Tumor Microenvironment-Sensitive Nanomedicine Delivery System Application Progress in Multidrug Resistant Breast Cancer

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Abstract. Breast cancer represents the most prevalent oncological diagnosis and the foremost cause of cancer-induced mortality in the female population globally. The development of multidrug resistance (MDR) continues to present a substantial impediment to effective treatment. Within this context, the tumor microenvironment (TME) is intricately linked to the initiation and progression of malignant neoplasms. Recently, cascade-responsive TME-sensitive nanodrug delivery systems (TMS-NDDS) have emerged as a focus of significant research interest for the treatment of MDR breast cancer. This paper outlines the key biochemical and physicochemical characteristics of the breast cancer TME—including acidosis, hypoxia, enzyme overexpression, and redox imbalance—and discusses their roles in tumor development and drug resistance. We further summarize recent advances in the design of TMS-NDDS that utilize cascade-responsive mechanisms for targeted drug delivery and release. These systems enhance tumor accumulation through both passive and active targeting, allow precise drug release under specific TME stimuli, modulate the immunosuppressive TME, and can be integrated with other treatment modalities such as photothermal and photodynamic therapies. This review offers insights into both MDR breast cancer and cascade-responsive TMS-NDDS, thereby facilitating future advances in research and therapy.

Keywords: Breast cancer; multidrug resistance (MDR); tumor microenvironment (TME); nanodrug delivery system; cascade response.

1. Introduction

Breast cancer occupies a prominent position among oncologic diagnoses in women globally. As reported in the most recent evaluation by the World Health Organization's International Agency for Research on Cancer (IARC), breast cancer accounted for 11.6% of all new cancer cases and was responsible for 6.9% of cancer-associated fatalities in 2022, thereby posing a considerable threat to female health [1]. However, MDR in traditional treatment and poor postoperative recovery effects are still problems to be solved [2]. TMS-NDDS therapy has emerged as a prominent focus in contemporary research. Engineered nanoparticles demonstrate enhanced penetration capabilities into the complex TME and achieve targeted delivery to its critical constituents [3]. In TMS-NDDS, nanoparticles play an effective role in passive delivery to tumor tissues and slow release of drugs [3]. TMS-NDDS is designed by the characteristics of low pH value in TME, a variety of enzymes, high expression of glutathione, and the fact that tumor tissues are more sensitive to high temperature can stably exist in the circulatory system and normal physiological tissues. Upon reaching tumor tissues, TMS-NDDS facilitates controlled drug release through cleavage of chemical bonds or structural decomposition, thereby contributing to reduced systemic toxicity and enhanced therapeutic efficacy of chemotherapeutic agents [4]. Furthermore, TMS-NDDS represents a novel strategic approach for addressing multidrug-resistant breast cancer. Wu et al. demonstrated that co-delivery of doxorubicin (DOX) and siRNA via tumor-targeted nanomicelles promotes synergistic chemo-gene therapy, effectively reversing multidrug resistance in breast cancer models [2]. Wu et al. found that the hybrid nano-formulation composed of pH-sensitive liposomes and small-sized nano-micelles also played a good role in inhibiting breast cancer [5]. Although a wide range of research has been carried out on TMS-NDDS in the past decades, there is still a lot of room for research on the design method of TMS-NDDS and its treatment measures for multidrug-resistant breast cancer. Consequently, this article

systematically examines the "cascade-responsive" design strategy of TMS-NDDS and its recent advancements in managing MDR breast cancer, with the objective of establishing a theoretical and practical foundation for TMS-NDDS-based therapeutic interventions against MDR breast cancer.

2. Application Advantages of Nano Drug Delivery System in Response to Multidrug Resistance (MDR) of Breast Cancer

2.1. The Core Role of TME in the Development and Drug Resistance of Breast Cancer

MDR describes the adaptive capacity of tumor cells to develop simultaneous resistance to multiple anticancer agents that differ in chemical structure, therapeutic targets, and mechanisms of action. In breast cancer, a key mechanism underlying MDR involves the upregulation of efflux transporter proteins, which actively pump chemotherapeutic drugs out of the cell, resulting in subtherapeutic intracellular drug concentrations and impaired efficacy. This reduces the intracellular accumulation of chemotherapeutic agents and promotes their inactivation [6,7]. Among the most widely characterized drug efflux transporters linked to multidrug resistance are P-glycoprotein (P-gp/ABCB1), multidrug resistance protein 1 (MRP1/ABCC1), breast cancer resistance protein (BCRP/ABCG2), and lung resistance protein (LRP). To counter these mechanisms, nanodrug delivery platforms can be engineered with high specificity toward molecular targets—such as surface-overexpressed carbohydrates, proteins, and lipids on malignant cells—thereby facilitating tumor-selective drug delivery and minimizing off-target toxicity [6]. The TME further significantly influences breast cancer pathogenesis. Comprising a diverse array of cellular and non-cellular components—including immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, inflammatory cells, lymphocytes, extracellular matrix (ECM), vasculature and chemokines—the TME plays a complex role in tumor behavior [3]. Through intricate cell–cell and cell–matrix interactions, many of these elements, particularly CAFs and infiltrating immune cells, promote a permissive niche that facilitates breast cancer progression [8-10]. Thus, while the TME may initially exert tumor-suppressive effects via immune regulation, it often evolves to foster drug resistance through alterations in tumor immunogenicity.

2.2. Key Features of the Breast Cancer TME

2.2.1 Biochemical characteristics

In the breast cancer TME, the vasculature is frequently characterized by aberrant regulation and compromised functionality, representing a key pathological feature. This precisely leads to a reduction in oxygen partial pressure, thereby inducing a hypoxic state. Hypoxia is manifested in approximately 40% of all breast carcinomas and 50% of locally advanced cases, a condition strongly correlated with the stabilization of oxygen-sensitive transcriptional regulators, specifically hypoxia-inducible factors (HIFs). Under oxygen-deprived conditions, breast cancer cells may either upregulate the HIF-1α signaling cascade or promote the heterodimerization of HIF-2α with HIF-1β, culminating in the assembly of the HIF-2 transcriptional complex. Furthermore, hypoxia may also drive non-canonical responses through HIF-independent mechanisms that regulate gene expression [11]. Notably, hypoxia within the breast cancer TME can promote an immunosuppressive environment. It contributes to immunosuppression through various pathways, including upregulation of CCL22 and CCL28 expression, promotion of macrophage polarization toward the pro-tumor M2 phenotype, and enhancement of immunosuppressive factor secretion [3]. These signaling pathways play crucial roles in tumorigenesis (Fig. 1), and investigating these mechanisms will provide insights and therapeutic targets for breast cancer immunotherapy.

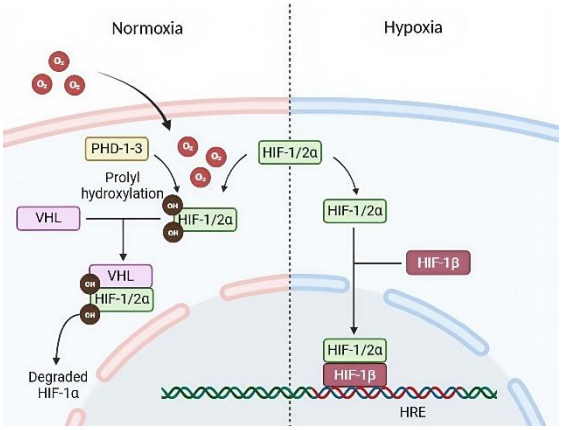

Fig. 1 Two or more references

2.2.2 Physicochemical characteristics and other characteristics

The breast cancer TME exhibits multiple physicochemical characteristics, among which acidosis is one of the most classic features. Over the past few decades, research on the TME has revealed that its pH is characteristically acidic. Due to the "Warburg effect," many breast cancer cells undergo a characteristic glycolytic shift, metabolizing glucose, which leads to substantial H+ production and lactate accumulation, consequently further reducing the TME pH and resulting in acidosis. Remarkably, under these conditions, the intracellular acidity of breast cancer cells is significantly lower than that of normal cells grown under similar acidic stress. This adaptation not only allows them to thrive in the acidic environment but also enhances their chemoresistance, invasiveness, metastatic potential, and ability to evade immune surveillance [9]. In addition to acidosis, increased stromal stiffness is another key physicochemical property of the breast cancer TME. Cross-linking of the extracellular matrix (ECM) within the breast cancer TME is markedly increased compared to both other tumor types and normal tissue, leading to significantly elevated tissue stiffness. The average stiffness of malignant breast tumors is considerably higher than that of benign lesions. Furthermore, interstitial hypertension is a characteristic feature of the neoplastic microenvironment in breast cancer, with pressure levels significantly surpassing those found in normal tissue. This is driven by hydrostatic microvascular pressure (MVP), resulting from high vascular permeability and compressed blood vessels. Additionally, solid stress within the breast cancer TME is significantly higher than in many other tumors [10]. Beyond these biochemical mechanisms, other mechanisms within the breast cancer TME have become a major research focus in recent years. However, findings remain limited, and numerous questions still await resolution.

3. Cascade Responsive TMS-NDDS and Its Design Strategy

3.1. The Basic Logic of Cascading Response and TMS-NDDS Type

Cascading response is a mechanism that enables the transmission and amplification of signals through multi-stage reactions, characterized by high selectivity and rapid response kinetics. TMS-NDDS can leverage the differences between the tumor microenvironment (TME) and normal physiological conditions to achieve cascaded drug release via chemical bond cleavage or structural depolymerization. Accordingly, TMS-NDDS can be designed as five types of nano-drug delivery systems: pH-sensitive, enzyme-sensitive, reduction-sensitive, temperature-sensitive, and dual/multi-stimuli-sensitive systems [3].

3.2. Core Building Blocks and Response Mechanisms

Cascading reaction, also referred to as a domino-type reaction, achieves sequential response through the carefully designed stepwise triggering of multi-stage reactions. Its core mechanism can involve the coordinated action of various modules, such as biological cascade modules, engineered

cascade modules, and cross-system modules. In a cascading response system, the product of an upstream reaction can act as a catalyst or activator for the subsequent downstream reaction, forming a chain reaction that enables progressive activation. Each stage of the reaction amplifies the signal intensity. Additionally, the cascading response can be dynamically regulated through positive enhancement mechanisms and negative feedback inhibition mechanisms [12]. From a research trend perspective, TMS-NDDS, based on cascading responses, demonstrates multiple advantages in the treatment of breast cancer, including rapid action and high targeting efficacy. However, current understanding of the specific mechanisms remains limited, warranting further exploration in the future.

4. Application and Mechanism of Cascade Response Strategy in Overcoming MDR Breast Cancer

4.1. Enhance Tumor Targeting and Accumulation

TMS-NDDS, based on cascading responses, exhibits enhanced targeting capability toward tumor tissues. Evidence indicates that doxorubicin-resistant breast cancer cells (MCF-7/ADR) can regain chemosensitivity through selective P-glycoprotein (P-gp) inhibition mediated by doxorubicin and siRNA co-encapsulated in micellar carriers. Notably, in vivo studies demonstrated that D-PECL3/si micelle complexes induced more pronounced suppression of MCF-7/ADR tumor growth [2]. The targeting mechanisms underpinning these effects fall into two primary categories: passive targeting, leveraging the enhanced permeability and retention (EPR) effect and active targeting. The EPR effect facilitates the initial localization of long-circulating nanoparticles—whose sizes exceed the threshold for renal clearance—within tumor tissues, owing to the characteristic hyperpermeability of tumor vasculature. Complementing this passive process, active targeting employs surface-grafted ligands on nanocarriers that achieve specific recognition and binding to receptors overexpressed on drug-resistant breast cancer cells, thereby markedly improving carrier-cell adhesion and internalization efficiency [13]. Based on current research, it is evident that cascading response-based TMS-NDDS possess a stronger ability to target breast cancer tissues. Although related studies are being actively pursued, published findings remain limited, and a lack of in-depth investigation into the mechanisms of action remains a major challenge.

4.2. Achieving Precise and Controlled Drug Release

TMS-NDDS, based on cascading responses, enables precise and controlled drug release at the target site. Zhang et al. found that exogenous stimuli such as light, heat, and ultrasound offer higher selectivity compared to endogenous stimuli and allow a certain degree of precision in regulating drug release. In a multistage drug release approach, nanocarriers are first triggered by intrinsic or externally applied stimuli within the breast tumor region. This activation initiates intermediate signaling cascades that become progressively amplified, thereby sharpening the therapeutic discrimination between malignant and healthy tissues. Although externally applied stimuli offer high spatial precision, they often suffer from limited responsiveness compared to endogenous triggers—a key limitation that remains to be addressed in subsequent investigations [12].

4.3. Modulating the Immunosuppressive TME

Cascading response-based TMS-NDDS can alter the immunosuppressive tumor microenvironment (TME) by targeting its key components, thereby reversing immunosuppression. Through engineered design, nanoparticles may be tailored to selectively target immunosuppressive cell populations and suppress the secretion of immunosuppressive cytokines, thereby reversing the TME phenotype from immunosuppressive to immune-supportive. Furthermore, TMS-NDDS can be conjugated with specific ligands for targeted delivery into the immunosuppressive TME, where they modulate its function and enhance therapeutic efficacy. Several nanodrugs, such as Doxil and

Abraxane, have already been approved by the FDA for clinical use [3]. Consequently, cascaded TMS-NDDS platforms capable of modulating the immunosuppressive tumor microenvironment contribute critical insights into the progression mechanisms of multidrug-resistant breast cancer and promote the advancement of targeted immunotherapeutic interventions.

4.4. Combination with Other Treatment Modalities

Cascading response-based TMS-NDDS have shown promising potential in combination with other treatment modalities for multidrug-resistant breast cancer. Studies have indicated that integrating photothermal agents with thermally sensitive nanocarriers permits spatiotemporally synchronized photothermal therapy (PTT) and precisely regulated drug release[14]. Similarly, photodynamic therapy (PDT) has been shown to induce significant cytotoxicity in multidrug-resistant breast cancer cells via the photo-triggered production of reactive oxygen species (ROS) [15]. Currently, research on TMS-NDDS combined with other treatments for multidrug-resistant breast cancer is still in its early stages, and related studies are relatively limited. It is anticipated that more findings will be reported in the future.

5. Conclusion

Multidrug resistance (MDR) continues to pose a major obstacle to successful therapeutic outcomes in breast cancer management. The complex and dynamic nature of the tumor microenvironment contributes substantially to disease progression and chemoresistance. Cascade-responsive TME-sensitive nanodrug delivery systems represent an innovative and promising strategy to overcome these challenges. By leveraging distinct biochemical and physicochemical properties of the tumor microenvironment (TME)—including acidosis, hypoxia, enzymatic overexpression, and redox dysregulation—these systems achieve targeted drug delivery, spatiotemporally controlled release, and reprogramming of immunosuppressive niches. Key benefits of TMS-NDDS comprise their capacity to promote localized drug deposition through both passive and active targeting strategies, minimize systemic side effects, and reverse resistance mechanisms via combinatorial delivery of multimodal therapeutics. Furthermore, the integration of exogenous stimuli such as light, heat, or ultrasound offers additional layers of control for spatiotemporal drug release. Despite promising preclinical results, several challenges remain. These include the limited depth of mechanistic studies, the relatively low responsiveness of some exogenous triggers, and the need for improved biocompatibility and safety profiles. Future research should focus on optimizing multi-stimuli-responsive nanocarriers, elucidating the underlying molecular mechanisms of cascade reactions, and advancing combination therapies with modalities such as photothermal and photodynamic therapy. In summary, TMS-NDDS platforms, which operate through cascade-responsive mechanisms, represent a promising strategy for transforming the therapeutic landscape of multidrug-resistant breast cancer. With continued innovation and translationally oriented research, these systems may soon provide new avenues for precision oncology and improved clinical outcomes.

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