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Nanoparticle Based Delivery of miRNAs to Overcome Drug Resistance in Breast Cancer

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Abstract

Nanoparticle-based targeted drug delivery is a successful strategy to overcome the side effect of chemotherapy. Nanoparticles based drug delivery systems that have been designed to enhance delivery of therapeutics to tumors, are a novel approach. Nanoparticles have reactive surface that can be readily modified with biocompatible coatings and loaded with therapeutic agents (miRNA, siRNA, antibody, anti-cancer drug etc..). MicroRNAs (miRNAs or miRs) are short non-coding RNAs which posttranscriptionally regulate growth, differentiation, apoptosis, motility, and malignant transformation. In addition, some miRNAs have been classified as proto-oncogenes. The levels of changed miRNA expression play significant role in the initiation of many diseases, including cancer, especially tumor progression and metastasis. Further studies, miRNA conjugation to drug carrier systems is used to target to cancer cells. In this review, we focus on miRNA carrier nanoparticles, and summarize novel advances about their use in drug resistance breast cancer therapy.

Keywords: miRNA; Magnetic nanoparticles; Breast cancer; Drug resistance

Introduction

Breast cancer is the most frequently diagnosed cancer and leading cause of cancer death in women worldwide [1]. Surgery combined with chemotherapy is currently the most effective strategy for breast cancer therapy. However, most treatments are unsuccessful due to secondary recurrence, metastasis, and drug resistance [2]. Development of new therapies will be important to enhance the clinical outcome of breast cancer [3]. While several new therapeutic agents have been approved for the treatment of breast cancer [4,5], their ability to prolong life has been limited due to the rapid development of resistance [6]. A promising strategy that utilizes the same principle is miRNA-based therapeutics, as a single miRNA can have multiple targets in both the tumor cells themselves and the tumor microenvironment [7-10]. MicroRNAs (miRNAs) are single-stranded, small (22 nucleotide-long), and evolutionarily protected non-protein-coding RNAs [8,11]. Current evidence indicates that miRNAs play critical regulatory roles in cell proliferation, cell death, apoptosis, immune response, cell cycle, senescence, invasion, metastasis, and angiogenesis [12-18]. MiRNAs can regulate hundreds of target genes and control signaling pathways [19,20]. However, their unsuccessfully delivery at tumor area cause off-target effects [21]. Nanoparticle based targeted delivery of miRNAs to specific their tumor side and cells are novel and alternative approaches in cancer therapy. We summarize polymer-functionalized nanoparticles as miRNA carrier that can potentially be applied to deliver miRNA as therapeutics to overcome drug resistance in breast cancer.

miRNAs in Drug Resistance Breast Cancer

Novel expanded miRNA families have been also discovered in breast cancer cell lines and human breast tissue samples. Increasing evidence suggests that miRNAs are involved in the development of resistant breast cancers through the regulation of estrogen resistance, apoptosis, drug transporters, epithelial mesenchymal transition (EMT), and cancer stem cells (CSCs). MiRNAs based microarrays and new generation of sequencing technologies have been reported on the association with breast cancer (Figure 1). For example, disturbance of miRNA-210 functions may contribute to tumor aggressiveness and poor prognosis [22,23], while miR-355 inhibits tumor [24,25]. In breast cancer cells, silencing of miR-21 [26-30] caused the inhibition of cell proliferation, the downregulation of Bcl-2 and the induction of apoptosis *in vitro* and *in vivo* models [29]. Recent studies have demonstrated the role of miRNAs in the regulation of the Bcl-2 family of proteins. Bcl-2 proteins are important regulators of apoptosis. Studies show that Bcl-2 is regulated by miR-34a, miR-21, miR-203, miR-143, and miR-16 [31-51].

Approximately 90% of chemotherapy failures are due to drug resistance [52]. Chemotherapeutic agents, such as etoposide, doxorubicin, paclitaxel, topotecan, and 5-fluorouracil, are used to early and locally advanced breast cancers, but many patients receving chemotherapy can develop a resistance. Most of studies have demonstrated that dysregulation of miRNAs have a key role in drug resistance [53]. The overexpression of ATP-binding cassette (ABC) drug transporters is an important reason for chemoresistance [54]. Pgp/MDR1 has important role as multiple drug resistance (MDR) transporters in drug disposition and distribution. Transcriptional regulation of MDR1 gene expression in drug resistance breast cancer cells by miRNAs has been reported in several studies. Polymorphisms of miR-24 miRNA binding site in the dihydrofolate reductase gene contribute to methotrexate resistance [55]. Zhu et al. demonstrated that the overexpression of miR-27a and miR-451 are involved in the development MDR in cancer cells [56]. Overexpression of miR-221 and miR-222 contribute to tamoxifen resistance in negative regulation

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of ERα, but silencing of miR-221 and/or miR-222 regulates ERα expression and tamoxifen sensitivity [57]. MiRNAs expression can also be used both as a potential therapeutic agent and a prognostic biomarker in drug resistant cancer cells [58].

Zhao et al., [59] investigated the effects of miR-21 on paclitaxel-resistance in human breast cancer MCF-7/PR and SKBR-3/PR cells. They found that the expression levels of MDR1, BCRP, MRP1, Bcl-2/Bax and miR-21 in MCF-7/PR and SKBR-3/PR cells were significantly higher than in parenteral MCF-7 and SKBR-3 cells. The protein levels of P-gp, Bcl-2 were found to be up-regulated, and Bax was down-regulated compared to the parental cells.

Doxorubicin, an anthracycline antibiotic, is a commonly used anticancer agent in many cancer types and its most serious side effect is heart damage [60]. MiRNA-134 has been reported to be down-regulated in doxorubicin-resistant MCF-7/ADR cell lines by Lu et al. Morever, MCF-7/ADR cells were transfected with miR-134 mimics.

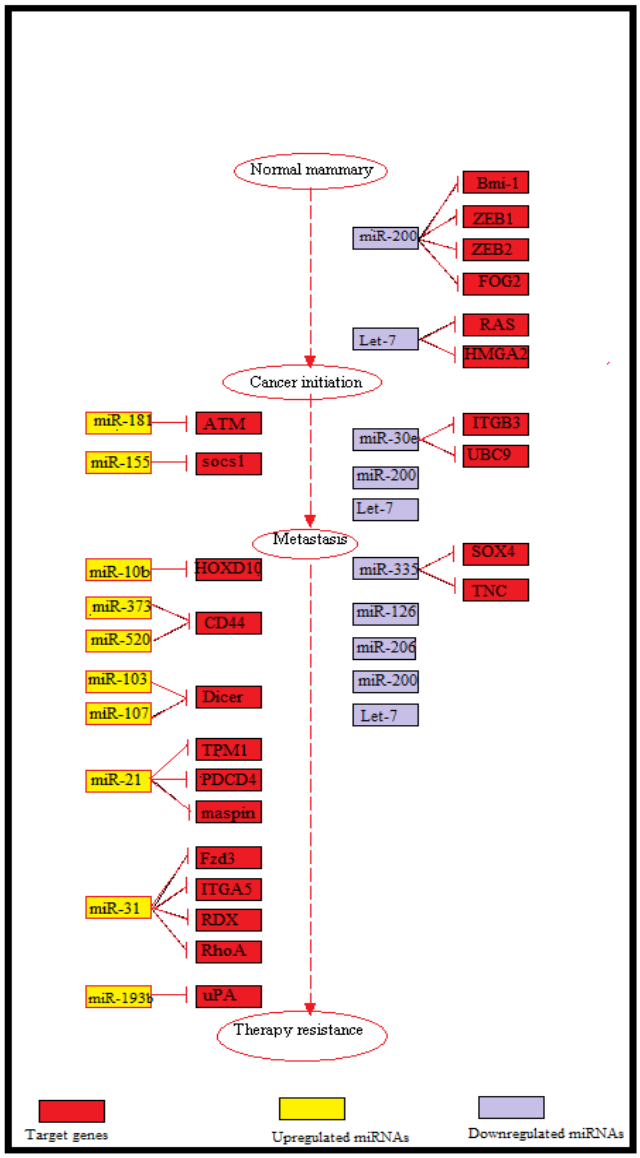

Figure 1: miRNAs in breast.

The results were supported with MTT assay that the cell proliferation was inhibited. They demonstrated to trigger apoptotic processes after transfection. The expression levels of ABC-C1 was upregulated in doxorubicin-resistant MCF-7/ADR cell lines [61]. Various studies indicated that upregulation of miR-451 expression levels down regulated the expression of MDR1 in the doxorubicin-resistant breast cancer cells [62]. In another study, miR-200c expression level was found to be downregulated in drug resistant MCF-7 cells when compared to drug sensitive MCF-7 cells. After transfected with miR-200c mimics, its upregulation may enhance the chemosensitivity to epirubicin in breast cancer cells [63-87]. Different miRNAs and target genes have been reported in drug resistance breast cancer cells as enlisted in Table 1 above.

miRNAs and Nanoparticle Delivery Systems

The use of nanotechnology for drug delivery is successful strategy to enhance the delivery of therapeutics to tumors. This technology has contributed to development of nano-scale particles that can be used different materials including polymeric, dendrimeric, and magnetic nanoparticles (MNPs) [88]. The primary goal of targeted drug delivery is to carry therapeutics agents loaded nanoparticles to targeted tissues and to reduce nonspecific drug toxicity in normal tissues. The most important characteristics for successfully synthesized nanoparticle-mediated drug delivery systems are stability, the high loading capacity of nanoparticles, size, and the flexibility to carry therapeutics [89-91].

Magnetic nanoparticles (MNPs) have significant advantages in medicine as they can be targeted in the presence of a magnetic field. The use of anticancer agents is critical in chemotherapy. Chemotherapeutic agents that also arrive throughout the blood circulation to non-targeted systems can cause toxicity in healty tissues and organs. Hence, development of anticancer agent loaded/conjugated MNP delivery systems can be decrease the toxicity and non-selectivity of anticancer drugs [92]. These magnetic based delivery systems will also increase the agent efficiency and drug circulation time. Additionally, it has been reported that MNP had been found to be safe in vivo and in vitro studies such as MNPs did not affect liver enzyme levels in the long term and also did not induce oxidative stress in rats [93-96].

Synthetic and natural polymers have been used to coat surface of nanoparticles such as dextran, poly (aniline), poly (ethylene glycol), and polyesters, such as poly (lactic acid) and poly (hydroxybutyrate). The surfaces of nanoparticles have been modified with different approaches to bind molecules and to enhance delivery. For example, when the surface of the nanoparticles has been modified with carboxyl and amine groups, the nanoparticles can be conjugated easily with proteins, drugs, si-/miRNA, antibodies, carbohydrates, etc. [97].

MiRNAs play key role as both oncogenes and tumor suppressors [98,99] and they have therapeutics potential in cancer treatment. However, its non-effective delivery mechanism includes some limitations [100]. Free miRNAs are not stable and have a very short half-life because of their degradation by nucleases in blood, serum and other body fluids or tissues [101]. Therefore, an effective miRNA carrier systems have been required for efficiently delivering these therapeutics into cancer cells [102,103] (Figure 2). A different carriers that excibits high stability and delivery efficiency, has been designed for miRNA delivery in breast cancer treatment (Table 2). When miRNAs are attached to the surface of nanoparticles, the efficacy of miRNA conjugated nanoparticles is more than free miRNA [104]. In recent years, down regulation of the expression of a tumor suppressive miRNA with nanoparticle based delivery has been reported to decrease

miRNAs	Target Gene	Drug	Cell lines	Ref
miR-139-5p	*Notch1*	Docetaxel	MCF7,MCF7/Docetaxel	[64]
miR-125a-3p	*BRCA1*	Docetaxel	MDA-MB-468/Docetaxel, MCF-7/Docetaxel, MDA-MB-468, MCF-7	[65]
miR-302a, miR-302b, miR-302c, and miR-302d	*BCRP*	Mitoxantrone	Mitoxantrone (MX)-resistant MCF-7 (MCF-7/MX)	[66]
miR-29a	*PTEN and GSK3β*	Adriamycin	ADR-resistant MCF-7 breast cancer cell subline (MCF-7/ADR)	[67]
miR-10b	*HDAC4*	Tamoxifen	Tamoxifen-resistance MCF-7	[68]
miR-155	*SOCS6-STAT3*	Tamoxifen	Tamoxifen sensitive and resistant MCF-7 and SKBR3 cells	[69]
miR-134	*ABCC1*	Doxorubicin	Doxorubicin- resistant and Doxorubicin-sensitive breast cancer samples	[61]
miR-193b	*MCL-1*	Doxorubicin	Doxorubicin- resistant and Doxorubicin-sensitive breast cancer samples	[70]
miR-125b	*Mcl-1*	Doxorubicin	Doxorubicin- resistant and Doxorubicin-sensitive breast cancer samples	[71]
miR-489	*SPIN-1*	Adriamycin	MCF-7, MDA-MB-231, MDA-MB-468, T47D , MCF-7/ADM (resistant to adriamycin) and drug-resistant tissues	[72]
miR-451	*Bcl-2*	Paclitaxel	Paclitaxel- resistant breast cancer samples	[73]
miR-141	*EIF4E*	Docetaxel	Docetaxel−resistant cells (MCF-7/DTX and MDA-MB−231/DTX) and Docetaxel−sensitive cells (MCF-7 and MDA-MB−231)	[74]
miR-217	*PTEN*	Tamoxifen, Etoposide, Lapatinib	MCF-7 and SKBR-3	[75]
miR-181b	*Bim*	Doxorubicin	Doxorubicin (DOX)-resistant T-47D cells (T-47D-R) and sensitive T-47D	[76]
miR-129-3p	*CP110*	Docetaxel	MDA-MB-231/Doc and MDA-MB-231	[77]
miR-873	*CDK-3*	Tamoxifen	Tamoxifen-resistant cells (MCF-7/TamR)and MCF-7/S	[78]
miR-125b	*Sema4C*	Paclitaxel	Paclitaxel-resistant (PR) breast cancer cells	[79]
miR-218	*Survivin*	Taxol and doxorubicin	Resistant MCF-7 and Cal51 cells	[80]
miR133a	*UCP-2*	Doxorubicin	Doxorubicin resistant MCF-7 and parental cell line MCF-7	[81]
miR-224-3p	*FUT4*	Adriamycin	Adriamycin-resistant MCF-7/ADR and T47D/ADR	[82]
miR-3646	*GSK-3β*	Docetaxel	MDA-MB-231/Doc MCF-7/Doc, MDA-MB-231/S and MCF-7/S	[83]
MiR-487a	*ABCG2*	Mitoxantrone	Mitoxantrone (MX)-resistant breast cancer cells (MCF-7/MX)	[84]
miR-221/222	*p27kip1*	Tamoxifen	Tamoxifen-sensitive and Tamoxifen-resistant MCF-7 cells.	[85]
miR-326	*ABCC1*	VP-16 and mitoxantrone	VP-16-resistant MCF-7 (MCF-7/VP), mitoxantrone-resistant MCF-7 (MCF-7/MX100) and MCF-7	[86]
miR-451	*ABCB1*	Doxorubicin	DOX-resistant MCF-7 cells (MCF-7/DOX) and MCF-7	[87]

Table 1: The list of miRNAs and target genes in drug resistance breast cancer cells.

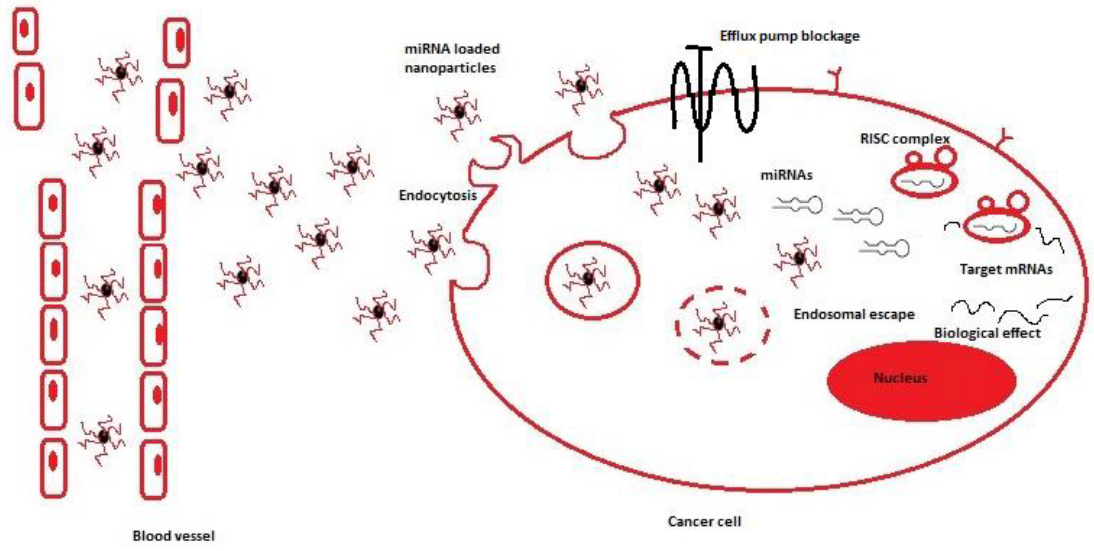

Figure 2: Mechanism of miRNA loaded/attached nanoparticle systems in cancer cells.

miRNAs	Nanoparticles	Breast Cancer Cell line	Ref
miR-145	Polysorbitol-mediated transporter (PSMT)	MCF-7	[114]
miR-34a	Hyaluronic acid-chitosan nanoparticles	MDA-MB-231	[115]
miR-145	Chitosan polyplex nanoparticles	MCF-7	[110]
miR-34a	PEGylated-thymoquinone-nanoparticle	MCF-7	[116]
miR-542-3p	Hyaluronic acid-coated PEI-PLGA nanoparticles	MDA-MB-231 and MCF-7	[117]
miR-145	Gold nanoparticle (Au-NPs)	MCF-7	[118]
miR-125a-5p	Lipid nanoparticles	21MT-1 and MCF-10A	[119]
miR-10b	Polylysine Nanoparticles	MDA-MB-231	[120]
miR-21	Poly (ethylene glycol) conjugated poly (lactic-co-glycolic acid) nanoparticles (PLGA-PEG-NPs)	MDA-MB-231 and SKBR3	[113]
miR-21 and miR10b	PLGA-b-PEG polymer NPs	MDA-MB- 231-Fluc-eGFP, mouse TNBC tumor xenograft model	[121]
miR-10b	Magnetic nanoparticles	MDA-MB-231-luc-D3H2LN	[122]
miR-129-5p	Poly(ethylene glycol)-b-poly(L-lysine)-b-poly (L-cysteine) (LCss) polypeptide nanoparticles	DOX-resistant MCF-7/ADR cells	[123]
miR-21, miR-145, and miR-9	Polyethyleneimine-modified MNPs	MCF-7	[124]
miR-let7a	Chitosan/Poly(c-Glutamic Acid)	MDA-MB231 and MCF-7	[111]
miR-21	Polyethylenimine (PEI)/poly (sodium 4-styrenesulfonates) (PSS)/graphene oxide (GO)	MCF-7/ADR	[112]

Table 2: Summary of current studies on the nanoparticle based miRNAs carriers in breast cancer cell line/in vivo model.

tumor growth in pre-clinical models [105-108]. Jin et al., demonstrated that polylysine-anti-mir-10b nanoparticle complex has inhibitory effect against breast cancer cells [109].

MiR-145, a tumor suppressor miRNA, is down regulated in cancer and can be introduced as a therapeutic agent in various cancers, including breast cancer. MiR-145 plasmid was transfected into MCF-7 cells by chitosan polyplex nanoparticles. Chitosan polyplex nanoparticles diminished the proliferation of MCF-7 cells by approximately 30% [110]. In another study, chitosan-PGA complex was conjugated with QD-miRNA let-7a-gold nanoparticles for delivery to MCF-7, MDA-MB231 breast cancer cells as model, showing its application potential in biomedicine [111]. MiRNA-21 overexpression related to the development multiple drug resistance in breast cancer. The polyethylenimine (PEI)/poly (sodium 4-styrenesulfonates) (PSS)/ graphene oxide (GO) has been designed as carrier for Adriamycin (ADR) and anti-miR-21. This strategy is the developing multifunctional nanocomplex to overcome MDR, might represent a promising novel therapeutic approach for the treatment of breast cancer [112]. Additionally, orlistat and antisense miR-21 loaded poly(ethylene glycol)-conjugated poly(lactic-co-glycolic acid) nanoparticles enhanced apoptotic effect compared with independent doxorubicin, anti-miR-21-loaded NPs, orlistat-loaded NPs or free orlistat treatments in MDA-MB-231, SKBR-3 and normal breast fibroblast cells [113-123]. Table 2 summarizes currently studies on nanoparticles as carriers for miRNA in breast cancer cells.

Recently published findings by Yu et al. [124] demonstrate that miR-21, miR-9, and miR-145 were combined with PEI-modified magnetic nanoparticles. Their research suggests that in nude mice, the volume and weight of tumors decreased to just 58 % of that in the control.

The hyaluronic acid /protamine sulfate nanocapsules have been used to deliver miR-34a into triple negative breast cancer cells or tissues. The delivery of miR-34a induced apoptosis and cell death, reduced migration, proliferation of breast cancer cells via targeting CD44 and Notch-1- signaling pathways [125]. In a similar study, doxorubicin and miR-34a loaded chitosan nanoparticles were delivered into breast cancer cells to increase therapeutic effects of drug [115,126].

Conclusion

miRNA could be a promising strategy for drug resistance breast cancer therapy. Clear evidences are given by the recent reports that miRNA and nanoparticles are beneficial in inhibiting the tumor growth. Various nanocarriers have been developed to deliver miRNA however these nanocarriers have limitations. The ideal nanoparticle delivery system should protect the miRNA from the RNAses and efficiently deliver to tumor cells. Efficient targeting and release of miRNAs using magnetic nanoparticles can reduce the required therapeutic dosage and cellular toxicity. In the future, miRNA conjugated magnetic nanoparticles will achieve a maximum effect of targeted therapy for treating drug resistant tumors. Therefore, further experiments will be needed on the interactions between the nanoparticle based delivery of miRNAs and drug-resistant cells, there has been very little written research on this point.

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