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Review Article

Exosomes-mediate microRNAs transfer in breast cancer chemoresistance regulation

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Abstract: Breast cancer is the most common and fatal type of cancer in women worldwide due to the metastatic process and resistance to treatment. Despite advances in molecular knowledge, little is known regarding resistance to chemotherapy. One highlighted aspect is the DNA damage response (DDR) pathway that is activated upon genotoxic damage, controlling the cell cycle arrest or DNA repair activation. Recently, studies have showed that cancer stem cells (CSCs) could promote chemoresistance through DDR pathway. Furthermore, it is known that the epithelial-mesenchymal transition (EMT) can generate cells with CSCs characteristics and therefore regulate the chemoresistance process. The exosomes are microvesicles filled with RNAs, proteins and microRNAs (miRNAs) that can be released by many cell types, including tumor cells and CSCs. The exosomes content may be cell-to-cell transferable and it could control a wide range of pathways during tumor development and metastasis. A big challenge for modern medicine is to determine the reasons why patients do not respond to chemotherapy treatments and also guide the most appropriate therapy for each one. Considering that the CSCs are able to stimulate the formation of a more aggressive tumor phenotype with migration and metastasis ability, resistance to treatment and disease recurrence, as well as few studies capable to determine clearly the interaction of breast CSCs with its microenvironment, the present review summarize the possibility that exosomes-mediate miRNAs transfer and regulate chemoresistance in breast tumor cells and CSCs, to clarify the complexity of breast cancer progression and therapy.

Keywords: Breast cancer, exosomes, microRNAs, chemoresistance

Introduction

Breast cancer is the most common type of cancer in women worldwide, comprising 23% of all cancer cases and causing 14% of cancer-related deaths [1]. Ductal and lobular types correspond to more than 90% of breast cancer cases. Breast cancer is a heterogeneous disease in which multiple cellular pathways are dysregulated leading to marked differences in prognosis, pattern of metastasis, treatment sensitivity and patient survival [2-4]. Gene expression profiling approaches have been defined the intrinsic subtypes [5] of the disease. However, multiparameter molecular tests such as differential expression of PAM50 [6] or MammaPrint/Blueprint [7] are not worldwide available.

In clinical practice, immunohistochemistry (IHC) tests for estrogen and progesterone hormone receptors (ER and PR, respectively), human epidermal growth factor receptor 2 (Her2), and Ki-67 protein expression are used to classify breast carcinoma into different groups in order to allocate the patient to individual therapies [8]. Systemic therapies based in hormone, cytotoxic agents and target antibodies are initially effective in controlling tumor growth. In contrast, several studies have demonstrated that a significant proportion of patients are inherently resistant to first-line therapeutic agents or develop resistance during the treatment, and thus exhibited tumor recurrence within the first year of diagnosis [9].

More recently, it has been observed that exosomes, microvesicles filled with RNAs, proteins and microRNAs (miRNAs), can be released by tumor cells and cancer stem cells (CSCs) and the released content could be able to control many different pathways during tumor develop-

ment and metastatic process [10, 11]. This review will summarize and discuss the possibility that exosomes-mediate miRNAs transfer and regulate chemoresistance of breast tumor cells and CSCs.

Breast cancer systemic therapy and molecular mechanism of chemoresistance

The decision on which systemic treatment should be prescribed is based on the predicted sensitivity to particular treatment method, benefit from their use, and individual risk of relapse. The adjuvant or neoadjuvant chemotherapies are based on sequential regimens of anthracyclines and taxanes that attach cancer cells through deoxyribonuclease and microtubule inhibition, respectively [12, 13]. Hormone therapy as tamoxifen or aromatase inhibitors are indicated for hormone receptor-positive breast cancer women [14-16]. In the last few years, mTOR and CDK inhibitors emerged as a treatment of advanced, hormone-therapy resistant luminal breast cancer [17, 18]. Targeted therapies, such as the monoclonal antibody trastuzumab, combined with chemotherapy are used in *HER2*-positive breast cancers and the drug combination have an undeniable beneficial impact on patients overall survival [19, 20].

Multidrug resistance is a phenotype exhibited by malignant cells characterized by resistance to multiple cytotoxic drugs involving alteration in both drug metabolism and transporter in cancer cells as well as different molecular mechanisms of action [21]. The mechanisms of tumor cells resistance can escape the cytotoxic effect induced by chemotherapy in two possible ways: (1) intrinsic, in which the patient does not respond to treatment because tumor cells are able to escape from pathways in which tumor cells are unable to uptake the drug and (2) acquired, in which initially the patient responds to the treatment but then becomes resistant. In both cases the treatment is ineffective leading to a poor prognosis [22].

It has been shown that the overexpression of ATP-binding cassette (ABC) efflux transporters in tumor cancer cells pump out drug molecules, decreasing their intracellular concentration, while increasing the healthy cells' drug exposure [23]. The molecular pathways associated with drug resistance include inhibition of both DNA repair and deregulation of survival/apoptotic pathways [24]. Furthermore, individual predictive factors such as the distinction into ER+ versus ER- cancers are also related to drug sensitivity/resistance [25].

DNA repair proteins play a key role in the maintenance of a healthy genome and when inactivated can impair the capacity of cancer cells to repair DNA cross-links caused by chemotherapy drugs [26]. DNA repair gene mutations have been associated with the development of breast cancer. It is believed that mutations may trigger both tumorigenesis and the influence of the therapeutic response [27]. *BRCA1* encodes a DNA repair protein and plays a key role in the development of hereditary breast cancer. This protein interacts with the RNA polymerase II complex and histone deacetylase enzyme, acting in transcription and DNA double strand break (DSBs) pathway [28]. BRCA2 protein is also involved in DSBs through interaction with RAD51 to start the homologous recombination process [29]. The risk of a *BRCA1/BRCA2* mutation carrier develop breast cancer is estimated at 60-80%. In addition, there are other DNA repair genes associated with breast cancer development, including mismatch repair genes as *MLH1, MSH2, PMSI, MSH6, PMS2* and DNA damage sensors as *ATM, ATR, CHK1, CHK2* and also *TP53* [27, 30, 31].

Some authors have postulated that *TP53* mutations with consequent repression of other genes involved in the *TP53* pathway are highly associated with chemoresistance [32]. In this regard, nonsense mutations in the *CHK2* gene, an upstream *TP53* activator, and *ATM*, a key activator of *TP53* and *CHK2* genes [33] may cause resistance against DNA damage drugs *in vivo* [34].

The DNA damage response (DDR) pathway is activated in the presence of genotoxic DNA damages. The DNA damage sensors send two signals, the first activates the checkpoint pathway that stops the cell cycle in both G1 and G2; the second signal leads to activation of DNA repair [35]. Some evidence has indicated that CSCs can promote chemoresistance [36] partly through DDR [37, 38]. Furthermore, it is known that the epithelial-mesenchymal transition (EMT) can generate cells with stem cell features and regulate chemoresistance process associated to CSCs. Indeed, a study conducted by Zhang et al [39] showed that

EMT regulators promote DDR and therapy resistance through a process involving *ATM* and *CHK1*.

Cancer stem cells are associated with chemoresistance

Despite genetic-molecular knowledge advances of breast cancer, this cancer remains the leading cause of cancer death among women worldwide, mainly due to the metastatic process and treatment resistance. It is suggested that a subpopulation of cells present in the tumor is resistant to chemotherapy and it could be able to initiate tumor growth and drive the disease progression [40, 41]. These cells have stem cell characteristics, and were first observed in breast tumors in 2003 [42]. There are two hypotheses to explain the origin of CSCs. The first one proposes that these cells result from the dysregulation of normal stem cells, resulting in tumor cells with self-renew and differentiation ability, mainly due to a high mutation rate and oncogenic transformation resulting from its long lifespan. The second hypothesis is that the CSCs develop from the EMT and are more susceptible to neoplasic transformation [41].

Several cellular pathways are responsible for regulating and maintaining the breast CSCs characteristics such as NOTCH, HEDGEHOG and WNT [38]. In addition, there are important transcription factors in this process, as factor nuclear kappa B (NFκB) and SRY-Box 9 (*SOX9*). It has been demonstrated that *SOX9* plays a key role in EMT induction, and its induction is essential to keep breast stem state [43]. Recently it was demonstrated that high levels of *SOX9* are associated with estrogen receptor (ER)-negative breast cancers, and also with a lower survival rate [44, 45].

The breast CSCs are identified by the expression of specific surface cell markers ($CD44^+/CD24^-$), the ability to grow in non-adherent conditions and the ability to self-renew [46]. It has been suggested that tumor cell population is composed of around 1% of CSCs, and this is sufficient to generate a phenotypically more aggressive tumor. In this sense, Ginestier and Wicha [47] showed that only 20 CSCs with $CD44^+/CD24^-/ALDH^+$ profile were able to form tumors *in vivo*.

An association between treatment resistance and breast CSCs has also been suggested, since there is a high number of $CD44^+/CD24^-$ cells in residual tumor post chemotherapy [48]. This fact might be explained by CSCs quiescent characteristic, which contrast with chemotherapy drugs action that target cells in fast cell division. Moreover, it has been reported that CSCs have high levels of anti-apoptotic proteins such as BCL-2 and Survivin as proteins involved in efflux pumping mechanisms that reduce the cellular ability to retain the drug [49]. Accordingly, chemotherapy would not affect the CSCs, thus exerting selective pressure in these cells, promoting clinical resistance and increasing tumor aggressiveness [41]. Therefore, to elucidate the molecular mechanism in which the CSCs can survive to therapy is fundamental to identify new therapeutic targets most suitable for each breast cancer type.

In addition, CSCs are associated with high cell plasticity, which is necessary for self-renewal and differentiation. It has been proposed that the cell plasticity is maintained by epigenetic changes including DNA methylation, histone modifications and non-coding RNAs [50]. So, the disruption of epigenetic changes can significantly contribute to tumor development, and may control the CSCs plasticity [51]. The induction of some epigenetic modifiers, such as *BMI1* and *EZH2*, has been associated with induction of plasticity within breast CSCs [52]. Moreover, there is a growing evidences supporting the role of miRNAs in the maintenance of CSCs [53].

miRNAs promote breast cancer chemoresistance

miRNAs are a class of small noncoding RNA that contain about 20 nucleotides in length and important as post transcriptional regulators once it has been demonstrated that they can regulate up to 60% of all coding genes. The miRNAs negatively regulate gene expression through their binding capacity with the 3' untranslated region (3'UTR) of the mRNA target, which consequently lead to a reduction in the protein translation [54]. miRNAs act as regulators in a broad biological process, and are dysregulated in almost all cancer types, including breast cancer.

A growing number of studies has been highlighted the relevance of miRNAs as drug-resis-

Table 1. List of microRNAs associated with drug resistance in breast cancer

miRNA	Target genes	References
miR-451	*ABCB1*	[60]
miR-326	*ABCC1*	[92]
miR-487a	*ABCG2*	[93]
miR-221/222	$p27^{kip1}$	[94]
miR-30c	*TWF1 and IL-11*	[94]
miR-31	*PKCepsilon*	[95]
miR-3646	*GSK-3β*	[96]
miR-224-3p	*FUT4*	[97]
miR-193b	*MCL-1*	[98]
miR-21	*PTEN* and *PDCD4*	[99]
miR217	*PTEN*	[100]
miR133a	*UCP-2*	[101]
miR-218	*Survivin*	[102]
miR-125b	*Mcl-1/Sema4C*	[103, 104]
miR-141	*EIF4E*	[105]
miR542-3p	*AKT*	[104]
miR-873	*CDK3*	[106]
miR-320a	*TRPC5 and NFATC3*	[107]
miR-149	*NDST1*	[108]
miR-129-3p	*CP110*	[109]

tance mediators, and consequently as a novel strategy for therapeutic intervention [55, 56]. In breast cancer, some miRNAs have been identified as drug resistance regulators (doxorubicin, mitoxantrone and tamoxifen). As an example, the overexpression of miR-21 can cause trastuzumab resistance by suppressing its target gene, *PTEN*, during long drug exposure period [57]. Additionally, Bockhorn et al. [58] reported that miR-30c suppresses *IL-11* expression and inhibit paclitaxel and doxorubicin resistance promoting EMT phenotype.

The chemotherapeutic failure observed in a wide range of anticancer agents, including anthracycline antibiotics, plant alkaloids, taxanes, and platinum-based drugs, is often attributed to the P-glycoprotein (P-gp) protein overexpression [59]. Kovalchuk et al [60] showed that P-gp-mediated resistance is associated with a low levels of miR-451 expression, which cannot target P-gp, increasing its expression in doxorubicin resistant MCF-7 cells. Furthermore, there is evidence showing miR-489 as a putative regulator of *MRP2* which down-regulation is associated with resistance to cisplatin and doxorubicin [56].

The effect of cytotoxic drugs such as doxorubicin, paclitaxel and cisplatin occurs through DNA damage. Several distinct cellular pathways are activated in response to genotoxic damage, including the cell cycle arrest and apoptosis. The balance between pro- and anti-apoptotic programs can also be regulated by miRNAs allowing that normal cells are shifted toward in cancerous cells. In this sense, Shen et al [61] found an ectopic expression of miR-155 and a consequent cell survival and resistance to tamoxifen induction in both *in vitro* and *in vivo*. They also found that miR-155 inhibition leads to apoptosis and enhance tamoxifen sensitivity. In a complementary way, van Jaarsveld et al [24] analyzed the response of 725 human miRNAs correlated to DNA damage induced by high dose of cisplatin and irradiation. They found that 121 miRNAs were differentially expressed in breast tumors compared to healthy tissue and the authors were also able to validate that miR-93, miR-183, let-7a, miR-141, miR-23b, miR-369-3p, miR-296-5p, miR-193a-3p and miR-34b were, in fact, deregulated in breast cancer.

The acquisition of chemoresistance involves multiple interacting factors and to better understand this process, He et al [62] used adriamycin and paclitaxel resistant MCF-7 cells to identify dysregulated targets thought RNA sequencing and the transcriptome profiles of coding mRNAs and non-coding small RNAs. They found that chemoresistant cells have similar changes in genes and miRNAs expression compared to chemosensitive cells. Additionally, it was also observed a good prognostic in triple-negative breast cancer patients receiving anthracycline-taxane-based neoadjuvant chemotherapy.

In the last years, miRNAs have also been indicated to act on CSCs, which are resistant to many conventional cancer therapies. Some studies have demonstrated the role of miRNAs in determining breast CSCs phenotype [63-65]. For instance, the miRNA let-7 has an important role in self-renewal and the undifferentiated state maintaining of breast CSCs [66], while miR-200 inhibits *BMI1* expression, playing a fundamental role in EMT and CSCs regulation. In breast cancer patients, miR-200 is repressed, which leads to *BMI1* activation and EMT process deregulation [63]. Another study showed

that miR-140 is dysregulated in breast tumor cells and contributes to CSCs formation, by targeting *SOX9* and *ALDH1* [67].

Therefore, miRNAs are proposed as potential novel biomarkers as well as therapeutic targets in new anti-cancer strategies based on CSCs mechanisms. To expand this idea, a very recent study employed next generation sequencing in order to compare the miRNA profiles of CSCs cells against parental cells. It was observed that several miRNAs (miR-4492, miR-4532, miR-381, miR-4508, miR-4448, miR-1296, and miR-365a) have strong association with breast cancer chemoresistance and self-renewal capability [68]. These miRNAs were responsible for tumor growth, migration, and invasion, oncogenic properties, and progression [69-71]. This finding suggests that the phenotypic behavior of breast CSCs may be regulated by miRNAs (**Table 1**).

Exososomes transmit chemoresistance to breast cancer cells

The interaction with local microenvironment is an important factor in breast cancer therapy. The communication of tumor cells with their microenvironment plays a key role in the development and progression of cancer, since these cells can access the oxygen and nutrients to support tumor growth. Furthermore, the tumor microenvironment composed by exosomes may enable the communication of a tumor cell with the neighboring cell, and thus promote invasion and migration [72].

Exosomes are small, lipid bilayer membrane vesicles of endocytic origin about 30-100 nm in diameter [73]. These microvesicles may be released by various cell types, including tumor cells, erythrocytes, lymphocytes, platelets, dendritic cells, adipocytes, and CSCs [74, 75]. The exosomes contains RNAs, miRNAs and proteins, which can be transferred from one cell to another [76]. This molecular transfer is extremely important, since it acts as a regulator of diverse cellular processes, helping us to understand the complexity of tumor progression and its therapy. Indeed, several studies have indicated that exosomes play important role in tumorigenesis, growth cell, progression, metastasis, and drug resistance [77-79]. The exosomal contents may vary according pathological conditions and original cell type. To date, 4563 proteins, 1639 mRNAs, and 764 miRNAs have been identified in exosomes from different species and tissues by independent examinations [77].

Although the mechanism by which the exosomes transfers RNA, miRNA and proteins is not completely understood, it has been suggested that it occurs by the plasmatic membrane fusion probably through acidic microenvironment [80]. Since these molecules can be found in body fluids, they can also be used as potential biomarkers for certain breast cancer subtypes and thereby drive the treatment response. For instance, saliva is used as a non-invasive method to detect cancers at an early stage, including breast [81]. Exosomes derived from breast cancer can interact with salivary gland cells and lead to secretion of salivary biomarkers, thus, the monitoring the miRNA, mRNA and protein expressions of salivary biomarkers among persons at high risk of breast cancer may serve as a promising tool for breast cancer detection.

Emerging evidence indicates that CSCs may contribute to breast cancer drug-resistance. Interestingly, the exosomes released from CSCs could “carry” this chemoresistance to tumor cells. Similarly, the exosomes released by tumor cells could increase the CSCs formation and contribute to the aggressiveness of the disease [82]. Some researchers have recently demonstrated that exosomes may contribute to tumor development by acting as a modulator of the balance between CSCs and parental cells [83, 84].

Specific cells-derived exosomes can transfer multi-drug resistance-associated proteins and miRNAs to target cells [85] and through drug packaging and exportation [86]. Moreover, exosomes may counteract the outcome of antibody drugs by modulating their binding to tumor cells [87]. For instance, the exosomes release from *HER2*-overexpressing breast cancer cells can bind to *HER2* antibody trastuzumab to inhibit its activity [88]. In an *in vitro* study, Lv et al [89] demonstrated that docetaxel resistance could be acquired by delivery of P-gp via exosomes. In a complementary way, others studies have showed that drug-resistant breast cancer cells can deliver miRNAs to sensitive ones by releasing exosomes [10, 90]. Indeed, the delivery of miR-222 via exosomes was shown as a

potential mechanism of adriamycin resistance in breast cancer cells [91].

Conclusion and future perspectives

Chemotherapeutic resistance, either intrinsic or acquired, results in poor prognosis in cancer patients. Identifying the individual causes underlying chemoresistance might guide a more appropriate therapy for each patient. Fortunately, the genetic content present in circulating blood can provide clues and help to change this scenario. Further studies evaluating the mechanisms of miRNAs transfer that regulate chemoresistance among tumor cells and CSCs, is indispensable during chemotherapy. This new knowledge might prevent chemoresistance and provide the key target for development of innovative therapeutic strategies.

It has been shown that CSCs have higher migration ability, metastasis, treatment resistance and disease recurrence. In the last years, miRNAs have been associated with CSCs maintenance, which might lead to drug-resistance to the most conventional cancer therapies. Therefore, miRNAs are proposed to be potential novel biomarkers, as well as therapeutic targets in new anti-cancer strategies. Some miRNAs expressed in CSCs are responsible for tumor growth, migration, invasion and treatment response, suggesting that the phenotypic behavior of breast CSCs may be regulated by such miRNAs. In this context, the miRNAs transfer from CSCs to other cells play important role in tumorigenesis, and drug resistance. This process can be mediated by exosomes, found in body fluids, and can be used as biomarkers for certain breast cancer subtypes and thereby drive the treatment response. Thus, monitoring these biomarkers among high-risk breast cancer patients might serve as a promising tool for breast cancer drug resistance determination. However, so far, there is a big barrier between current knowledge of a full drug sensitivity prediction. A reasonable approach is to consider the individual determinants that govern chemoresistance to roll back the cancer recurrence and increase the patient lifespan.

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Disclosure of conflict of interest

None.

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