognize and purify specific antigens. Cellular vaccines involving nanomaterials improve the efficacy of cancer-immunity reactions by instigating the mass-recruitment and activation of

immune cells against tumors with the help of immunogenic specific antigens or stimulating factors [62, 63]. Tumor cell lysate-loaded SNAs vaccines enhanced the co-delivery of the adjuvant and antigen to immune cells in comparison to non-SNA conjugated mixtures of lysates and oligonucleotides. Oxidized TNBC lysates increased anti-tumor effects of SNAs through enhanced activation of dendritic cells and the induction of long-term immunological memory [64]. In addition to just injecting nanovaccines for immunization, a recent attempt to design a telecontrolled nanovaccine platform for personalized cancer immunotherapy has been accomplished. The individualized nanovaccines were generated by covering the membranes of 4T1 cells with R837-loaded nanocarriers and then encapsulated into the ultrasound-responsive self-healing hydrogel system. Significant anti-tumor immune efficiency was confirmed after multiple rounds of ultrasonic stimulation in animals inoculated with such nanovaccines encased in hydrogel [65]. In situ nanovaccines can deliver payload to target cells and the microenvironment to achieve a spatiotemporal release, improving therapeutic effects and decreasing adverse reactions [66]. HELA-Exos, an in situ DC vaccine, is served for the treatment of TNBC by delivering TLR3 agonist Hiltonol as well as the ICD inducers ELANE via employing modified tumor-cell-derived extracellular vesicles. HELA-Exos had substantial anticancer effects in organoid and animal models of TNBC, promoting cDC1 activation in situ and eventually triggering strong tumor-specific immune responses of CD8 T cells [67]. SPNI, an acidic-TME-responsive nanoparticle, allows for specific stimulation of TLR7 agonists to mature DCs. Eventually, experimental animals establish immunological memory with high infiltration and proportion of various T cell subsets [68]. What calls for special attention is that these vaccinations have the possibility of triggering mild-to-moderate adverse effects. Furthermore, clinical efficacy must be confirmed further.

Oncolytic viruses

After being delivered into cancer cells, oncolytic viruses actively proliferate and lyse the tumor cells. They can trigger the immune response by reprogramming cancers to get “hot” (ready to engage the immune system), ultimately result-

ing in persistent tumoricidal activity [69, 70]. However, antigen-presenting cells interact with OV's because they are regarded as xenogeneic. Because of this antiviral immunity, OV's would most likely be eliminated from the system before reaching the cancer cells [71]. Artificially modified OV's, as well as formulations with a suitable vehicle, an active targeted part, and a better exposure profile, are usually required to further improve the therapeutic efficacy. In a study, the recombinant NDV that expressed the DC chemokine MIP-3 was encapsulated in an iRGD-liposome and named iNDV3-LP. The results showed that iNDV3-LP enhanced tumor ICD effect as a result of increased viral replication. The immunosuppressive TME was reversed when OV's triggered significantly suppressed tumor angiogenesis and intense tumor-specific cellular and humoral immunity [72]. To overcome the hurdles associated with therapy of progressive and metastatic neoplasms, Howard et al. [73] employ the magnetic targeting of bacterially produced MAG to boost the distribution of OV's. Through increasing concentration in solid tumors and evading immunosurveillance for systemic toxicity reduction, this unique biotechnological strategy clearly illustrates that the MAG-OV compound enables several levels of specific tumor magnetic targeting. Recombination with other genes promoting the expression of immune stimulants was recently explored to evaluate the effect of OV's on TNBC. Subsequent research looked into VSV's capacity to suppress TNBC progression [74]. In mouse and human TNBC cell models, the cytotoxic effect of recombinant VSV (VSVd51) was evaluated, and its efficacy in antitumor immune reactions was confirmed. VSV has considerable therapeutic efficacy by recruiting NK cells and CD8 T cells. VSV, in combination with checkpoint blockade, may be able to treat TNBC due to its function on the immune system. This influence on the immune system clearly indicates that VSV, integrated with checkpoint blockade, may be beneficial in the management of TNBC. Moreover, virus-like nanocomposites, also defined as noninfectious protein shells or capsids of viruses without a genome, can be employed as nanomaterials alone or in combination with a variety of immunoregulatory stimulants. Tumor vaccines based on the oncolytic vesicular stomatitis virus have been demonstrated in research to enhance TNBC outcome via boosting the activities of

natural killer cells and CD8⁺ T lymphocytes [75]. However, because cancer patients are frequently treated with chemotherapy, radiotherapy, as well as other therapies that may suppress the immune response, there is a potential that OV would cause significant side effects associated with virus infection.

Passive immunization

Some individuals cannot generate an adequate immune response on their own. Derivatives of antibodies and immune cells are natural nanomaterials that directly kill tumor cells and supply immediate anti-tumor immunity once put into treatment. In this section, we will discuss nanobiotherapy of antibody derivatives and engineered immune cells to treat TNBC.

Antibody derivatives

The advances of new-format therapeutic antibodies in cancer therapy suggest that multifunctionalization will be a major focus in antibody development [6, 76]. Due to the antibody's excellent targeting capabilities, antibody conjugates, such as ADCs and AOCs, demonstrate enhanced bioavailability properties to kill tumor cells with payload-induced cytotoxicity and oligonucleotide functionality [77, 78]. A recent attempt to develop polymer nanoparticles named P/PEAL_{siCD155} realized the asynchronous blockade of PD-L1 and CD155. P/PEAL_{siCD155} NPs can efficiently target the tumor and trigger a significant intra-tumor anti-tumor response of CD8 TILs in the 4T1 TNBC tumor model. In addition to achieving spatiotemporal targeting of the surface receptor and intracellular mRNA, P/PEAL_{siCD155} NPs may enhance CD155-mediated immune surveillance in the early stages while inhibiting CD155-mediated immunological escape in the later stages [79]. Free adenosine inhibits effective CD8 T cell activation within LNs and protects tumor cells by inhibiting CD8 T cell killing effects. The adenosine receptor 2A inhibitor SCH-58261-loaded aPD1-ANCs allowed for the co-delivery of ICB and adenosine inhibitors to targeted immune cells, as well as specific ANC accumulation among blood plasma and LN-resident lymphocytes [80]. Multispecific antibody-based treatments, such as T cell activation and engagement of innate and adaptive immune cells, have been intensively researched to leverage

the local TME in an antigen-dependent manner. The nanocarrier platform of synthetic multivalent antibodies retargeted exosomes (SMART-Exos) was employed to redirect and activate cytotoxic T lymphocytes against TNBC cells. In an in vitro cytotoxicity experiment and a human TNBC xenograft mouse model, SMART-Exos expressing CD3 and EGFR targeting antibodies were capable of crosslinking T cells and EGFR-positive TNBC cells and inducing a powerful antitumor immune response [81]. In addition, Chen et al. developed dual-functional super bispecific nano-antibodies S-BsNA_{CSF1R&CD47} and S-BsNA_{KLRG1&PDL1} on the basis of a versatile antibody-immobilization platform named Fc-NPs. S-BsNA could establish a close physical connection between effector cells and tumor cells. Activated innate immune cells may produce an amplified antitumor effect by directly phagocytizing (for TAMs) or delivering cytolytic granules (for NK cells) to surrounding tumor cells [82]. Because of low penetration into solid tumors and Fc-mediated bystander activation of the immune system, the application of full-length antibodies in cancer treatment is limited in some circumstances [83]. Recent advancements in antibody engineering have improved the synthesis of several types of antibody fragments. Further development based on these simplified antibodies is expected to solve current problems.

Immune cell engineering

The potential to treat cancer by the back-infusion of native therapeutic cells is extraordinary. However, due to the quick loss of functioning induced by plenty of immunosuppressive mechanisms within the TME and limited tumor penetration after in vivo transfer, its tumoricidal effect against TNBC remains elusive. A variety of nanomaterial-engineered immune cell delivery strategies have been suggested as potential approaches to clinical translation due to their enhanced clinical potency and safety. Because of their small cellular size, high nucleus-to-cytoplasm ratio, nonphagocytic nature, and low rates of endocytosis, T cells do not take up nanoparticles as readily as cancer cells. There has been little research that applies to direct T cell-targeted therapeutic delivery utilizing nanomaterials. For the control-release of the IFN inducer ORY-1001, Zhai et al. [84] constructed an epigenetic nanoin-

ducer OPEN, decorated by a T lymphocyte membrane that is engineered with programmed cell death protein 1 (PD1). OPEN enhances IFNs expression while hampering IFN-induced immune checkpoint upregulation, leading to an 8- and 29-fold increase, respectively, in intratumoral infiltration of total and active cytotoxic T cells, as well as a substantial suppression of xenograft tumor progression. OPEN's unique shell generally expresses other ICRs, providing the ability to recognize and block various ICLs, enabling OPEN to overcome multigenic resistance to ICB induced by IFN. To date, allogeneic NK cells have been clinically validated for adoptive transfer immunotherapy [85, 86]. On the other hand, NK cells have a short half-life in the bloodstream and do not have tumor-specific cell receptors [87]. A recent study to generate aptamer (PDGC21-T)-engineered NK cells (ApEn-NK) revealed that ApEn-NK attached to TNBC cells preferentially and caused apoptosis in target cells in vitro [88]. In addition, ApEn-NK treatment inhibited lung metastasis more effectively than parental NK-92 cell treatment, according to ex vivo imaging in the MDA-MB-231 xenograft model. Notably, as ApEn-NKs proliferate in vivo, surface-engineered aptamers will get diluted. The antigen-destroying property of M2-like TAMs in tumors is unfavorable because it limits CD8 T cell activation [89]. However, it is unclear whether antigen presentation by TAMs happens immediately at the tumor site or in the tumor-draining lymph node. E64-DNA was a lysosome-targeted DNA nanodevice delivering the classical cysteine protease inhibitor E64 and selectively targeting TAMs with organelle-level specificity. Reprogramming the lysosome endows the nanoparticles with a novel, therapeutically effective property. Reduced cysteine protease activity in M2-like TAM lysosomes activates CD8 T lymphocytes and slows cancer progression. As a result, enhancing antigen presentation in M2-like TAMs improves adaptive immune response even in suppressive TME [90]. To date, there has been no report of nanoparticles engineered into CAR cells for TNBC treatment. In other types of cancer related studies, several engineered immune cells could eliminate MDSCs or tumor-associated fibroblast that are importantly referred for TNBC treatment [91, 92]. The utilization of new biomaterial-based compositions, the development of innovative nanocarrier mechanisms for manufacturing CAR

cells in vivo, and the investigation of multifunctional nanocarriers with precise cargo localization and controlled release should all be the focus of further optimization and enhancement [93, 94].

Immune regulation

Immune regulation has been increasingly exploited in TNBC treatment owing to the significant immune reaction to cancer cells. Numerous nanocarriers have been generated to boost immune responses to TNBC [95, 96]. In the below section, we will be discussing nanosystem-mediated immune regulation therapeutics delivering DNA, RNA, and cytokines for managing TNBC.

DNA

The encapsulation of DNA-nanoparticles allows the entire delivery platform to contain both nanocarriers and DNA features, and in certain circumstances, synergistic benefits may be obtained. The DNA-nanoparticles not only serve as a vehicle to prevent DNA from quick elimination in the circulatory system and deliver DNA to the tumor location, but also facilitate the absorption, improve intrinsic distribution, and prolong DNA retention in tumor tissues, leading to cancer remission [97, 98]. DNA has higher stability than RNA and is less prone to degeneration by endonucleases, rendering it an appealing alternative for the therapy of many malignancies. Zhang et al. [99] developed Fe_3O_4 magnetic nanoparticles that were decorated with 3-aminopropyltriethoxysilane and loaded with CpG (FeNP/CpG). In vivo, FeNP/CpG suppressed tumor growth and lung metastasis by increasing CpG absorption of bone marrow derived DCs (BMDCs). It also inhibits adverse reactions of free CpG as a single agent therapy, such as systemic inflammation that is out-of-control. He et al. [100] developed a unique gene-delivery nanoparticle named FDMCA that can not only convey plasmid-encoded MIP-3 to TNBC cells but also release MIP-3 to trigger the immune response. The expression of CD80, CD86, and MHCII in DCs was upregulated when 4T1 tumors were transfected with FDMCA-pMIP-3, substantially boosting DC maturation and suppressing macrophage M2 polarization. The vessel count in each group demonstrated that FDMCA-pMIP-3-treated tumor tissues had a considerably lower incidence of

CD31 vasculature in vivo. Lung metastases in mice treated with FDMCA-pMIP-3 were considerably suppressed in the Balb/c mouse model of 4T1 mammary tumor. In order to promote ICD, NA could potentially act as scaffolding, delivering numerous anti-agents to tumor cells [101]. Hence, NAA-guided active targeting has gained a great deal of attention. Unlike antibodies, NAA is usually non-immunogenic or low-immunogenic [102]. Since DNA is negative charged and reactive to its surroundings, it is tough for it to cross through the cell membrane [103, 104]. Relying on genetic engineering technology such as Crispr, viral vectors including lentiviruses, adenoviruses, and adeno-associated viruses can transfer DNA to tumors [105]. Nonetheless, the immune adverse response and off-target risks induced by virus-based DNA-delivery particles generate a sense of caution. Furthermore, tumor heterogeneity and adaptive resistance pose challenges to single DNA delivery.

RNA

Exonic, intronic, and untranslated regions can be targeted by RNA nanotechnology, which can interact with pre-RNA (in the nucleus) and upregulate or downregulate gene expression [106]. Because of their capacity to block a variety of genes engaged in immunosuppression, RNA-based nano-delivery systems have higher specificity, a larger range of targets, and strong pharmacological characteristics [107, 108]. Targeting CD73 as a management option for TNBC could be a possibility. In 4T1 breast cancer-bearing mice, application of CD73 siRNA-loaded chitosan-lactate nanocomposites in combination with tumor lysate pulsed DCs vaccination resulted in significant antitumor activity [109]. Increased adenosine formation in the TME was discovered as a consequence of CD73 overexpression [110]. Adenosine regulates T lymphocytes' reactions and differentiation via interacting with various receptors on immune cells, primarily A2AR [111]. For silencing the A2AR gene, Masjedi et al. [112] developed PEG-chitosan-lactate nanocarriers loaded with A2AR-specific siRNA. Suppressing A2AR in T cells restricted their maturation into Tregs by downregulating the PKA/CREB axis and upregulating NF- κ B. PEG = MT/PC/siVEGF/siPIGF NPs is an innovative dual-stage pH-sensitive carrier that can promote reeducation in the

type-switch of M2 macrophages into M1 macrophages and reverse the tumor-immunosuppressive TME [113]. TME also plays an essential part in tumor growth and progression, provoking various strategies for tumoricidal therapies. T cell activity has been reported to be influenced by acidic TME. Lactate dehydrogenase A, which converts pyruvate to lactic acid in tumor cells, is essential for tumor acidity [114]. It was established that cationic lipid nanomaterial delivery of siRNAs targeting lactate dehydrogenase A in 4T1 breast tumor-bearing mice neutralizes tumor pH, induces penetration of CD8 T and NK cells, and inhibits cancer formation [115]. Poly (b-amino esters) has recently been employed in vivo to deliver the CRISPR-Cas9 genome engineering system and knockdown Cdk5 [116]. In TME, knockout of Cdk5 drives PD-L1 to be downregulated, which results in significant T cell-mediated immunological effects. In 4T1 tumor-bearing mice, this effect inhibits tumor proliferation and invasion. Due to high transfection efficiency, viral vectors are appealing, even though they have challenges with safety and immunogenicity.

Cytokines

Cytokines are immunological components that play a significant part in the anti-tumor immune reaction. The application of cytokines as tumoricidal drugs or targets in cancer treatment has proven to be tremendously promise [117]. Despite their promising curative effects, cytokine therapies are limited by systemic side effects caused by non-specific absorption of circulating cytokines by cell types particularly rich in the relevant receptor. To counteract these unfavorable consequences, cytokine attachment to nanoparticles was investigated, and it has since become a well-accepted approach for extending blood circulation and decreasing adverse effects in normal tissues [118]. Mitragotri and colleagues recently published an article presenting a cell-based delivery approach in which IFN- γ "backpacks" were attached to macrophage surfaces [119]. The macrophage-cytokine nanodrug avoided phagocytosis over five days in vitro. When compared to free IFN- γ therapy in a 4T1 breast tumor model, combined macrophage boosted M1 macrophage polarization and improved overall survival. Granzyme B is a cytotoxic ser-

ine protease produced by CD8 T lymphocytes and natural killer cells following cellular immune activation [120]. To imitate the functionality and consequences of CD8 T cell and NK cell stimulation, Qian and colleagues [121] developed innovative hyaluronic acid-based nanoparticles called TCiGNPs for delivering granzyme B to tumor tissues. TCiGNPs are destroyed by hyaluronidase in TME, and granzyme B is released to provide antitumor activity, according to an *in vivo* assay utilizing MDA-MB-231 mammary mouse model. TME immunosuppression is primarily mediated by IL-10, a significant cytokine [122]. Shen et al. [123] generated a lipid-protamine-DNA nanocomposite with a recombinant plasmid expressing proteins to snare IL-10. In the 4T1 breast cancer mouse model, the utilization of these nanocomponents improves CTL infiltration and suppresses tumor progression. In the extremely invasive 4T1 mammary tumor model, Ramesh et al. [124] revealed that lipid nanocarriers loaded with agonists of the CSF-1 receptor and MAPK pathways improve the anti-tumor M1-like phenotype at TME and tremendously decrease cancer progression. In addition, cytokines can be adsorbed and delivered by nano sponges to the precise site. Hu et al. [125] utilized Pluronic F127 as a hydrophilic thermo-sponge shell to co-deliver PTX and IL-12, significantly enhancing CTL-mediated immune activity and inducing M1 polarization of macrophages, inhibiting immunosuppressive TME. Furthermore, Wu et al. [126] generated DC2.4-derived nanovesicles to deliver DOX and cytokines (IL-2 and IFN- γ), and found that these biomimetic nanovesicles propelled CD45 leucocytes and Ly6G neutrophils into the TME.

Future directions and outlook

Currently, the biological mechanisms involved in TNBC are still abstruse. Bidirectional communication between the tumor cells and TME substances includes the corresponding regulators and metabolic cross-talk in TME [127]. Increased TME cognition in TNBC provides a wealth of information about potential therapeutic strategies [26]. A growing body of research indicates that nanobio-delivery systems offer a great deal of opportunity in terms of improving therapeutic outcomes. Nanotechnology can modify TME and regulate the immune response against TNBC by stimulating DC maturation and

activation [128], re-educating TAM differentiation [129], or triggering the CTL response [130]. Biosubstance-derived compounds can also increase nanoparticle targeting, biocompatibility, and safety [131], as well as provide a sustainable and effective treatment option for TNBC and metastatic spread via facilitating patients' innate immune defenses and modulating immune system, or combinatorial. Accurate identification of biological properties and interactions will encourage the innovation of next-generation nanotechnology for combinatorial therapy for effective tumor treatment.

Furthermore, nanodrug delivery systems are a new area of science that is gaining attention, and their clinical application is still in its early stages [132]. Actually, tremendous hurdles exist for the application of clinically feasible therapeutics in this field and need to be solved to establish a considerable level of integration among nano-delivery systems, immune response, and adverse reactions. Firstly, nonbio-based nanoparticles usually have a response to TME owing to chemical activity toward acid and reactive oxygen species, but they have limited targeting capabilities (most depending on EPR) [44]. Even though they have active targeting feasibility with strong biocompatibility, natural bio-based nanoparticles rarely permeate internal tumors. The nanotherapeutic aspects are projected to widen, and the combination of the advantages of these two targeting mechanisms should guarantee both biosafety and tumor-antagonizing effect [133]. Secondly, nanobio-system administration methods remain unsatisfying. The majority of research has focused on delivering nanobio-medicines via intravenous infusion. Patients suffer from continuous and multiple injection punctures, which becomes a new hurdle to overcome. Oral administration with less pain and improved compliance seems to be a novel and innovative approach that may be a beneficial supply strategy in upcoming cancer treatments [134]. Thirdly, biosafety is essential for clinical applied generalization. The observation time for the biosafety of the nanomaterials ranges from 12 to 72 hours, which is insufficient. To completely avoid potential negative effects, the observation time needs to be extended. Furthermore, the possible biosafety hazards of biosubstance-based nano-formulation must be considered. For example, the off-target possibilities

of NA still exist within patients and are hard to trace [135]. The process of cell or protein nanoparticle fabrication may denature proteins, and some suspect antigens may induce abnormal immune activation [136]. Overall, researchers need to overcome the above limitations to perfect the nano-immunotherapy strategies of TNBC, and we anticipate that remarkable improvement toward clinical translation will be accomplished in the upcoming future.

Conclusions

The heterogeneity of TNBC has served as the foundation for the development of viable biotherapeutic alternatives. A more integrated and coordinated understanding of the intrinsic and extrinsic characteristics of the TNBC ecosystem will be a significant advance for biotherapy in extending clinical benefit. While immunotherapy has provided novel and effective therapeutic options, utilizing such immunostimulatory drugs without modifications has resulted in disadvantages such as rapid elimination and off-target effect. Nanoparticle-based immunotherapy holds great potential to overcome these limitations, so as to extend clinical benefit and improve the outcomes of patients with TNBC. An expanding amount of research has demonstrated promising efficacy and tolerability of nanomaterials-mediated cancer immunotherapy in addition to these general immunotherapy techniques. However, biosubstance-based nanoparticles are still far from clinical application according to the current status and existing obstacles. It is crucial to maintain focus on how to translate these strategies towards a clinic in the future.

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Disclosure of conflict of interest

None.

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