Nanomaterial Technology and Triple Negative Breast Cancer

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Triple negative breast cancer (TNBC) is a malignant breast cancer subtype that is prone to progression, with high associated metastasis and five-year mortality rates and an overall poor prognosis. Chemotherapy is usually administered to treat TNBC without additional targeted therapies. Novel nanomaterials have a variety of excellent physical and chemical properties and biological functions (including targeting specificity), and contrast agents and drug delivery vectors based on nanotechnology are progressing towards a more accurate and targeted direction. This review discusses the mechanisms of action and prospects for the use of nanotechnology in the treatment of TNBC, thus providing potential new strategies for the diagnosis and treatment of TNBC.

Keywords: nanomaterial, nanotechnology, nanobiosensors, triple negative breast cancer, drug delivery, vaccines

INTRODUCTION

Cancer is a major public health problem worldwide and the second leading cause of death in the United States. Cancer mortality rates have been rising throughout most of the 20th and 21st centuries, with 1,898,160 new cancer cases and 608,570 cancer deaths expected in the United States as of 2021 (1). From 2010 to 2016, the five-year overall survival rate for all diagnosed cancers in the United States was 67% (68% for Caucasians and 63% for African Americans) (1, 2). Prostate cancer (98%), melanoma (93%) and female breast cancer (90%) had the highest associated survival rates, while pancreatic cancer (10%), liver cancer (20%), esophageal cancer (20%) and lung cancer (21%) had the lowest survival rates (3, 4).

Improved cancer survival rates seen in recent decades are mainly due to advances in diagnosis and treatment, specifically reflecting advances in screening, diagnosis, and surgery (e.g., pathological staging, thoracoscopic surgery). Therapies for metastatic disease include targeted therapy (e.g., precision medicine), chemotherapy, radiotherapy, immunotherapy (e.g., programmed cell death protein-1 and programmed death ligand-1 inhibitors), and novel material-based therapies (1, 5–9).

Abbreviations: COVID-19, coronavirus disease 2019; HER2, human epidermal growth factor receptor 2; ER, estrogen receptors; PR, progesterone receptors; TNBC, triple negative breast cancer; BL1, basal like 1; BL2, basal like 2; ML, mesenchymal like; MSL, mesenchymal stemlike; LAR, intracavitary androgen receptor; IM, immune regulation; ROS, reactive oxygen species; TME, tumor microenvironment; DOX, doxorubicin.

The disruptive effects of the coronavirus disease 2019 (COVID-19) pandemic on healthcare delivery include disruptive effects with respect to the diagnosis and treatment of cancer patients due to delays in diagnosis and treatment, reduced access to care, and delays or closures of healthcare facilities and systems. These factors are likely to result in short-term, spurious declines in cancer rates followed by an increase in advanced disease and associated cancer mortality rates (1, 10, 11).

BREAST CANCER

Women comprise 49.5 percent of the global population, and are disproportionately represented among elderly people over age 60. In fact, due to population growth and aging, the global cancer burden for women has been increasing in all countries regardless of income level. Breast cancer is the most common malignancy among women worldwide, with one study estimating that approximately 160,000 patients with advanced breast cancer were diagnosed in the United States as of 2017 (12).

Due to the influence of multi-modal factors, such as genetic susceptibility, lifestyle, and other environmental factors, breast cancer incidence and mortality show extreme variance across countries and demographics (13). For example, breast cancer incidence is higher in high-income regions (e.g., 92 per 100,000 in North America) as compared with low-income regions (e.g., 27 per 100,000 in Central Africa and East Asia) (14). However, many low-income and middle-income countries, including countries in sub-Saharan Africa and developing countries in Asia, have low breast cancer incidence rates due to delays in healthcare delivery, late diagnoses, and limited access to treatment due to low mammography coverage and limited overall treatment options (15).

At the molecular level, breast cancer molecular signatures include the activation of human epidermal growth factor receptor 2 (HER2, encoded by *ERBB2*), the activation of hormone receptors (estrogen receptors and progesterone receptors), and *BRCA* mutations (16, 17). Intrinsic classifications delineated in 2000 distinguish four breast cancer subtypes: Luminal A and Luminal B, HER2-enriched, and triple negative breast cancer (TNBC). This classification system shifts the clinical management of breast cancer from a cancer burden-based approach to a biologically-centered approach. Currently, clinical practice classifies five breast cancer subtypes (luminal A, luminal B, HER2-enriched (HER2+), basal-like and normal-like) based on histological and molecular characteristics, including TNBC. TNBC is defined according to the following criteria: estrogen receptor-negative (ER–), progesterone receptor-negative (PR–), HER2–, high grade, and high Ki67 index tumors, either NST (no special type) histology or special type histology (metaplastic, adenoid cystic, medullary-like, secretory), and a generally poor prognosis (18).

There are differences in prognosis among breast cancer subtypes. Approximately 10-15% of TNBC cases present with poor prognoses due to the lack of targeted therapy for TNBC, aside from chemotherapy (19, 20). Morphologically, approximately 90% of TNBC cases present as infiltrating ductal carcinoma, while the remaining cases are classified as apocrine carcinoma, lobular carcinoma, adenoid cystic carcinoma, and metaplastic carcinoma (21–23). There are six different TNBC subtypes, including basal like 1, basal like 2, mesenchymal like, mesenchymal stemlike, intracavitary androgen receptor, and immune regulation subtypes. TNBC heterogeneity clinically refers to different breast cancer subtypes presenting with a triple negative phenotype. Gene expression profiles and genetic outcomes for each class show differences, thus illustrating the inherent complexity of TNBC (21).

Triple-negative breast cancer is more likely to recur as compared with other breast cancer subtypes, with five-year specific survival rates of 85% for stage 3 triple-negative cancer, as compared with survival rates ranging from 94-99% for hormone receptor-positive and ERBB2-positive cancers (24). The distribution of breast cancer molecular subtypes varies by race, with African and African American women having the highest rates of TNBC. TNBC presents with a higher rate of metastasis and the highest proportion of poorly differentiated or undifferentiated grades among all subtypes. These factors result in reduced survival rates (25).

BREAST CANCER DIAGNOSIS AND TREATMENT

Therapeutic strategies for treating breast cancer include local therapies (e.g., surgery, radiotherapy) as well as systemic therapies. Molecular subtypes have a profound influence on the therapeutic strategies selected for breast cancer. Specifically, systemic therapies have been developed primarily on the basis of molecular characteristics, including targeted chemotherapy, endocrine therapy for hormone receptor-positive diseases, anti-HER2 therapy for HER2-positive diseases, polymerase inhibitors for *BRCA* mutation carriers, and novel immunotherapy modalities (18).

In addition to surgical topical treatment, patients with hormone-receptor-positive cancer need endocrine therapy. A few of these patients also receive chemotherapy. Patients with ERBB2-positive cancer are treated with ERBB2-targeted antibodies or small molecule inhibitors combined with chemotherapy. Patients with triple-negative cancer typically receive only chemotherapy or radiation. Whether breast cancer patients receive radiotherapy is determined according to their specific indications. More and more patients are choosing to undergo systemic treatments, including targeted preoperative chemotherapy (i.e., neoadjuvant chemotherapy) following preoperative puncture examination (24). Breast cancer treatments based on nanotechnology are the focus of the current review.

NANOTECHNOLOGY AND CANCER

Advances in nanotechnology over the past two decades offer potential new strategies for treating various diseases (26–32).

Nanotechnology-based contrast agents and drug delivery vectors for disease diagnosis and treatment are progressing towards a more accurate and targeted direction. Currently, nanocarriers are mainly comprised of polymers, metals, lipids, nucleic acids, and proteins, including nanoparticles/tubes, micelles, dendrimers and liposomes (33). These smart nanoparticles can encapsulate drugs or probes and are coated with specially modified ligands that bind to receptors expressed at cell sites and ultimately affect cell function for the accurate and effective diagnosis and treatment of disease (34, 35).

Nanooncology is a branch of nanomedicine. Cancer diagnosis and treatment based on nanotechnology has received wide attention on a worldwide scale in the past decades (36–40). For example, in diagnostics, some nanoparticles have been developed into biomolecular vectors that can detect cancer biomarkers and play an important role in assisting cancer detection and monitoring cancer biomarkers, including proteins, antibody fragments, DNA fragments, and RNA fragments (37). For example, nanobiosensors are very sensitive and can detect multiple protein biomarkers within seconds (41, 42). Additionally, nanotechnology assisted molecular diagnostic technology has been increasingly implemented in imaging applications, which is conducive to the identification of cancer at an earlier and more accurate stage (43, 44).

In terms of treatment, nanotechnology has unique physicochemical properties, including a high surface volume ratio. In recent years, drug delivery systems based on nanomaterials, including micelles, nanoemulsions and liposomes, have been widely used. Nanomaterials can bind and load bioactive molecules, including DNA, RNA, drugs, and proteins. These bioactive molecules can easily cross many biological barriers and can easily be transported to the target. Therefore, nanomaterials are widely used in the loading and delivery of drugs for treating various cancers so as to improve the efficacy of chemotherapy combined with radiotherapy and photodynamic cancer therapy (7, 25, 45–47). To achieve complete tumor eradication, therapeutic agents need to be infused at extremely high levels. Moreover, within cancer immunotherapy using nanotechnology, nanoparticles carry T cells or natural killer cells and higher concentrations of anti-cancer drugs, achieving a strong and lasting anticancer immune response due to low concentrations of immune regulators (48, 49). Advances in nanotechnology, including virus-like sizes and high surface-volume ratios and surfaces that can be modified to precisely target specific cell types can be widely used in designing cancer vaccines (50).

Additionally, the cancer microenvironment plays a critical role in determining cancer survival and reducing mortality. Microenvironmental factors, such as cancer hypoxia or hyperglycemia and inflammation, are also directly associated with the survival and expansion of cancer cells. Interventions aimed at changing the microenvironment of cancer cells can induce cancer cell death and form the basis for new anticancer therapies (51).

NANOTECHNOLOGY AND TNBC

TNBC is an important and recalcitrant breast cancer subtype. The treatment of patients with TNBC remains an immense clinical challenge, characterized by aggressive progression, high metastasis rates, and poor overall prognoses (52). Because standard endocrine therapy (i.e., HER2 targeting therapy) does not affect TNBC, anthracycline-based drugs and taxane chemotherapy are major means to achieving TNBC systemic treatment. These treatment modalities are highly effective. However, many cycles of chemotherapy and high doses of cytotoxic drugs employed to destroy cancer cells are likewise toxic to nearby healthy cells, causing adverse systemic effects such as hair loss, gastrointestinal symptoms, and thrombocytopenia (53, 54).

Moreover, chemotherapy resistance caused by P-glycoprotein overexpression, DNA damage repair, topoisomerase II mutations, low solubility and bioavailability of chemotherapy drugs, and the immune escape of cancer cells limits the therapeutic effects of drugs on TNBC. Chemotherapy resistance results in a recurrence rate of 50% and a mortality rate of 37% for TNBC (55, 56). Invasive proliferation, heterogeneity, and cancer resistance to therapeutic drugs are extreme challenges in the treatment metastatic breast cancer, which mainly metastasizes to local lymph nodes, bones, and the lungs (57).

Therefore, in order to avoid non-specific targeting and chemotherapy side effects among TNBC patients, the need to open up new molecular targets and treatments is much more urgent than for other types of breast cancer. Nanotechnology-based drug delivery systems are auspicious tools that can selectively target tumors and eliminate the cytotoxicity of drugs to other organs (58).

Drug Delivery Systems for Nanotechnology

Nanodrug delivery systems mostly rely on enhanced permeation and retention effects for targeting drug delivery (59). In general, nanoparticles that can be applied to cancer treatment within nanoscience have the following physiochemical properties: tailored size and conformation, appropriate encapsulation capacity, high adhesion to the cancer environment, selective localization, enhanced cancer internalization through endocytosis, sustained and controllable drug release, a long cyclic half-life, minimal systemic toxicity, and safe biological elimination (60, 61). Research on the high expression of cancer targets and ligands *via* nanomaterials combined with other therapies (such as photodynamic therapy, chemotherapy, and radiotherapy) to produce therapeutic synergistic effects will be the key to the application of nanomaterials within TNBC.

Photothermal therapy (PTT) is ineffective in the treatment of TNBC due to the lack of effective therapeutic targets. In order to solve this problem, Cheng et al., used gold nanocage (AuNC) as a photothermal conversion agent combined with anti-heat shock protein monoclonal antibody (cmHSP) as a target ligand in order to prepare a microwave triggered heat shock protein (HSP)-tar gold nanosystem (CMHSP-AUNC). Microwave irradiation can effectively activate HSP70 overexpression in TNBC, thus meaningfully improving the targeting ability, accumulation in cancer area, and anti-cancer efficacy of CMHSP-AUNC (62). Xu et al. developed a nanoemulsion formulation with high stability for the systematic delivery of puerarin nanoPue. This modality reshapes the stromal microenvironment through nanoparticle

treatment, down-regulates intracanceral reactive oxygen species (ROS) and oxidative stress, meaningfully reduces the connective tissue formation response within different types of solid tumors and enables nanoparticles to infiltrate more effectively into cancer parenchyma. Simultaneously, nanoPue, a powerful tumor microenvironment (TME) modulator, meaningfully improves the cancer immune microenvironment as well as the therapeutic efficiency of α-PD-L1 in TNBC models (63). Bhattacharya et al. have also developed thyquinone (TQ)-loaded hyaluronic acid (HA) coupled with Pluronic ® P123 and F127 copolymer nanoparticles (HA-TQ-NPS) as selective drug carriers to deliver anticancer phytochemical TQ to TNBC cells. HA-TQ-NPS meaningfully promotes apoptosis, anti-metastasis, and anti-angiogenesis in TNBC cells *via* upregulation of microRNA-361 with no associated toxicity to normal cells (64).

Nanomaterials as Adjuvant Immunotherapy for TNBC

The immune microenvironment affects the occurrence and development of breast cancer according to the principles of immune monitoring and immune editing. In the early stages of tumorigenesis, the immune microenvironment plays an anti-cancer role mainly through the cytokine environment (i.e., activated CD8+ and CD4+ T cells). In contrast, once the cancer becomes aggressive, the cellular composition of the microenvironment, including fibroblasts and the cytokine content associated with cancer, facilitates cancer promotion and is invaded by breast cancer cells (63).

Using immune cells within targeted cancer therapy is in line with the concept of using internal mechanisms within the host immune system to fight cancer. In this study, Prof. James Allison and Prof. Tasuku Honjo, the winners of the 2018 Nobel Prize in Medicine, investigated the use of immune checkpoint blockades in cancer treatment *via* inhibiting negative immune regulation. Immunotherapy has achieved some success thus far, thereby providing a new therapeutic strategy for TNBC treatment. Current immunotherapies include immune checkpoint blockers, cytotoxic T lymphocyte (CTL) exchange activation, adaptive cell transfer therapy (ACT), and TME regulation. Nanotechnology presents a novel immunomodulatory strategy that can be implemented as a personalized immunotherapy modality for TNBC (65).

Nanotechnology provides efficient and intelligent nanodelivery systems that facilitate the delivery of immune-stimulating adjuvants and cancer antigens to enhance antigen presentation and immunity and aid in the treatment of metastases. Nanoparticle carriers improve the solubility and bioavailability of immunotherapy modalities, including protection from degradation, thereby increasing therapeutic efficacy. Currently, nanoparticles (NPs) are already implemented to help improve antigen expression pathways by delivering epigenetic regulators and immune-stimulating cytokines (66). For example, Tran et al. evaluated different polyethylene-oxidation-polylactic acid (PEO-PLA) copolymer micelles, with vorinostat (HDACi) demonstrating better biosolubility, an increased half-life, and improved pharmacokinetics as compared with other modalities (67). NP-carrying bevacizumab and CRLX101

likewise showed good efficacy in TNBC treatment (68). Sulforaphane (SFN) downregulates histone deacetylase (HDAC6) mediated phosphatase and inhibits MDA-MB-231 and MDA-MB-468 cells. The expression of tensin homolog (PTEN) induces autophagy, meaningfully increasing the sensitivity of TNBC to doxorubicin (DOX). Thus, inhibition of cancer growth *via* autophagy induction due to SFN combined with therapeutic DOX may provide an effective approach for TNBC treatment (69). Although targeted nanodrugs have good potential, due to the biological distributions, pharmacokinetics, targeted population biodegradability, immunogenicity, and the complexity of dosing system design for nanodrugs, only a portion of nanodrug systems (e.g., polymer micelles, liposomes, nanoparticle couplings) progress to the clinical administration stage. More research is needed with respect to TNBC nanodrugs.

Vaccines Based on Nanotechnology

Cancer vaccines are comprised of cancer cells and/or cancer antigens and lead to an effective anti-cancer host immune response. Cancer vaccines include DNA vaccines, Ab vaccines against idiotypic types and cancer-associated pathogens, and dendritic cell vaccines (70, 71). In Liu's study, the researchers (including the authors of the current review) constructed nanoparticles to deliver an mRNA vaccine encoding the cancer-associated antigen MUC1 to dendritic cells (DCs) in lymph nodes, thus activating cancer-specific T cells. In this study, combining a simple mRNA vaccine with an anti-CTLA-4 monoclonal antibody meaningfully enhanced the anti-cancer host immune response and anti-cancer effects. These data support the use NP as messenger RNA vaccine vectors as well as the combined implementation of TNBC immunotherapies, NP-based messenger RNA vaccines, and CTLA-4 inhibitors (52).

CONCLUSIONS

Triple negative breast cancer is a difficult and often intractable disease because of its high heterogeneity and low associated survival rates. Currently, the available treatment methods for patients diagnosed with TNBC are limited, especially with respect to refractory TNBC. Novel nanotechnology modalities represent auspicious strategies for efficient and accurate diagnoses and targeted therapies for TNBC due to their tailored physical and chemical properties and biological functions. Our work guides and informs future research directions and will ultimately contribute to informing medical guidelines.

AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study and writing of the manuscript. KH and HC undertook the research, YW and ZN wrote the main manuscript text and prepared figures. YW revised the article critically for important intellectual content and final approval of the version to be submitted. All authors contributed to the article and approved the submitted version.

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