Review Paper

RNA-loaded Nanoparticles in Breast Cancer Stem Cell Therapy: A Review Article

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ABSTRACT

Breast cancer (BC) remains a major public health concerns affecting a significant number of women every year. While various therapeutic strategies exist to treat BC, but many current treatments adversely impact healthy cells, leading to considerable side effects. Further challenges in oncology include the development of the resistance of cancer cells to treatment, the limited duration of drug efficacy, and insufficient drug retention at the tumor site. This study aimed to advance diagnostic and therapeutic methodologies for cancer continues to be a critical and active field of study. One of the new and interesting technologies to treat cancers is the use of nanoparticles (NPs), which have opened a new window for the diagnosis and treatment of cancer in humans. These NPs are used by binding to cells to carry various drugs and ligands to cancer cells, especially BC stem cells (BCSCs). This article examines recent research on the application of diverse nanosystems—including metal NPs, polymers, liposomes, and nanomicelles—for the diagnosis and treatment of BC stem cells (BCSCs). While the utilization of these nanosystems presents significant challenges and limitations, a deeper understanding of their properties holds the potential to revolutionize the management of BC. Consequently, this review explores current therapeutic strategies for BC and their associated constraints. Furthermore, it highlights NPs as a promising frontier for tumor diagnosis, imaging, and therapy, with a specific focus on the advancements involving ribonucleic acid (RNA)-loaded NPs.

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Introduction

Breast cancer (BC) is the second most crucial malignancy among women globally and the main cause of death for a large percentage of their population [1]. Today, there are many trials to treat and diagnose BC. One of the new methods is the use of nanoparticles (NPs), which overcome the limitations of many old methods, such as surgery and chemotherapy [2]. From the past until now, surgery for removing breast tissue has been a common and effective method in the treatment of BC. The use of the florescent nanoprobe can increase the accuracy during surgery and increase the probability of the success of the effective treatment process [3]. Surgery followed by chemotherapy or radiotherapy is the standard treatment for most cancers, including BC. However, the side effects of these methods on healthy cells and tissues, limit their use in treatment. Radiation therapy is a common and effective method to increase the survival of patients and can lead to cell death by inducing DNA damage in cancer cells. However, insufficient DNA damage and rapid DNA damage response after radiation therapy limit the success rate and efficacy of treatment [4]. Another limiting factor of treatment is the presence of resistant and self-renewing cells in the tumor microenvironment. BC stem cells (BCSCs) are heterogeneous subsets of tumor-initiating cells from BC that have some stem cell markers and persist after chemotherapy. Given that BCSCs are important in tumor recurrence, and given that the biological behaviors of BCSCs are very complex, it is crucial to determine their functions, to present more information about their biology, biomarkers, and strategies for targeting them in cancer [5]. Therefore, in this study, we first review the characteristics of BCSCs, and then, after examining their diagnosis and treatment methods in recent studies, we describe new methods of diagnosis and treatment based on NPs. In addition, this study aimed to review the studies related to the application of NPs carrying ribonucleic acid (RNA) for BCSC treatment.

Type of stem cell

Stem cells represent a distinct class of cells defined by their dual capacity for self-renewal and differentiation into specialized cell lineages. They are vital for growth, tissue repair, and regeneration throughout the life of the organism. Stem cells are categorized based on two principal criteria: Their developmental potential (differentiation capacity) and their source of origin. Among the most versatile are pluripotent stem cells, such as embryonic stem cells—obtained from the inner cell mass of blastocysts—and induced pluripotent stem cells, which are generated by reprogramming adult somatic cells. These can give rise to virtually all cell types in the body. In earlier developmental stages, totipotent stem cells possess the ability to form both embryonic and extra embryonic tissues. In contrast, multipotent stem cells, such as mesenchymal and hematopoietic stem cells resident in adult tissues, are restricted to producing cell types within a specific germ layer. Further along the spectrum are oligopotent and unipotent stem cells, which function as progenitor cells with progressively more limited differentiation potential [6].

Stem cells have significant therapeutic potential due to their unique properties and ability to repair damaged cells in the body. In recent years, they have received much attention due to their significant therapeutic properties and potential applications in regenerative medicine. Here are some of the key benefits of stem cell therapy.

Cell replacement and regeneration

Stem cells can replace damaged or diseased cells in the body due to their ability to differentiate into different types of specialized cells. Stem cells can restore damaged tissues by filling cell pools and re-establishing normal tissue homeostasis [7-9].

Potential treatments for neurological disorders

Treatment using stem cells is promising for the treatment of diseases, such as Alzheimer's and Parkinson's. Today, new methods have been developed to extract microglia from human pluripotent stem cells, which allow the investigation of cell interactions along the neuro-inflammatory axis, especially in the context of Alzheimer's disease [10].

Regenerative potential in other diseases

Treatment with stem cells has shown potential for the treatment of cardiovascular diseases, pulmonary disorders, endocrine metabolic diseases, reproductive disorders, etc. Stem cells can regenerate damaged heart tissue, improve heart function, and reduce symptoms in conditions, such as heart failure and ischemic heart disease [11]. They can also help to restore lung tissue and improve respiratory function in diseases, such as chronic obstructive pulmonary disease and pulmonary fibrosis [12].

Overall, the ability of stem cells to differentiate into cell types and their paracrine effects contribute to tissue regeneration in diverse medical conditions and highlight their promise in advancing therapeutic options. These stem cells express a unique set of cell surface markers that can be used to identify and isolate specific stem cell populations. The most common positive markers reported for MSCs include CD105, CD44, CD73, CD90, CD29, CD13, CD34, CD106, CD146, CD54 and CD166 [13, 14].

Mammary stem cells (MaSCs)

MaSCs play an essential role in both the development and ongoing homeostasis of the mammary gland. These cells possess the defining ability to self-renew and to differentiate into the gland's distinct cellular lineages, such as the ductal and basal cells. Recent studies have identified key surface markers, such as CD24, CD29, and CD49f, which are necessary for the isolation and identification of these cells in human and mouse tissues [15]. MaSCs can be classified into multipotent and unipotent subtypes, multipotent MaSCs can differentiate into both myoepithelial and luminal cell types, while unipotent MaSCs can differentiate into myoepithelial or duct cells depending on their specific markers [16].

It has been found that gene expression profiles in mammary stem cells change from neonatal stages to aging stages in mice. These changes affect their fundamental characteristics and functional capabilities, which are crucial for understanding aging processes in the mammary gland [17]. Aging changes the composition and function of breast stem cells. Research indicates that the proportion of certain subtypes of luminal cells decreases with age, which may contribute to the increased risk of BC in older women [18].

Research shows that the mammary epithelium responds to local and systemic signals that coordinate ductal morphogenesis. In addition, inhibition of the mammalian target of rapamycin (mTOR) signal can significantly reduce the activity of MaSC and highlight the potential of therapeutic interventions in the prevention of BC [19]. The microenvironment surrounding breast stem cells significantly affects their behavior and characteristics. Cytokines and their interactions with other cell types in the tumor microenvironment can affect the self-renewal and differentiation capabilities of BCSCs [5]. Advances in single-cell sequencing technology have enabled more precise characterization of MaCS cells, providing insights into their heterogeneity and functional states. This technology is critical for analyzing complex biology and its role in cancer. Targeting MaSCs and BCSCs is a promising strategy for BC treatment. Identifying specific markers and pathways involved in the regulation of MaSCs can lead to new targeted therapeutic approaches to reduce recurrence and metastasis [20].

Phenotyping of BCSCs and their markers

BCSCs are the focus of attention in BC research due to their role in tumor initiation, metastasis and resistance to treatment. BCSCs constitute a minor yet critically important population within the diverse cellular makeup of a breast tumor with high self-renewal and differentiation ability. This subtype has significant heterogeneity with changes in gene expression profiles associated with different phenotypic states, including mesenchymal and epithelial characteristics, with dynamic flexibility that allows them to adapt to the tumor microenvironment [21, 22]. Research shows that BCSCs contribute to resistance to treatment, especially conventional treatments, and this requires targeted approaches to effectively eliminate these cells. Strategies under investigation include the use of agents that disrupt the quiescent state of BCSCs and combination therapies, which combine BCSC-targeted therapies with standard chemotherapy [23].

Recent genetic profiling has shown that certain genes, such as *CD44*, *GDF3*, and *GJB1*, are differentially expressed in BCSC subsets, underscoring the potential of these markers to serve as therapeutic targets or prognostic indicators. Identifying these phenotypic subsets increases our understanding of the biology of BCSCs and their impact on patient outcomes, and provides the basis for therapeutic strategies in BC management [24]. BCSCs are characterized by specific surface markers that play a crucial role in tumor progression, metastasis, and resistance to treatment. Recent studies have identified key surface markers, such as CD44, CD24, aldehyde dehydrogenase 1 (ALDH1), and CD133, which are related to the stem-like properties of these cells and their ability in tumorigenesis and metastasis (Figure 1). The CD44+/CD24- phenotype is particularly noteworthy because of its association with tumor aggressiveness and poor prognosis. In addition, markers, such as epithelial cell adhesion molecule (EpCAM) and C-X-C chemokine receptor type 4 (CXCR4), are involved in the migratory abilities and metastatic processes of BCSCs. Identification of these markers is essential for the development of targeted therapies to eliminate BCSCs and overcome drug resistance. The expression of transcription factors Sox2, Oct4, and Nanog are also associated with BCSC properties, indicating pluripotency. Ongoing research emphasizes the need for new biomarkers that can facilitate effective targeting of BCSCs in clinical settings and aim to improve patient outcomes and reduce relapse rates [25-27].

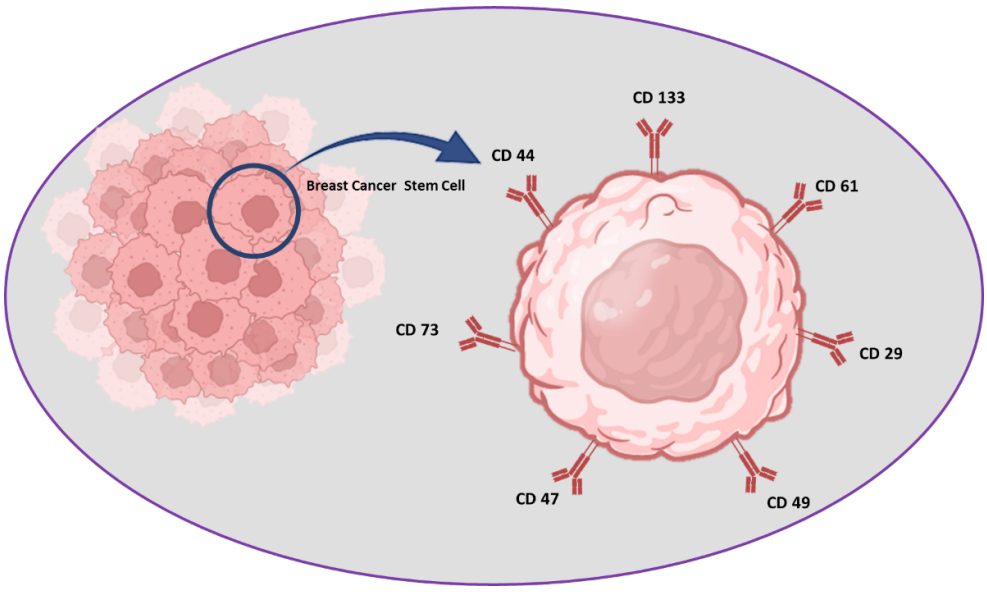

Figure 1. The most crucial surface markers of BCSCs

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BCSCs treatment strategies

Several therapeutic strategies for BC are specifically designed to target BCSCs. Common approach involve directing treatments against the specific surface markers expressed by these cells, metabolism, tumor microenvironment, and inhibiting BCSC-dependent signaling pathways [28]. Although there are various methods to destroy cancer cells and treat BC, including surgical intervention, hormone therapy, chemotherapy, and radiotherapy, some of these methods, including chemotherapy, also have destructive effects on healthy cells. In today's medical era, the use of radiation therapy for BC is beneficial depending on the type of surgery and the stage of the cancer. Cancer stem cells, by being resistant to radiation, reduce the response to radiation therapy [29]. Separate treatment methods are explained below.

Targeting signaling pathways

Inhibition of Sphingosine Kinase 1 (SPHK1): SPHK1 is an enzyme that contributes to the production of sphingosine-1-phosphate and is a key metabolite in multiple essential processes for cellular life, including growth, maintenance of viability, and migratory capacity. It is also known to be an important regulator of BCSC survival. Inhibition of SPHK1 using specific inhibitors (such as FTY720, and PF543) induces apoptosis in BCSCs and increases the effectiveness of common chemotherapy such as doxorubicin [30].

Wnt/β-catenin pathway modulation: β1, 4-Galactosyltransferase V (B4GalT5) is an enzyme involved in the synthesis of glycoproteins. This enzyme is associated with the activation of the Wnt/β-catenin signaling pathway and promotes BCSCs properties. Targeting this pathway may provide a strategy to reduce the BCSCs population and enhance therapeutic responses [31].

Targeting of BCSCs markers

Recent studies have introduced targeting specific markers associated with BCSCs. For example, inhibiting the CD44 and CD24 receptors (one of the main markers of BCSCs), reducing the population of stem cells in tumors, and potentially improving patient outcomes. In addition, agents that target aldehyde dehydrogenase 1 (ALDH1) activity (which has been introduced as a marker of BCSCs in some studies) are being investigated to eliminate BCSCs and prevent tumor recurrence [21].

Chemotherapy and radiotherapy

Conventional chemotherapy and radiotherapy selectively kill differentiated cancer cells while preventing the growth and differentiation of BCSCs that can lead to tumor regrowth. However, recent advances increase the effectiveness of these therapies by combining them with agents that specifically target BCSCs. For example, the use of chemotherapeutic agents in conjunction with inhibitors of signaling pathways critical for BCSCs maintenance, such as the Wnt/β-catenin and Notch pathways, has shown higher therapeutic potential in clinical models [23, 28].

Combined treatments

Endocrine therapy and notch signaling inhibition: It has been shown that the combination of endocrine therapy with Notch inhibitors in estrogen receptor positive BC leads to the prevention of death-associated protein 6 (DAXX) degradation, which is a novel anti-breast cancer suppressor candidate (*BCSC*) gene. This combination aims to eliminate BCSCs and reduce the risk of recurrence associated with endocrine therapy [32].

Spheroid culture techniques: The establishment of selective culture methods for BCSCs from patient-derived tissues allows the analysis of their characteristics and responses to different treatments. This method has shown an increase in the proportion of stem cells and facilitates the study of targeted therapies [32].

Nanomedicine

Nanomedicine as a new field in cancer treatment, especially in the field of BCSC, has attracted much attention. In recent years, many researches have been conducted in this field, which have investigated the applications of nanomaterials and NPs in targeting and treating cancer stem cells. Due to their small size, NPs can easily penetrate tumor tissues and help to increase the drug concentration in the tumor area. NPs can act as drug carriers and specifically target cancer stem cells, which reduces side effects and increases the effectiveness of treatment. Nanomedicine can help improve the delivery of chemical drugs to cancer stem cells. This can help increase the rate of cell death in cancer cells and reduce drug resistance. Also, the use of NPs in combination with other treatment methods, such as chemotherapy and radiation therapy, can improve treatment results [33-35].

Challenges in treating BCSCs

Tumor heterogeneity

The heterogeneity of BCSCs within tumors is a key challenge in BC treatment. Different BCSCs subpopulations may respond to different therapies, which complicates the development of effective treatment protocols. This variability can lead to different levels of treatment efficacy among patients [36].

Drug resistance

A problem of the treatment in BCSCs is their ability to resist conventional therapies due to their quiescence and expression of drug efflux pumps. This resistance lead to significant challenges in achieving effective therapeutic outcomes, which lead to BCSCs survive and regrow after treatment [5].

Challenges of immunotherapy

BCSCs can create an immunosuppressive microenvironment that limits the effectiveness of immunotherapeutic strategies. Understanding how BCSCs evade immune detection is important to improve the success of these therapies [36].

Treatment design

Many promising strategies face hurdles when transitioning from preclinical studies to clinical trials. Issues such as patient selection, identification of biomarkers, and trial design can prevent the transformation of laboratory findings into effective treatments [36].

Nanomedicine and NPs

Nanomedicine is an interdisciplinary field that can help in the diagnosis, treatment, and prevention of diseases, especially in the treatment of BCSCs. Cancer stem cells are known as the main cause of metastasis and disease recurrence, and for this reason, their removal is of great importance [37]. Nanomedicine has many applications, the most crucial of which are drug delivery (they can act as drug carriers and deliver drugs in a targeted manner to specific body tissues, such as tumors), disease diagnosis (for example, as biological markers of action and are effective in the early diagnosis of diseases, especially cancer) and targeted treatments (they can specifically bind to cancer cells and destroy cancer cells using different methods, such as heating NPs with a laser) [38].

In recent years, several researches have been conducted in the field of using NPs to improve BCSC targeted therapies. Particles with dimensions less than 100 nm are called NPs, which have unique physical and chemical properties. These features are created by their high surface-to-volume ratio and their nanostructured structure. NPs can be made of various materials, such as metals, oxides, carbon, and polymers and are used in various fields, such as medicine, electronics, the environment and the food industry [39]. For example, gold NPs are used in laser treatments and disease diagnosis due to their unique optical and chemical properties. They can act as drug carriers, as well as be used in thermal treatments to destroy cancer cells [38]. Therefore, considering that nanomedicine as a new tool in cancer treatment, especially in targeting cancer stem cells, has a high potential to improve treatment results, it is expected that with continuous progress in this field, nano-based treatments as part of Standard treatment protocols will be used shortly.

Application of NPs in BCSC diagnosis

Globally, BC is a leading cause of cancer-associated mortality among women. The complexity of BC, characterized by the different types and presence of BCSCs, requires innovative diagnostic and therapeutic strategies. Due to their unique physical and chemical properties, NPs are increasingly recognized for the diagnosis and treatment of BC, especially in targeting and overcoming BCSC-related challenges. Recent studies have reported several types of NPs that are particularly effective in BC applications:

Advanced imaging techniques

One of the applications of NPs is their use in imaging methods used in BC diagnosis to improve the quality of images. Their unique optical and electronic properties make it possible to increase the contrast in imaging techniques, among these NPs, the following can be mentioned:

Quantum dots: NPs with a size below 10 nm and semiconductors that can provide high-resolution imaging of cancer cells and make it possible to identify BCSCs in tumors.

Magnetic NPs: These NPs can be used as a contrast agent in magnetic resonance imaging (MRI) due to their low toxicity, high half-life, multiple functions, and better contrast. These NPs are used in MRI to enhance the visibility of tumors and their microenvironments and help to detect BCSCs.

Gold NPs: These NPs have been used in various imaging techniques, including computed tomography and photoacoustic imaging, to improve the diagnosis of BC and its stem cell populations [40, 41].

Targeted drug delivery

NPs facilitate targeted drug delivery systems that can specifically target BCSCs. This is performed through:

Surface modifications: NPs can be engineered to bind to specific markers on BCSCs and allow selective delivery of therapeutic agents. For example, human EGF receptor 2 (HER-2)-targeted NPs are being developed to deliver drugs directly to HER-2-positive BC cells, which often include BCSCs [42].

Nanotheranostics: This strategy integrates both diagnostic and therapeutic functions within a unified nanoparticle platform. For instance, NPs can be engineered to trigger drug release upon encountering specific tumor conditions, enabling precise targeting of BCSCs and a significant reduction in impact on surrounding healthy tissues [43].

Overcoming chemical resistance

NPs also play an essential role in counteracting the chemoresistance commonly observed in BCSC. Creative formulations such as:

Photothermal and photodynamic treatments: In these types of treatments, NPs are used that produce heat or reactive oxygen species upon activation by light, which selectively destroy BCSCs while preserving normal cells. This method can help to overcome the resistance of cancer stem cells to standard chemotherapy [43, 44].

Combination therapies: NPs can be used to simultaneously deliver multiple therapeutic agents, including immunotherapies and chemotherapies, increasing their efficacy against resistant stem cell populations. This multifaceted approach is vital to prevent tumor recurrence and metastasis [43, 45].

NPs-based methods in the treatment of BCSC

In recent years, the use of NPs for BC treatment process has increased. The specific size of NPs and their ability to penetrate and target tumor sites, high level of reactivity, unique physicochemical properties, high surface-to-volume ratio, and superior reactivity compared to their bulky counterparts have led to NPs overcome to the problems of traditional drugs such as low efficacy, low penetration in tumoral tissues, and drug systemic toxicity and achieve accurate and efficient drug delivery in tumor sites. These features made them unique for early diagnosis, improved treatment, and diagnosis of many human diseases, such as cancer. Also, receiving and transporting drugs in nanocarriers through the bloodstream prevents the rapid clearance of the drug, the benefits of tumor imaging, and the ability to carry thousands of drug molecules, as well as increase their solubility, stability, and resistance, and ultimately lead to improving the treatment process [46]. Therefore, the nanosystem can significantly increase the treatment efficiency and provide a new effective therapeutic strategy for cancer treatment.

Recently, various NPs have been discovered and synthesized that can selectively target tumor cells without harming healthy cells or organs. Different NPs play different roles and play a crucial role in the destruction of

tumor cells and tumor stem cells in BC. Near infrared (NIR) radiation between tumor cells and nanoparticle carriers leads to the absorption of light and its conversion into thermal energy and is used locally to kill tumor cells. A study was conducted to investigate the anti-angiogenic mechanism of quinacrine-gold hybrid NPs (QAuNP) and NIR in patient-derived BCSC cells. Results indicated that QAuNP combined with NIR radiation suppressed kilodalton heat shock proteins (HSP-70) expression in BCSCs, disrupting the kilodalton (HSP-70)/transforming growth factor beta (TGF-β) pathway, reducing TGF-β secretion, and consequently impairing TGF-β-driven angiogenesis [44]. NPs enable the controlled, sustained release of high-concentration chemotherapeutic agents, allowing for the potent suppression and elimination of tumor cells. Consequently, NPs -mediated targeted drug delivery has emerged as a highly promising strategy in BC therapy [47]. Researchers have proposed several nanoparticle-based strategies to target and eliminate BCSCs. These therapeutic approaches focus on directing NPs to BCSC-specific surface markers, inhibiting key signaling pathways essential for BCSC maintenance, disrupting the differentiation process of BCSCs, and altering the metabolic vulnerabilities of these cells. Additionally, targeting the breast tumor microenvironment itself is a critical complementary strategy.

NP-based delivery systems offer significant advantages in this context. They can transport anti-BCSC pharmacological agents directly to the target cells, thereby enhancing drug bioavailability while minimizing off-target effects. Furthermore, the surface of NPs can be functionalized with specific ligands that bind to overexpressed receptors on BCSCs, significantly improving targeting precision.

The primary nanosystem delivery strategies encompass the direct transport of anti-BCSC drugs to tumors, the co-delivery of conventional chemotherapeutic agents alongside anti-BCSC drugs, and the targeted delivery of actively therapeutic agents against BCSCs [48].

To date, there have been no reports of significant side effects from NPs compared to conventional treatments. According to recent studies, hormonal agents in polyethylene glycol-coated NPs easily enter BC cells [49]. NPs systems are crucial in the effectiveness of anticancer drugs. For example, delolactone, an anticancer drug, has weak effects on cancer stem cells. However, Das et al. [50] by combining poly(lactic-co-glycolic acid) (PLGA) NPs and dulolactone reduced metastasis in BCSCs and increased their chemical sensitivity to drugs.

Currently, researchers pay special attention to nanocarriers, such as albumin NPs, metal-based NPs, lipid NPs, liposomes, polymer NPs, and micelles, to deliver drugs to cancer tissue [51]. Therefore, we examine their features.

Albumin as a biodegradable nanocarrier can bind to a wide range of drugs and endogenous molecules and is used as a clinical adjunct in many formulations and drugs. The use of albumin-based NPs can lead to a long half-life, thus maintaining the effective concentration of the drug in the blood. Also, covalent modification on the surface of albumin NPs using free carboxyl and amine groups and various cross-links can increase their tumor targeting ability, especially for drugs with poor pharmacodynamic and pharmacokinetic properties [52]. In 2021, Prajapati et al. [53] used albumin NPs loaded with hydrophilic doxorubicin to treat BC cells, and the results showed high toxicity of the drug on cancer cells with minimal effect on healthy breast tissue cells. Although many studies have investigated the effects of albumin NPs on BC cells, no study has yet specifically investigated the effects of albumin NPs on BCSCs.

Gold, silver, and iron oxide NPs are highly effective in cancer therapy. Their low toxicity, compact size with high surface area, and stable thermal characteristics allow for improved tumor targeting, gene silencing, drug transport, and diagnostic applications. Importantly, NPs of particular sizes exhibit a natural tendency to concentrate within tumors rather than healthy tissue, thereby inhibiting the rate of cancer progression [54]. Shamsian et al. [55] through the combination of SAHA/Wnt-b catenin antagonist with gold NPs (AuNPs) led to inhibit the proliferation of BCSCs. Research by Wang et al. [56] demonstrated that AuNPs, when activated by NIR radiation to induce hyperthermia, significantly promoted mitochondrial-dependent apoptosis in BCSCs. This bioactivity was driven by mechanisms, including direct mitochondrial impairment, the induction of oxidative stress, elevated caspase-3 activity, and a shift in the balance of apoptosis-regulating proteins—specifically, an upregulation of pro-apoptotic factors (Bax, P53) alongside a downregulation of anti-apoptotic Bcl-2. Consequently, this treatment effectively suppressed both the viability and the self-renewal capacity of BCSCs.

Liposomes have a phospholipid that surrounds a water core and leads to the formation of small spherical vesicles in the presence of water. Lipid-based NPs, including liposomes, solid lipid NPs, and nanostructured lipid carriers, are characterized by their high biocompatibility and biodegradability. These properties make them particularly valuable for oncological applications. Their

diagnostic and therapeutic potential is enhanced by several key attributes: An extended circulation half-life that prolongs drug activity, the capacity to transport both hydrophobic and hydrophilic compounds, and the ability to provide controlled release of combination therapies. Furthermore, their surfaces can be modified to respond to specific pH conditions or conjugated with targeting antibodies for precise tumor cell identification.

As a key category of lipid NPs, liposomes offer considerable benefits for drug delivery. With diameters below 400 nanometers, they can passively accumulate in tumor tissue through permeable vasculature. Their characteristic amphiphilic architecture—featuring an aqueous interior enclosed by a lipid bilayer—allows for the co-encapsulation of water-soluble compounds in the core and lipid-soluble drugs within the membrane. This dual-loading versatility, along with mechanisms, such as membrane fusion or endocytic uptake, positions liposomes as robust and adaptable carriers for diverse therapeutic molecules [57]. Yang et al. [58] found that liposome-loaded chitosan could stably bind to CD44 overexpressed in BCSC, and showed a significant antitumor effect in vivo. Yu et al. [59] pointed out the anticancer effects of liposome-conjugated fluvastatin through inhibition of 3-hydroxymethylglutaryl coenzyme A reductase, proliferation, angiogenesis, and metastasis of BCSC cells. Polymeric NPs with a diameter between 1 and 1000 nm, consisting of two or more different hydrophobic chains, are used in drug detection and targeting. The most crucial advantages of polymer-based NPs systems are regulation of drug release and minimal degradation in the bloodstream. Polymer-based nanosystems offer the advantage of sustained and controlled release for both water-soluble and lipid-soluble pharmaceutical agents. By regulating drug kinetics, these systems avoid toxic concentration spikes while maintaining therapeutic doses, thereby reducing adverse effects. A widely utilized material in this category is PLGA, a copolymer approved by the Food and Drug Administration (FDA) for various medical applications. PLGA is favored for its low cytotoxicity, high biocompatibility, predictable degradation profile, and ability to accumulate in tumors via the enhanced permeability and retention effect [60].

Polymeric micelles have a relatively small size of 10-100 nm with a supramolecular core-shell structure composed of biocompatible amphiphilic copolymers in aqueous conditions. Due to their ability to solubilize hydrophobic drugs as well as imaging agents, they are considered a new platform for cancer diagnosis and treatment applications. In addition, encapsulating the drug inside the polymer core can stabilize the drug by delaying the degradation and enzymatic inactivation. Some of these polymeric micelles have antitumor effect, and low systemic toxicity, which are currently undergoing clinical trials [61]. Based on the study of Gener et al. [62], polymeric NPs loaded with Zileuton™, a potent inhibitor of BCSC cells, led to a decrease in the number of BCSCs in the tumor and effectively reduced circulating tumor cells in the bloodstream and blocked metastasis.

NPs carrying RNA in the treatment of BCSC

Next, we examine the role of crucial RNA subtypes in the BCSC treatment process (Figure 2).

MicroRNAs (miRNAs) are a group of small endogenous non-coding RNA molecules that regulate gene expression and play a crucial role in the response of cancer cells to ionizing radiation and pharmacological agents. miRNA expression changes can be useful for understanding the mechanism of response to radiation-induced DNA damage [63]. Expression of miR-223 (a potential tumor suppressor) in BC patients after radiation therapy has been observed to suppress cancer recurrence through epidermal growth factor (EGF)/EGF receptor (EGFR) ability [64]. For these reasons, miRNAs can be good cancer biomarkers for diagnostic, prognostic, and therapeutic responses that can improve the efficacy of cancer treatment. miRNAs loaded with NPs through targeting BCSC surface markers (CD133 and CD44), transporters, HSP, and critical signaling pathways such as Notch, Akt, Hedgehog, KLF4, and Wnt/β-catenin lead to the destruction of BCSC cells [65, 66]. The expression of Let-7 microRNA is frequently reduced in multiple cancer types, particularly within BCSCs. Conversely, cyclin-dependent kinase 4 (CDK4) shows elevated expression in tumor cells positive for HER-2. Capitalizing on these molecular profiles, one investigation designed a co-delivery strategy by encapsulating both Let-7 miRNA and CDK4-targeting silencing RNA (siRNA) within cationic liposomes. To direct this payload specifically to HER-2-positive cells, the liposomes were conjugated with Herceptin (trastuzumab), creating a targeted therapeutic system for BC [67]. Lin et al. [68] TV-circRGPD6 nanoparticle significantly inhibits BCSC expression. In metastatic BCSCs, TV-circRGPD6—either alone or combined with docetaxel—exerted potent therapeutic effects. This activity is mediated by the inhibition of metastasis through the miRNA-26b/YAF2 pathway.

siRNA, which is also called short interfering RNA, is a group of double-stranded RNA and non-coding RNA (lncRNA) molecules that, such as miRNA, have a length of 20-27 bp. The rapid enzymatic breakdown of RNA in

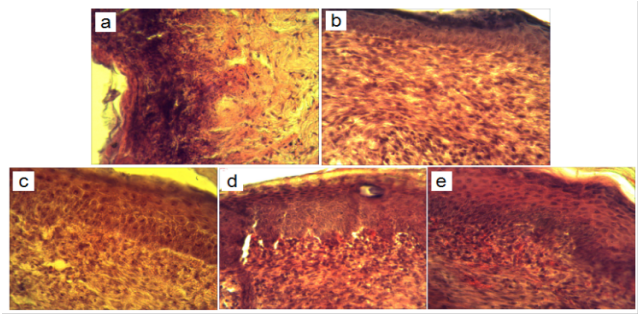

Figure 2. The role of NPs carrying RNA in BCSC treatment process
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Note: NPs bound with an active substance (drug, antibody, or RNA) bind to surface receptors on BCSC. After endicytosis, the NPs breaks down and the active substance is released, leading to cell death by inhibiting or activating a cascade of signaling pathways.

the vascular system presents a significant challenge to its therapeutic use. Studies have shown that BC cells can easily absorb lipid NPs and thus reduce tumor growth. In this regard, in a study, gedunin was used as a secondary metabolite in a neem tree along with a new liposomal nanocarrier for the simultaneous delivery of gedunin and siRNA and improving the antiproliferative activity of gedunin. Lipo-Ged-siRNA showed more anti-proliferative effects in BCSC. In addition, Lipo-Ged-siRNA affected the expression of *ABCB1*, *Cyclin D1*, *Bax*, and *p53* genes in BCSC [69]. In another study, new NPs targeting glutathione (GSH) response (SSBPEI-DOX@siRNAs/iRGD-PEG-HA) were presented. They are constructed through the electrostatic assembly of anionic siRNAs and polyethyleneimine-doxorubicin (SSBPEI-DOX). SSBPEI-DOX can be degraded to less cytotoxic polyethyleneimine (PEI). Due to the enrichment of glutathione (GSH) reductase in the tumor microenvironment, the disulfide bond (-SS-) in SSBPEI-DOX can be specifically reduced to enhance the controlled release of siRNA and DOX in mesenchymal stem cells (MSCs). siRNA can specifically induce apoptosis or necrosis of BCSCs in combination with the traditional chemotherapy drug DOX [28].

LncRNAs are RNA molecules longer than 200 nucleotides that do not encode proteins. Evidence increasingly indicates they play essential roles in regulating key cellular processes in cancer, such as growth, invasion, migration, apoptosis, and metastasis. HOX transcript antisense intergenic RNA (HOTAIR) and metastasis associated lung adenocarcinoma transcript 1 (MALAT1) are two lncRNAs identified in malignancies of various origins and are responsible for the poor prognosis of cancer patients. In a study, ionizable lipid NPs were used in combination with HOX RNA-HOTAIR lncRNA and MALAT1 lncRNA, and a significant reduction in tumor volume and BCSCs was observed [70]. However, more studies focus on mature tumor cells and less on BCSC.

New ways to treat BCSC

BCSC accumulation is associated with treatment resistance or relapse of BC tumors. Targeted drug delivery systems based on NPs have advantages for delivering anti-BCSC agents to target sites. Hence, treating BC using a BCSC targeting system based on NPs is a promising strategy. Such targeted drug delivery systems can overcome the barriers to biodistribution of nanosystems. Using different NPs, such as liposomes and different micelles, the drug can be delivered to the BCSC in a targeted manner. These NPs target surface markers or signaling pathways in cancer cells [71]. One of the new methods that has received attention today for the treatment of cancer and BCSC cells is the use of RNAs; however, obstacles, such as the rapid loss of RNAs in the bloodstream and before reaching the target cells limit their effectiveness. Therefore, it is suggested to use the combination

of NPs with RNAs to prolong their effects and also for more stability. Also, we suggest using antioxidant compounds, such as ellagic acid plant extracts, curcumin, etc. in combination with them to improve the effectiveness of the nanoparticle-RNA complex. In addition, the use of nanoparticle-RNA complex in the same ship of cancer cells with healthy stem cells and the use of cell therapy can provide a more suitable treatment solution.

Conclusion

To successfully treat cancer, it is necessary to pay attention to all the cells in the tumor environment from the attack of cancer stem cells, but despite many advances, our knowledge about this cell population is very little. At present, there are still many problems in the targeted application of NPs for the treatment of BCSC. However, the development of nanocarrier systems to target BCSCs, and complete technological transformation are crucial to reduce BC recurrence and metastasis. The innovation of this article is in the introduction of RNA-based nanocarrier systems and also provides new ideas for early detection and targeted treatment of BCSCs.

Ethical Considerations

Compliance with ethical guidelines

This article does not contain any studies with human participants or animals performed by any of the authors.

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Authors' contributions

Conceptualization, review & editing: Zahra Sadeghi and Hossein Salehi; Supervision: Hossein Salehi; Methodology, investigation and writing the original draft: Zahra Sadeghi, Sharare Rahnama and Saman Sadeghpour Salamat; Data collection: Zahra Sadeghi, Sharare Rahnama, Saman Sadeghpour Salamat.

Conflict of interest

The authors declared no conflicts of interest.

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