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Research Progress of siRNA Systems in Breast Cancer Therapy

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Abstract. Breast cancer remains the leading cause of cancer-related deaths among women globally, with treatment facing significant challenges due to drug resistance and metastasis. RNA interference technology, particularly via siRNA, offers a novel strategy for precision therapy. This review comprehensively examines the mechanisms and applications of nanotechnology-mediated siRNA delivery systems. Methodologically, it involves systematic analysis of the design principles underlying polymeric, lipid-based, and metallic nanocarriers to evaluate their efficacy in enhancing cellular uptake, promoting endosomal escape, and protecting siRNA from degradation; additionally, it combines preclinical and clinical data to evaluate these delivery platforms' pharmacodynamic characteristics and therapeutic results. Results demonstrate that siRNA nanocarriers significantly enhance targeted gene-silencing efficiency, exhibiting potent anti-tumor activity in breast cancer models. However, clinical translation is hampered by limitations in specificity, immunogenicity, and evolving regulatory frameworks. To advance clinical application, future research should focus on developing stimuli-responsive nanovectors and combining them with immunotherapy or chemotherapy regimens.

Keywords: Breast Cancer, siRNA Delivery, Nanocarriers, Clinical Translation

1. Introduction

Breast cancer remains the leading cause of cancer-related mortality among women worldwide, with over 2.3 million new cases reported in 2022, exacerbated by challenges such as metastasis, drug resistance, and the aggressive nature of triple-negative breast cancer (TNBC) subtypes [1,2]. Traditional cytotoxic chemotherapeutics—including anthracyclines, taxanes, and carboplatin—provide only limited therapeutic benefits while inducing adverse effects such as gastrointestinal reactions, myelosuppression, and liver dysfunction. Immunotherapy drugs such as paclitaxel, cobitinib, atezolizumab and albumin bound paclitaxel are also associated with severe abdominal pain, vaginal bleeding, muscle cramps, paralysis, leukopenia, anemia, cardiotoxicity and other adverse reactions [3-6].

Cells can further evade chemotherapy by activating anti-apoptotic pathways, rendering drug resistance a pervasive and severe issue. This resistance is associated with endocrine resistance, multidrug resistance proteins, breast cancer resistance protein, DNA repair mechanism alterations, and cancer stem cell resistance. These multifaceted challenges underscore the urgent need for

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innovative therapeutic strategies. In this context, RNA interference (RNAi) technology, particularly through small interfering RNA (siRNA), emerges as a promising avenue for precision therapy. siRNA can specifically silence oncogenes implicated in tumor growth, invasion, and immune evasion, such as Bcl-2, survivin, and PD-L1. However, the clinical translation of siRNA faces significant hurdles, including enzymatic degradation, inefficient cellular uptake, and the need to balance specificity and immunogenicity. To address these challenges, nanotechnology-based delivery systems are being explored to enhance siRNA stability, cellular uptake, and tissue-specific targeting. This review aims to summarize the existing siRNA delivery system schemes for breast cancer treatment, discuss the development and application of these delivery systems, and highlight the current challenges and future directions. Given the broad applicability of these principles, this review, while focusing on breast cancer, also holds relevance for siRNA delivery applications in other diseases.

2. Molecular mechanisms underlying breast cancer development

Mutations in Key Transcription Factor Genes: Transcription factors play pivotal roles in breast cancer progression. For instance, sustained activation of the STAT3 gene promotes tumor cell proliferation and survival [7]. Additionally, overexpression of the MYC gene drives cell cycle progression, while mutations in the GATA3 gene may impair breast cell differentiation [8,9]. Abnormal activation or suppression of these transcription factors is a major molecular driver in breast cancer initiation and progression. siRNA-based therapeutic strategies targeting these factors via siRNA, such as siSTAT3, siMYC, and siGATA3, may offer novel avenues for breast cancer treatment.

Gene Mutations Promoting Apoptosis Escape: Apoptosis evasion represents another critical step in breast cancer development. Overexpression of the Bcl-2 gene suppresses apoptosis, thereby promoting tumor cell survival [10]. High expression of the Survivin (BIRC5) gene is also associated with tumor cell viability [11]. siRNA therapies targeting these apoptosis-related genes, such as siBcl-2 and siSurvivin, may help restore tumor cell apoptosis sensitivity, thereby inhibiting breast cancer progression.

Gene Mutations Promoting Tumor Metastasis: Tumor metastasis is a key factor in poor breast cancer prognosis. Key molecules in the epithelial-mesenchymal transition (EMT) process, such as Snail, Twist, and ZEB1, along with angiogenesis-related molecules like VEGF-A and VEGFR1/2, all play roles in tumor invasion and metastasis [12-14]. High expression of matrix metalloproteinases (MMPs) is also associated with tumor invasiveness [15]. The integrin signaling pathway plays a vital role in tumor cell adhesion, migration, and invasion. siRNA therapies targeting these metastasis-associated molecules, such as siSnail, siVEGF, and siMMP-9, may help inhibit breast cancer metastasis.

3. Applications of siRNA in breast cancer therapy

Targeting Dysregulated Transcription Factors: Dysregulated transcription factors represent important therapeutic targets in breast cancer. For instance, siRNA targeting STAT3 and MYC can suppress the activity of these transcription factors, thereby inhibiting tumor cell proliferation and survival [16]. Additionally, siRNA targeting GATA3 may help regulate cell differentiation and inflammatory responses [17]. These siRNA therapeutic strategies may offer more precise treatment options for breast cancer patients.

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Targeting Abnormal Apoptosis-Related Genes: Apoptosis evasion is a key survival mechanism for breast cancer cells. siRNA therapies targeting Bcl-2 and Survivin can promote tumor cell apoptosis, thereby inhibiting tumor growth and spread [18,19]. These siRNA therapeutic approaches may help restore tumor cell sensitivity to chemotherapeutic drugs, enhancing treatment efficacy.

Targeting Abnormal Genes Associated with Metastasis: Tumor metastasis poses a major challenge in breast cancer treatment. siRNA therapies targeting metastasis-related molecules such as Snail, Twist, ZEB1, VEGF-A, VEGFR1/2, HIF-1α, MMP-9, and αvβ3 integrin can reduce tumor invasiveness and metastatic potential [15,20,21]. These siRNA-based strategies may help decrease breast cancer recurrence and metastasis, thereby improving patient survival rates.

4. Research progress in siRNA nanodelivery systems

4.1. Types of delivery carriers

Nanocarrier technology has significantly transformed the landscape of siRNA delivery, leading to substantial improvements in molecular stability, cellular uptake, and tissue-specific targeting. Within this broader analytical framework, these advances are largely attributable to the precise engineering of material properties and nanostructural design. Current delivery systems can typically be classified into one of four principal categories.

4.1.1. Polymeric nanocarriers

Polymeric nanocarriers have increasingly emerged as versatile vehicles for siRNA delivery, primarily due to their favorable biocompatibility, high cargo capacity, and ease of chemical modification. Among these, polyethyleneimine (PEI) and chitosan tend to stand out in the literature. PEI's frequent use is explained by its ability to form stable complexes with siRNA through electrostatic interactions and promote endosomal escape, likely due to the well-documented proton sponge effect [22]. However, PEI’s significant cytotoxicity has driven extensive research into safer alternatives, such as low-molecular-weight crosslinked PEI or PEGylated versions [23].

Additionally, copper sulfide–PEI–siRNA complexes demonstrate the ability to enhance siRNA loading and improve cellular uptake in most metastatic breast cancer models studied [24]. From this particular interpretive perspective, chitosan, on the other hand, appears to be valued for its biodegradability and mucoadhesive properties, but typically needs some form of modification—carboxymethylation, for example—to improve its solubility under physiological conditions. What appears particularly significant about recent developments is that chitosan carriers conjugated with MUC1 aptamers exhibit increased tumor specificity and therapeutic efficacy across several cancer models [25,26].

4.1.2. Lipid-based nanocarriers

Lipid-based nanocarriers have emerged as the leading platforms for siRNA delivery, with the approval of Patisiran by the FDA underlining their clinical relevance. Their effectiveness is largely attributable to high biocompatibility and their ability to mimic natural membrane fusion processes [27]. In terms of technical approaches, two strategies dominate: first, optimized cationic liposomes composed of DOTAP and DOPE in a 1:1 ratio, which achieve a zeta potential exceeding 50 mV to ensure efficient siRNA complexation; and second, ionizable lipid nanoparticles (LNPs), which utilize pH-sensitive lipids that stay neutral during systemic circulation but become protonated in endosomes, thereby facilitating targeted siRNA release. Both platforms employ conjugated ligands

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—such as folate or RGD peptides—to enhance tumor targeting specificity [28]. Recent preclinical studies have demonstrated that liposomal formulations co-delivering Bcl-xL siRNA with chemotherapeutics like paclitaxel or crizotinib can induce synergistic apoptosis and achieve a cumulative drug release of over 64% within 12 hours in breast cancer models [2]. Furthermore, hybrid systems incorporating polymers or natural exosomes are being developed to expand the potential for co-delivery of siRNA and chemotherapeutics.

4.1.3. Inorganic/metal nanocarriers

Within this broader analytical framework, inorganic nanocarriers, which are notable for their distinctive optoelectromagnetic properties, appear to support what could be characterized as the integration of gene silencing therapy, diagnostic imaging, and physical treatment modalities—forming what appear to be genuinely multifunctional siRNA delivery systems. Gold nanoparticles, for instance, can enable precise, spatiotemporally controlled siRNA release in response to external triggers such as laser irradiation, while also appearing to induce photothermal effects that may potentially enhance therapeutic outcomes [29]. These findings demonstrate that graphene oxide-based platforms are highly effective as siRNA carriers, primarily due to their large surface area, which enables substantial adsorption [30,31]. Additionally, further functionalization with cell-penetrating peptides improves tumor targeting—highlighting their significant potential in oncological applications [32-34].

Hollow mesoporous copper sulfide nanoparticles (CuS), from this particular interpretive perspective, seem to exemplify a high degree of multifunctionality. As vectors apparently responsive to near-infrared stimuli, they appear to exhibit a potentially impressive photothermal conversion efficiency. What appears to follow from this analysis is that upon activation, these nanoparticles release Cu^{2+}/Cu^{+} ions, which appears to provide evidence that may support the induction of cuproptosis through DLAT oligomerization and concurrently produce reactive oxygen species for chemodynamic therapy [24]. What appears significant in this context, however, is that despite these promising advances, comprehensive biosafety evaluations remain essential, particularly given the multifaceted nature of this evidence and concerns regarding potential metal accumulation and its associated toxicity.

4.1.4. Co-delivery systems

Integrated co-delivery systems that combine siRNA with immunomodulators or chemotherapeutics are emerging as promising strategies to overcome tumor heterogeneity and drug resistance. For example, cationic liposomes can deliver Bcl-xL-targeted siRNA along with agents like paclitaxel or crizotinib, disrupting microtubule dynamics and blocking anti-apoptotic signaling to exert a dual cytotoxic effect [35]. pH-sensitive micelles can release their therapeutic payloads in response to the acidic tumor microenvironment, enabling sequential delivery for enhanced efficacy. Copper sulfide-silk fibroin nanoparticles loaded with PD-L1 siRNA integrate gene silencing with photothermal therapy, cuproptosis induction, and immunogenic cell death, achieving significant preclinical results such as 60% suppression of PD-L1 expression and 56% primary tumor regression. Biomimetic nanoparticles and exosome-based delivery systems improve drug biodistribution and cellular uptake by leveraging their inherent biocompatibility. However, challenges remain before clinical translation, including precise drug-siRNA ratio control, batch-to-batch reproducibility, and rigorous safety evaluations for regulatory approval and large-scale production.

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4.2. Delivery optimization methods and related challenges

Recent advancements in siRNA nanodelivery have led to the development of highly specialized carriers designed to enhance delivery efficiency and biosafety. For instance, galactosamine conjugation enables siRNA to exploit the asialoglycoprotein receptor pathway, significantly extending its circulation time and enhancing hepatocyte uptake. However, this approach still encounters significant obstacles in penetrating solid tumors, primarily due to the abnormal vasculature and increased interstitial fluid pressure typically found in the tumor microenvironment [36,37].

Consequently, research focus has shifted towards surface modifications with tumor-specific ligands, such as RGD peptides that recognize integrins, or transferrin that binds to overexpressed transferrin receptors on many cancer cells [38,39]. Additionally, the incorporation of polyethylene glycol (PEG) or zwitterionic polymers is critical, as these components can shield nanocarriers from immune detection—enhancing their “stealth” properties and extending circulation time [40]. Considering the complexity of these findings, innovative “smart” nanocarriers have emerged to address the intricacies of the tumor microenvironment. These findings point towards ATP-responsive delivery systems that employ boronic ester linkages, which can react to oxidative stress and acidic pH, as well as polyplexes with thioketal bonds that respond to both pH and reactive oxygen species [41,42]. These systems enable more controlled siRNA release in response to ATP gradients characteristic of metastatic niches. More recently, dual-stimuli sensitive designs have combined triggers like pH with enzymes, or redox with light, to further fine-tune the specificity of siRNA release within tumors [43].

Despite these remarkable developments, several barriers remain before clinical translation can be achieved. Within this framework, it is essential to optimize siRNA chemical modifications—such as 2'-O-methyl and phosphorothioate substitutions—to reduce off-target effects and increase nuclease resistance [44-46]. Additionally, rigorous comparison between different carrier systems is warranted; while solid lipid nanoparticles offer high biocompatibility, metallic vectors like gold nanoshells introduce potential long-term toxicity [47,48]. Moreover, there is a need to systematically address challenges including scalable manufacturing, long-term formulation stability, and the risk of immunogenicity, such as the potential activation of the complement system. Ultimately, the successful translation of siRNA nanomedicines from preclinical models to clinical oncology will likely depend on integrating computational modeling, such as molecular dynamics simulations, and high-throughput screening strategies. These approaches are vital for overcoming multifaceted barriers and realizing the therapeutic potential of siRNA-based interventions in cancer treatment.

5. Current challenges, limitations, and future development directions

siRNA-mediated RNA interference is widely used in research to silence protein-coding genes with known mRNA sequences. SiRNA has the ability to target any protein, including those difficult to be druggable, and is superior to monoclonal antibodies and small molecule inhibitors in inhibiting druggable pathways, overcoming the limitations faced by traditional targeted the therapeutics [49]. Due to the short length, small molecular weight and high anionization of siRNA, it is easy to be cleared and degraded in the renal system, and the generated by-products will also lead to adverse immune reactions [50]. At the same time, siRNA can also be recognized as an exogenous RNA inducing increased production of interferons or cytokines, which in turn leads to off target effects (that is, siRNA molecules will unexpectedly silence non target genes and interfere with normal cellular processes) or cytotoxicity. Successful delivery of siRNA to target cells also often faces

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difficulties in being degraded and cleared by nucleases. In addition, due to the hydrophilic and negatively charged nature of siRNA molecules, it is difficult to penetrate the biofilm to be obtained and utilized by target cells, and the cell intake rate is low. Even the delivery system required for siRNA can induce immune responses.

Preclinical research, safety assessment, regulatory approval, and manufacturing processes pose multiple challenges to the development of siRNA therapy. Currently, the preclinical assessment of siRNA is primarily based on human tumor xenograft models and immunodeficient mice. However, these models have clear drawbacks: on the one hand, siRNA cannot fully assess off-target toxicity because it lacks cross-activity on murine proteins due to its targeting of human proteins; On the other hand, the model may inaccurately estimate the actual efficacy of siRNA, because it may not accurately reflect the adaptive immune response triggered by tumor antigen release or the potential regulatory effect of siRNA on immune cells. Although the mouse model with a complete humanized immune system has more advantages in predictive value, its high cost limits its application in routine research.

Through clinical studies, siRNA therapy must methodically assess its long-term consequences and unforeseen biological interactions in order to be considered safe. Comprehensive pharmacokinetic, pharmacodynamic, and toxicological data are necessary for regulatory approval. The approval process is complicated and time-consuming since it is challenging to gather the required data because of the distinct molecular characteristics of siRNA. Furthermore, the secret to achieving commercial application is the scalable production method. However, the widespread promotion of its therapeutic transformation is hampered by the high prices and technological obstacles that still plague the current large-scale production [49].

6. Conclusion

The application of siRNA-based therapies in breast cancer treatment has shown significant promise, particularly in targeting oncogenes such as Bcl-2, Bcl-xL, and survivin. Nanotechnology-mediated siRNA delivery systems have demonstrated the ability to enhance cellular uptake and endosomal escape, thereby improving the efficiency of targeted gene silencing. These advancements are especially notable in aggressive subtypes like triple-negative breast cancer (TNBC). However, several challenges remain in translating these therapies from preclinical models to clinical practice. Key issues include the specificity of siRNA delivery, the risk of immunogenicity, potential off-target effects that may silence essential genes, inadequate penetration of the blood-tumor barrier, and evolving regulatory frameworks. Future research should focus on developing "smart" stimulus-responsive nanovectors to improve targeting accuracy and reduce side effects. Additionally, combining siRNA therapy with other treatment modalities, such as immunotherapy or chemotherapy, may enhance therapeutic efficacy and overcome drug resistance. Moreover, optimizing siRNA chemical modifications to reduce off-target effects and increase nuclease resistance is crucial. This includes exploring 2'-O-methyl and phosphorothioate substitutions, among others. Systematic comparisons between different carrier systems are also necessary to identify the most effective and safe delivery methods. While solid lipid nanoparticles offer high biocompatibility, metallic vectors like gold nanoshells must be carefully evaluated for potential long-term toxicity. Addressing challenges related to scalable manufacturing, long-term formulation stability, and the risk of immunogenicity will be essential for the successful clinical translation of siRNA therapies. Integrating computational modeling and high-throughput screening strategies will play a pivotal role in overcoming these hurdles and realizing the therapeutic potential of siRNA-based interventions in cancer treatment.

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