Advancements in Tumor Microenvironment-Responsive Intelligent Nanomedicine Delivery Systems for Breast Cancer Treatment

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Abstract. Breast cancer severely threatens women's health. Traditional therapeutic approaches face numerous limitations, including an inability to overcome significant physiological and pathological barriers, as well as notable toxic side effects. Tumor microenvironment-responsive intelligent nanomedicine delivery systems leverage the characteristics of the tumor microenvironment to deliver drugs, offering new hope for breast cancer treatment. This article comprehensively reviews the research progress of these systems in breast cancer therapy, including the characteristics of the tumor microenvironment, design principles of various responsive nanomedicine delivery systems, application examples, and future directions for development.

Keywords: Tumor microenvironment; intelligent nanomedicine delivery system; breast cancer treatment.

1. Introduction

Breast cancer (BC) is characterized by the uncontrolled proliferation of mammary cells, with the specific type and location of cancerous cells determining the classification of the disease in women [1]. It can be categorized into biological and clinical subgroups as well as histological types [2], including ductal, invasive, ER+, triple-negative, among others, and has the potential to metastasize through the blood and lymphatic systems. Globally, BC is the leading cause of cancer-related deaths in women [3] and ranks as the second most common cause of cancer mortality among women in China [4]. According to the "2022 Global Cancer Statistics Report," there were 2,308,897 new cases of female BC, representing a cumulative incidence risk of 5.1% and accounting for 11.6% of all cancer cases. The cumulative mortality risk was 1.4%, making up 6.9% of cancer deaths and positioning BC as the fourth leading cause of cancer mortality worldwide [5]. Concurrently, the incidence of BC in China is on the rise, with projections estimating 413,800 new cases by 2030 [6]. Pioneering experiments by the Bissell group have demonstrated that tumor epithelial cells can only proliferate within an abnormal microenvironment composed of altered extracellular matrix (ECM) and other non-transformed cells, such as fibroblasts, myofibroblasts, immune cells, myoepithelial cells, and endothelial cells [7-10]. The tumor microenvironment (TME) significantly influences drug penetration and efficacy. For instance, the density of the ECM and the state of the basement membrane can impede drug penetration into deeper tumor regions, and tumor cells can alter the composition and structure of the ECM to reduce drug concentration within the tumor. Moreover, the aberrant state of tumor vasculature complicates drug delivery to target sites. Beyond structural heterogeneity, the TME often exhibits metabolic abnormalities, including acidosis, hypoxia, and oxidative stress, with elevated levels of reactive oxygen species (ROS), glutathione (GSH), enzymes, or ATP [11-12]. Conventional treatments like surgery, radiotherapy, and chemotherapy often fail to completely eradicate BC cells, resulting in suboptimal therapeutic outcomes (the five-year survival rate for BC in China is 83%) and potentially severe adverse effects that significantly impact patient quality of life. For example, approximately 80% of BC cases are hormone receptor-positive (HR+), with most patients undergoing endocrine therapy. While endocrine therapy can reduce the recurrence rate of HR+ BC by 30%-50%, it may also induce serious adverse effects, including hot flashes, bone loss, arthralgia, genitourinary syndrome of menopause (GSM), and decreased libido [13].

Nanoparticle drug delivery systems utilize nanoscale materials as carriers to distribute drugs specifically to diseased tissues or target cells, thereby minimizing impact on healthy cells [14]. These systems have been extensively explored in cancer therapy due to their diverse sizes and shapes, surface modifications, stability, improved drug solubility, reduced toxicity, and targeting capabilities, such as the enhanced permeability and retention (EPR) effect [15]. For instance, Abraxane® (albumin-bound paclitaxel) has been approved by the FDA for the treatment of metastatic breast cancer. However, further research has revealed limitations in the efficacy of conventional nanoparticle carriers, with treatment adherence rates as low as 66% outside clinical trial settings [13], alongside significant toxic side effects. The unique characteristics of the TME, such as acidosis [16], hypoxia, ROS [17], abnormal protein expression, and stromal cell abnormalities, present opportunities for the development of targeted drug delivery systems. In response, researchers have optimized and intelligently modified traditional nanoparticle carriers, developing a plethora of intelligent nanoparticle drug delivery systems responsive to the TME. These include systems responsive to abnormal metabolic environments (pH, ROS, ATP, etc.) and those targeting the structural heterogeneity of the TME (abnormal vasculature, immune cells, ECM, etc.). These advancements hold promise for significantly increasing drug concentration at tumor sites, enhancing therapeutic efficacy, and improving targeting precision while reducing toxic side effects.

This article provides a comprehensive review and analysis of the research progress in TME-responsive nanoparticle drug delivery systems, offering insights into the construction and research methodologies of related systems. It aims to provide new perspectives and references for the design and investigation of targeted nanoparticle drug delivery systems for cancer, as well as for the selection of effective systems as clinical drug candidates.

2. Tumor Microenvironment Characteristics of Breast Cancer

The tumor microenvironment (TME) refers to the intrinsic environment in which tumorigenesis and tumor growth occur. It is composed of malignant tumor cells, various stromal cells (such as tumor-associated fibroblasts, endothelial cells, immune cells, and infiltrating inflammatory cells), extracellular matrix (ECM) components (including collagen, laminin, matrix metalloproteinases, integrin family members, etc.), and various signaling molecules [18]. Compared to normal tissues, tumor tissues often exhibit abnormal features such as blood vessel irregularities, weak acidity (pH 6.8), abnormal temperature, overexpression of specific enzymes, and hypoxia. The specificity of the tumor microenvironment presents both challenges and opportunities for cancer treatment. On the one hand, the interactions between cancer cells and the tumor microenvironment increase the malignancy and treatment difficulty of cancer. For example, the heterogeneity of hypoxia and weak acidity in the TME promotes tumor metastasis and multi-drug resistance. On the other hand, the tumor-specific microenvironment can also serve as a target for drug delivery design, enhancing the therapeutic effects of drugs. In particular, tumor microenvironment-responsive nanodelivery systems have shown promising prospects in the fields of anticancer targeted delivery and controlled drug release. This paper will introduce the current research progress of intelligent nanodrug delivery systems for breast cancer treatment, focusing on two major aspects: the response to abnormal metabolic conditions in the tumor microenvironment (such as low pH, high ROS, and high ATP) and the response to structural heterogeneity in the tumor microenvironment (such as fibroblasts, immune cells, endothelial cells, extracellular matrix, and blood vessels).

3. Tumor Microenvironment-Responsive Smart Nanodrug Delivery Systems

3.1. pH-Responsive Nanodrug Delivery Systems

pH-responsive nanodrug delivery systems utilize the acidic environment of tumor tissues to achieve targeted drug release. The design principle is based on materials or chemical bonds that undergo structural changes under acidic conditions. For example, certain polymer materials contain

pH-sensitive groups, such as tertiary amines or carboxyl groups. At normal physiological pH, these groups remain in an undissociated or partially dissociated state, and the nanocarriers maintain a stable structure. Upon entering the acidic microenvironment of tumors, these groups undergo protonation or dissociation, leading to changes in the nanocarrier's conformation, solubility, or chemical bond cleavage, thus releasing the drug [19].

N. Illy et al. [19] prepared low pH-responsive mPEG-b-PEEGE amphiphilic copolymers, with the hydrophobic segment containing acid-sensitive acetal side groups. Under pH 5.3 conditions, the hydrolysis of the acetal side groups leads to the gradual breakdown of the curcumin-loaded nanoparticles, significantly enhancing the solubility and half-life of curcumin. These nanoparticles effectively deliver the drug during cellular uptake via endocytosis in the acidic tumor microenvironment. Furthermore, cytotoxicity studies demonstrated that mPEG-b-PEEGE exhibits good biocompatibility and anticancer efficacy.

Liu et al. (2023) [20] loaded the anticancer drug doxorubicin (DOX) onto magnetic nanomaterials Fe_3O_4@$mSiO_2$, and then formed a pH-sensitive polydopamine (PDA) coating on the surface through dopamine oxidation polymerization in alkaline conditions, resulting in a DOX/Fe_3O_4@$mSiO_2$@PDA magnetic nanodrug delivery system. Release curves indicated that this system has pH responsiveness and controlled drug release characteristics. The Fe_3O_4@$mSiO_2$@PDA system also showed good biocompatibility and antitumor effects. In breast cancer cell experiments, this drug delivery system effectively entered cells and released the drug in the acidic lysosomal environment, significantly inhibiting the growth of breast cancer cells.

Shen et al. [21] introduced oligonucleotides dissolved in PBS into a pH-responsive polymer PEG 8-PDPA 100-PEG 8 THF solution to prepare oligonucleotide-loaded MNPs, which were then encapsulated in HApt to form HApt-MNPs. In the acidic tumor microenvironment, HApt-MNPs exerted specific cytotoxic effects on HER2-overexpressing SK-BR-3 breast cancer cells, demonstrating better cellular uptake, reduced cell viability, and increased apoptosis. However, the therapeutic effect on MCF7 breast cancer cells was relatively low. Developing nanodrug delivery systems specifically targeting MCF7 breast cancer cells may become a key research focus.

3.2. ROS-Responsive Nanodrug Delivery Systems

Reactive oxygen species (ROS) can damage the DNA and proteins of tumor cells and have become increasingly important in cancer therapy [22]. Magnetic iron oxide nanoparticles (MIONPs) can promote the conversion of endogenous H_2O_2 into ROS, thereby initiating a new form of iron-dependent programmed cell death known as ferroptosis [23]. For instance, magnetic near-infrared photosensitive micelles (CSO-SS-Cy7-Hex/SPION/Srfn) have been developed as a strategy for tumor imaging-guided ferroptosis therapy (FT) [24,25]. This approach combines an aldehyde dehydrogenase inhibitor targeting cancer stem cells (CSCs) undergoing ferroptosis, enhancing ferroptosis via GSH depletion and effectively eradicating malignant breast tumors [26].

Luteolin (Lut) is a natural flavonoid polyphenolic compound that can serve as a chemo preventive and chemotherapeutic agent for breast cancer [27]. Wang et al. [28] used a modified nanoprecipitation/self-assembly method to prepare ROS-responsive nanoparticles Lut/FA-Oxi-αCD NPs, which were loaded with luteolin and folic acid (FA). These nanoparticles exhibited a high drug loading capacity, significantly inhibiting the growth of 4T1 tumors in mice, and demonstrated excellent biocompatibility with no noticeable toxicity. This ROS-responsive nanocarrier provides a promising strategy for clinical applications (Figure 1).

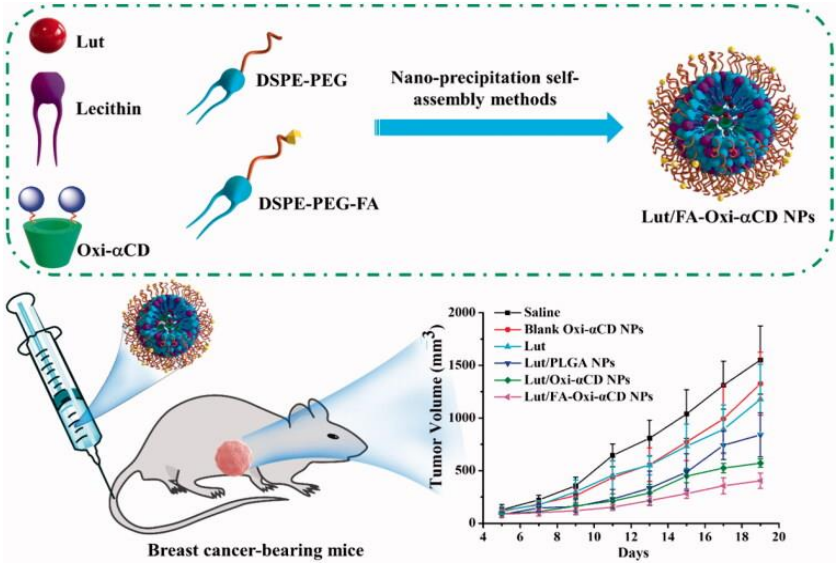

Figure 1: Preparation of LUT-loaded ROS-responsive nanoparticles and their antitumor application in the 4T1 tumor-bearing mouse model [28].

3.3. GSH-Responsive Nanodrug Delivery Systems

The high intracellular concentration of glutathione (GSH) in tumor cells provides a target for designing GSH-responsive nanodrug delivery systems. These systems typically utilize chemical bonds sensitive to GSH, such as disulfide bonds, to connect drugs with nanocarriers. In tumor cells, the high concentration of GSH can reduce the disulfide bonds, causing the drug to dissociate from the carrier and enabling drug release [14].

Since TAT peptides can easily penetrate cell membranes, TAT-based drug delivery strategies have significantly improved cellular uptake in various in vitro studies [29-32]. Sun et al. [17] constructed effective redox-sensitive nanoparticles TAT-DSPEPEG/PEI-SS-PLA/DOX (abbreviated as TPSPD) for the treatment of breast cancer. These nanoparticles use GSH-sensitive disulfide bonds to link drugs to the carrier, and they possess characteristics such as suitable particle size, good serum stability, and long circulation time. In the presence of GSH, the particle size of TPSPD nanoparticles increases significantly, indicating that TPSPD can respond to oxidative environments and trigger release, promoting drug accumulation. Furthermore, in vivo experiments demonstrated that TPSPD nanoparticles exhibit good antitumor activity and reduce systemic toxicity. Therefore, TPSPD nanoparticles hold promise as a potential cancer therapy strategy.

3.4. ATP-Responsive Nanodrug Delivery Systems

ATP-responsive nanodrug delivery systems take advantage of the high ATP concentration in the tumor microenvironment to achieve targeted drug release. These systems typically include molecules or structures that specifically recognize ATP, such as ATP aptamers. Aptamers, as a new class of nucleic acid-based materials, are being developed for their element recognition and therapeutic abilities, thus introducing a new environment for creating stimulus-responsive switches in drug delivery systems [33]. When ATP aptamers are combined with smart nanocarriers, they can be specifically recognized and activated by ATP, inducing the direct release of preloaded anticancer drugs into tumor cells and the microenvironment [34].

Metal-organic frameworks (MOFs) are a new generation of hybrid organic-inorganic materials [35-37], possessing characteristics necessary for drug delivery, such as a high surface area and large pore sizes for drug encapsulation. Through various techniques, MOFs can be scaled down to nanosize, creating NMOFs as nanocarriers. Chen et al. [38] combined these nanocarriers with aptamers to design an intelligent ATP-responsive drug delivery system. In this study, NMOFs loaded with chemotherapeutic drugs, such as doxorubicin (DOX) (or fluorescent agents), were capped by hybridizing sequences containing ATP and AS1411 aptamers and their complementary nucleic acids.

When cancer cells are exposed to high ATP concentrations, NMOFs are unlocked and released via the formation of ATP-aptamer complexes, thereby releasing their contents.

Additionally, Sameiyan E's team [33] developed an ATP-responsive DNA nanostructure for targeted delivery of KLA peptide and anti-miR-21 antibodies, achieving good synergistic therapeutic effects on breast cancer cells. This nanostructure consists of two main sequences: (1) ATP and AS1411 aptamers; (2) anti-miR-21 antibodies. On one hand, the AS1411 aptamers confer high selectivity to the nanostructure. On the other hand, they facilitate the entry of KLA peptides and anti-miR-21 antibodies into breast cancer cells. Due to the high ATP concentrations inside tumor cells, ATP binds to the aptamers, promoting the disassembly of the DNA nanostructure and restoring the functionality of anti-miR-21 antibodies. This nanostructure holds promise as a feasible approach for synergistic treatment of breast cancer.

3.5. Enzyme-Responsive Nanodrug Delivery Systems

The occurrence and development of tumors, as well as the overexpression of related genes, can significantly alter the expression and activity of certain enzymes in the intracellular and extracellular environments of tumor cells. Taking advantage of this characteristic, enzyme-responsive nanodrug carriers can respond to specific enzymes to achieve tumor targeting and trigger drug release [39].

In the application of matrix metalloproteinase (MMP)-responsive nanodrug delivery systems, Xiao et al. [40] combined the broad-spectrum MMP inhibitor BB2516 with paclitaxel (PTX) nanocrystals and MMP-sensitive casein to prepare a dual-load nanocarrier (Fig. 2). The system utilizes the enhanced permeability and retention (EPR) effect to deliver the carrier to the tumor microenvironment, where it is specifically degraded by MMP enzymes. The released BB2516 and PTX effectively inhibit MMP activity and successfully block cancer cell metastasis, providing a viable approach for treating metastatic breast cancer. Additionally, Liu et al. [41] synthesized PLGA-MMP-2-PEG and used it to encapsulate perfluoropentane (PFP) and disulfiram (DSF), creating PFP@PDM-PEG nanodroplets. In the 4T1 tumor mouse model, PFP@PDM-PEG enhanced cellular uptake by significantly promoting the release of PEG in response to MMP-2. Furthermore, PFP@PDM-PEG inhibited the expression of active MMP-2, thereby suppressing the formation of vascular mimicry (VM). This approach holds potential as a new strategy for the clinical treatment of triple-negative breast cancer.

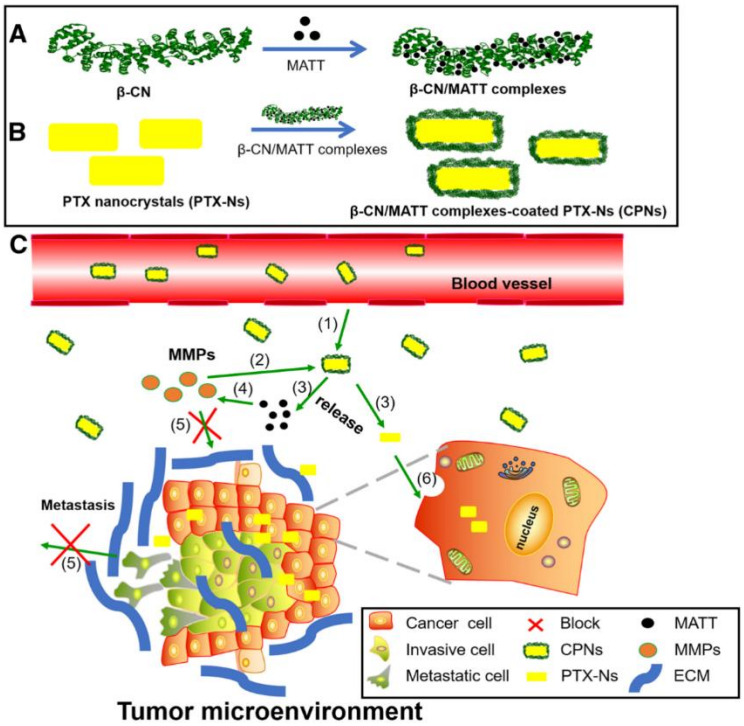

Figure 2: Preparation Process of Composite Coated CPNs and Their In Vivo Activity [40].

3.6. Multi-Responsive Nanodrug Delivery Systems

To enhance the targeting and therapeutic efficacy of nanodrug delivery systems, researchers have developed multi-responsive systems that can respond to various factors in the tumor microenvironment.

For instance, pH/GSH dual-responsive nanodrug delivery systems combine the acidic nature and high GSH levels characteristic of tumor tissues. By incorporating both pH-sensitive and GSH-sensitive chemical bonds or materials, these systems enable dual-trigger drug release within the tumor microenvironment [22]. Li et al. [42] reported a dynamic nanovalve system based on cucurbit[7]uril. In this study, protonated diamine-modified poly(glycidyl methacrylate) (PGMAs) were grafted onto the surface of mesoporous silica nanoparticles (MSNs) through disulfide bonds. Then, cucurbit[7]uril was introduced to form a 1:2 host-guest complex with protonated diamines, thus encapsulating doxorubicin (DOX) and forming dynamic supramolecular crosslinked polymer chains as separable gatekeepers. Under conditions of low pH and high glutathione (GSH) concentration, the host-guest complex is disrupted, and the disulfide bonds are cleaved, leading to favorable release performance. MTT assays revealed significant inhibition of cell growth in the A549 cancer cell line. Similarly, Na Re Ko et al. [43] developed a novel dual-stimuli-responsive nanoparticle DL-CNPs, based on graphene quantum dots loaded with DOX. When DL-CNPs larger than 200 nm were injected intravenously, they accumulated in the breast cancer region via the enhanced permeability and retention (EPR) effect. After internalization, DL-CNPs were exposed to low pH and high GSH levels, leading to the release of both Herceptin and DOX. These novel DL-CNPs demonstrated high cellular uptake and low toxicity, effectively inhibiting SK-BR-3 breast cancer cell activity both in vitro and in vivo.

4. Intelligent Nanodrug Delivery Systems Based on Tumor Microenvironment Structural Heterogeneity

4.1. Immune Cell-Responsive Nanodrug Delivery Systems

4.1.1 Macrophages

M1/M2 macrophages play a critical role in tumor progression. M1 macrophages have traditionally been considered anti-tumor, while M2 macrophages contribute to various pro-tumorigenic outcomes, such as angiogenesis, immune suppression, tumor cell proliferation, and metastasis [44]. Liu et al. [45] prepared iron oxide nanoparticles (MIONPs) that were surface-modified with o-phenylenediamine (OPA), enabling the monitoring of dynamic changes in the M2/M1 macrophage phenotypes within tumors, providing insights into prognosis for macrophage-mediated immune cancer therapies. Additionally, Gu et al. [46] designed iron-SiO_2-based metal-organic framework nanoparticles (MIL 88 B) capable of loading RSL 3, an inducer of ferroptosis. The MIL 88 B nanoparticles damage mitochondrial function, forcing M2 macrophages to undergo glycolytic metabolism, ultimately inhibiting tumor growth and metastasis.

4.1.2 Natural Killer (NK) Cells

Natural killer (NK) cells possess potent cytotoxicity and can identify and eliminate tumor cells. However, the persistent hypoxia in the tumor microenvironment induces M2 macrophages to secrete TGF-β and IL-10, which significantly suppress NK cell activity. To address this, Murphy et al. [47] employed a double-emulsion solvent evaporation method to prepare PLGA-MnO_2 nanoparticles (NPs), which have continuous oxygen generation capabilities. These NPs reduce hypoxic conditions within tumor spheroids, thereby enhancing NK cell cytotoxicity and interferon-γ secretion. These nanoparticles offer a new tool for improving NK cell-based immunotherapy.

Selenium is an essential trace element that can provide effective protection for breast cancer. Gao et al. [48] developed polymer nanoparticles (PSeR NPs) containing diselenide bonds, capable of responding to radiation stimuli to achieve controlled drug release. Selenium produced by radiation-

induced oxidation directly inhibits tumor cell growth and enhances NK cell-mediated immunotherapy by reducing HLA-E expression. These selenium-containing nanoparticles enable a combination of chemotherapy, radiotherapy, and immunotherapy, offering a novel treatment strategy for breast cancer.

4.1.3 T Cells

$CCR9^+$ T cells mediate a strong anti-tumor response. However, the sole chemokine for $CCR9^+$ T cells, CCL25, is not expressed in human triple-negative breast cancer (TNBC). To address this, Chen et al. [49] designed a nanoparticle delivery system (NP-siCD47/CCL25) that sequentially releases CCL25 protein and CD47 small interfering RNA (siRNA) at the tumor site. NP-siCD47/CCL25 significantly increases the infiltration of $CCR9^+CD8^+$ T cells in breast cancer tumors, downregulates CD47 expression in tumors, and suppresses tumor growth and metastasis through T cell-dependent immune responses. This study proposes a strategy to enhance immune therapy by promoting the infiltration of $CCR9^+CD8^+$ T cells.

4.2. Tumor-Associated Fibroblasts (CAFs)

Tumor-associated fibroblasts (CAFs) can promote the malignant characteristics of tumor cells and enhance their resistance to treatment. Therefore, targeting CAFs with nanoparticles is critical for enhancing the efficacy of chemotherapy and immunotherapy. Yuan et al. [50] developed composite nanoparticles named PI/JGC/L-A, which efficiently encapsulate JQ1, C18 ceramide, and gemcitabine. These nanoparticles demonstrated excellent stability, high drug encapsulation efficiency, and targeting capabilities. In vitro and in vivo experiments showed that these nanoparticles transformed CAFs into drug reservoirs, enabling targeted delivery and controlled release. This resulted in effective tumor growth inhibition and prolonged survival in mice. Rodponthukwaji et al. [51] developed anti-FAP antibody-conjugated nanoparticles (anti-FAP-OMF@NPs) by emulsification-solvent evaporation, which targeted FAP-positive CAFs. These nanoparticles exhibited excellent biocompatibility, high toxicity, and enhanced penetration capabilities, making them a promising approach for breast cancer therapy.

4.3. Vascular Endothelial Growth Factor (VEGF)

Vascular endothelial growth factor (VEGF) is a key regulator of tumor angiogenesis, promoting endothelial cell proliferation, migration, and the formation and development of blood vessels. VEGF expression is elevated in the tumor microenvironment, making it an ideal target for molecular therapies. Semkina et al. [52] coated iron oxide nanoparticles with bovine serum albumin and polyethylene glycol, covalently coupling anti-VEGF monoclonal antibodies onto the surface. Doxorubicin (DOX) was physically loaded onto these nanoparticles. These magnetic nanoparticles exhibited prolonged circulation times, significantly accumulated in 4T1 tumors compared to non-targeted nanoparticles, and notably prolonged mouse survival by approximately 50%, achieving tumor therapy and diagnosis. Moreover, RNA interference targeting VEGF expression is a promising strategy to suppress tumor growth. Chen et al. [53] prepared CaP/siRNA nanoparticles using co-precipitation and encapsulated them in polycaprolactone (PCL) to form multi-cationic liposomes (PLCP). The PLCP-mediated VEGF siRNA significantly reduced VEGF expression in vitro. In vivo experiments showed that the combined treatment of PLCP/VEGF siRNA and DOX effectively inhibited tumor angiogenesis and growth. This nanoparticle system offers a potential new strategy for breast cancer treatment.

4.4. Extracellular Matrix (ECM)

The extracellular matrix (ECM) plays a fundamental role in maintaining cell proliferation, differentiation, and tissue homeostasis. It can also create an immune-suppressive environment that provides a sturdy barrier for tumor survival and progression [54]. Thus, designing ECM-targeted nanodrug delivery systems is an urgent challenge. Lysyl oxidase, which is involved in the

crosslinking of collagen and elastin in the ECM, tumor cell migration, and adhesion, has been identified as a key target. De Vita et al. [55] targeted lysyl oxidase by preparing lipid nanoparticles using the thin-film hydration method. The nanoparticles were conjugated with anti-lysyl oxidase antibodies via covalent bonds to form Lipo-EPI-LOX. When loaded with DOX, these nanoparticles exhibited significant inhibition of triple-negative breast cancer (TNBC) cells both in vitro and in vivo. These nanoparticles demonstrated prolonged survival, low cytotoxicity, and strong biocompatibility, proving their feasibility for TNBC treatment and their potential as ECM-targeted agents. Type IV collagen-binding peptide (C4BP) has a strong affinity for breast tumors. Ikeda-Imafuku et al. [56] conjugated bromelain to hyaluronic acid (HA) via C4BP to form C4BP-HA-Bro. This ECM-targeted peptide efficiently delivered ECM-degrading enzymes (bromelain) to the 4T1 tumor, significantly improving DOX tumor penetration. The C4BP-HA-Bro system can remodel the ECM microenvironment and enhance the efficacy of other anti-cancer nanodrugs.

Table 1 Nano drug delivery system based on ECM components

ECM Component	Preparation Method	Nanoparticle	Function or Application	Reference
Gelatin	Solvent removal	GN-ClAlPc	Photodynamic therapy.	[57]
Collagen	Electrostatic spray deposition	Collagen nanoparticles	Drug controlled release.	[58]
Fibrin	Microfluidic droplet generation	FBN	Supports cell migration, wound healing in vivo.	[59]
Hyaluronic Acid	Self-assembly	Prodrug@DOX	Enhances drug targeting and therapeutic efficacy.	[60]
Chondroitin Sulfate	Self-assembly	PTX/CQE NPs	Inhibition of MDR (multidrug resistance) and anti-metastatic effects.	[61]

5. Conclusion and Outlook

Intelligent nanodrug delivery systems responsive to the tumor microenvironment offer new approaches and methods for the treatment of breast cancer. By specifically responding to the tumor microenvironment, these systems enable targeted drug delivery and precise release, thereby improving therapeutic efficacy while reducing side effects. However, there are still numerous challenges in this field that require further optimization of carrier design, exploration of combination therapies, and enhancement of clinical translation. Future research in this area could focus on the following aspects:

1. **Development of Novel Responsive Materials**: For instance, the design of nanodrug delivery systems based on new chemical bonds, such as metal-sulfur bonds or selenium-nitrogen bonds.
2. **Multifunctional Design**: Incorporating targeting molecules onto the surface of nanoparticles, introducing therapeutic functions (e.g., photothermal therapy, gene therapy), and integrating with artificial intelligence.
3. **Clinical Applications and Translation**: Advancing clinical trials to further validate the safety and efficacy of these systems.

With continuous research and development, intelligent nanodrug delivery systems responsive to the tumor microenvironment are expected to play a significant role in breast cancer treatment, offering new hope for patients.

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