

THE ROLE OF MICRORNA-200C IN CHEMORESISTANT BREAST CANCER

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ABSTRACT

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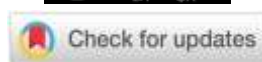
Breast Cancer,
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Abstract:

Breast cancer is a non-communicable diseases and also major health problem in the world. Based on data from WHO in 2012, the incidence of breast cancer reported as 1.67 million cases. One cause of highest morbidity and mortality in breast cancer is chemoresistance. Many pathways could cause chemoresistant in breast cancer. The one of pathways are from genetic such as miR-200c. Base on the other study, mir-200c act an apoptosis inducer and inhibit metastasis in chemoresistant breast cancer cells. The mir-200c act the role in specific target cells in chemoresistant breast cancer. Meanwhile, the expression of miR-200c induces Mesenchymal Epithelial Transition (MET) by inhibits ZEB 1 or 2 and TGF- β 2 as anti-metastases in chemoresistant breast cancer. miR-200c has a promising potential as a new treatment for chemoresistant breast cancer, because of its potent pro-apoptotic and anti-metastatic properties.

Abstrak:

Kanker payudara adalah penyakit tidak menular dan juga menjadi masalah kesehatan utama di dunia. Berdasarkan data WHO pada 2012, kejadian kanker payudara dilaporkan sebanyak 1,67 juta kasus. Salah satu penyebab morbiditas dan mortalitas tertinggi pada kanker payudara adalah chemoresistance. Banyak jalur dapat menyebabkan chemoresistant pada kanker payudara. Salah satu jalur berasal dari genetik seperti miR-200c. Berdasarkan penelitian lain, mir-200c bertindak sebagai penginduksi apoptosis dan menghambat metastasis dalam sel kanker payudara yang resisten terhadap chemoresistant. Mir-200c berperan dalam sel target spesifik pada kanker payudara yang chemoresistant. Sementara itu, ekspresi miR-200c menginduksi Mesenchymal Epithelial Transition (MET) dengan menghambat ZEB 1 atau 2 dan TGF- β 2 sebagai anti-metastasis pada kanker payudara tahan chemores. miR-200c memiliki potensi yang menjanjikan sebagai pengobatan baru untuk kanker payudara tahan chemores, karena sifat pro-apoptosis dan anti-metastasis yang kuat.



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INTRODUCTION

Breast cancer, including non-communicable diseases and also major health problem in the world. The prevalence of breast cancer has a high morbidity and mortalities after cervical cancer [1]. According to statistics of the World Health Organization (WHO) in 2012 [2], breast cancer incidence occurred as many as 1,67 million with a mortality rate of 90% at an advanced stage or metastasis. Based on data from the International Agency for Research on Cancer (IARC) in 2012 [3], breast cancer incidence of 40 per 100.000 women. The pathogenesis of breast cancer can occur by various factors. The highest proportion of breast cancer in gene mutation on BCRA 1 and 2 are 85%, while 15% occurred in HER2+, estrogen receptor (ER) and going triple negative breast cancer (TNBC) [2]. Based on these risk factors, may lead to the risk of chemoresistant breast cancer [4] [5].

Based on these risk factors, preventive efforts are needed on the incidence of chemoresistant breast cancer. One of them with surgery and combination chemotherapy efforts in order to induce apoptosis in chemoresistant cancer cells. However, previous studies showed results that prevention efforts are less significant in reducing the incidence of chemoresistant breast cancer. Due to the often-reported cases of breast cancer after an advanced stage like stage 3, 4 or circumstances have metastasis [6]. It is a risk factor to the increased incidence of chemoresistant breast cancer. Based on these issues often cause difficulties in chemoresistant breast cancer therapy. Amounting to 90% of breast cancer incidence chemoresistant occurred despite prior chemotherapy [5]–[7].

Therapy used in the treatment of breast cancer with a combination chemoresistant therapy the results to improve the effectiveness and sensitivity of chemotherapy. However, previous studies showed no significant effects occur in

inducing apoptosis in chemoresistant breast cancer cells [8]. In addition, the side effects of combination chemotherapy are not a positive impact on patients [9] [10]. It is necessary modalities to minimize side effects and improve quality of holistic therapy as effort chemoresistant breast cancer management.

The latest study was currently in the management of chemoresistant breast cancer switched to therapeutic use [6]. One of them is a microRNA (microRNA), which has the potential to inhibit the pathogenesis of cancer. MicroRNA is short RNA, one of which miR-200c which has a function to regulate the proliferation, apoptosis, angiogenesis, metastasis and invasion of cancer cells and chemoresistant [11]. The role of specific miR-200c can be an effective therapy in the management of chemoresistant breast cancer [12]. Based on the results of Chen *et al* [11]. That miR-200c have the potential to increase the sensitivity of the target cells with chemotherapy. Also supported by studies that show the expression of miR-200c can increase sensitivity to chemotherapy doxorubicin in chemoresistant breast cancer. Moreover, the expression of miR-200c can be as anti-metastasis of chemoresistant breast cancer cells [13] [14].

Seeing the overall potential of miR-200c, it could be the major marker in the management of chemoresistant breast cancer. Thus, the potential of miR-200c could be an innovation breakthrough therapy for treatment of chemoresistant breast cancer. Thus, it is necessary to further discuss the modalities specifically, so as to provide a bright prospect in the development of related sciences chemoresistant breast cancer management.

DISCUSSION

miR-200 Family

miRs are short, non-coding RNA molecules that function to regulate gene expression at the post-transcriptional level

by binding complimentary 3' untranslated region (3' UTR) sequences of target mRNAs, thereby repressing gene expression. miRs were first reported in the 1990s as regulatory sequences involved in *C. elegans* development, however, they have since been further characterized as gene-repression elements that affect gene-expression profiles in more than 100 animal species [15].

The majority of miRs are encoded within intron regions of genomes, and are transcribed by RNA polymerase II into primary transcripts referred to as pri-miRs. In the canonical miR pathway, pri-miRs are cleaved by an RNAase III-Drosha complex in order to yield pre-miRs. Alternatively, miR transcripts called mirtrons are produced independently of the RNAase III-Drosha complex [16]. Pre-miRs and mirtrons are transported from the nucleus by exportin 5 into the cytoplasm and processed by Dicer into short (± 22 nucleotides), double-stranded miR/miR molecules that subsequently form an RNA-induced silencing complex (RISC) with Argonaute and other proteins. In the RISC complex, one strand of the miR duplex functions to bind complementary sequences in the 3'UTR and thereby repress target genes, while the other strand is degraded [17]. miRs are regulated in part by RNA-binding proteins that help determine the context in which miRs are available for target-gene repression [18]. Because miRs have been shown to target many important signaling proteins and transcription factors that govern immune processes and differentiation, it is not surprising that these molecules have important roles during immune responses to microbial infections, including those that affect the CNS [19].

Infection of the CNS results in significant changes in miR expression profiles, many of which facilitate various aspects of immune processes [17] [18]. It should be noted that there is a growing body of literature that discusses miRs encoded by viruses that influence viral

pathogenesis, however, they are beyond the scope of this review. One miR that has gained considerable attention in recent years is mammalian-encoded miR-200 family which numerous reports have implicated in regulating metastatic cells. Here we provide a discussion of several examples in which miR-200c during chemoresistant in breast cancer [20].

The miR-200 family was first discovered to directly target and down-regulate the E-cadherin transcriptional repressors ZEB1 and ZEB2, leading to restoration of an epithelial phenotype in breast cancer cell lines, characterized by an increase in E-cadherin expression, and decreased migration and invasion [14]. Expression of the miR-200 family correlates with an epithelial-like phenotype in the National Cancer Institute (NCI) panel of 60 cancer cell lines, and suppresses EMT in several additional cancer models, including bladder, colorectal and lung. Although genes encoding ZEB1/2 are the best-studied targets of the miR-200 family, the small consensus binding sequence of miRs results in many bioinformatically predicted targets [14] [21].

Resistance to chemotherapy is a critical aspect of tumorigenesis also associated with acquisition of an EMT phenotype [22]. The miR-200 family has been found to be involved in maintaining sensitivity to two classes of chemotherapeutics to date, microtubule targeting agents, and DNA damaging drugs [23]. Indeed, miR-200 expression correlates with sensitivity to EGFR blocking agents in bladder cancer, and restoration of miR-200 family members increased sensitivity to EGFR inhibitors in mesenchymal-like cell lines [24].

The miR-200 family has now been confirmed to directly target other genes involved in various aspects of EMT [25]. One aspect of EMT that has been particularly well studied is the increase in migratory and invasive capacity. Targeting and repression of the genes encoding

ZEB1/2 by miR-200c and the resultant increase in E-cadherin decreases migration and invasion [25] [26].

Regulation of miR-200c

The epithelial mesenchymal transition (EMT) program is key to cancer progression and metastasis and has been linked to generation of CSCs [27]. Our previous work has shown that tumor suppressor p53 plays a role in regulating both EMT and EMT-associated breast CSCs through transcriptional activation of microRNAs involved in regulation of stemness, including miR-200c (miR-200c) [28]. Functional (wild-type) p53 trans activates miR-200c through direct binding to the miR-200c promoter, and loss of p53 in mammary epithelial cells leads to decreased expression of miR-200c and activates EMT program, accompanied by increased CSC-like population [27] [28].

Re-expressing miR-200c suppresses genes that mediate EMT and stemness properties and thereby reverts the mesenchymal and CSC-like phenotype caused by loss/mutation of p53 to a differentiated epithelial cell-like phenotype [29]. Notably, studies have shown that miR200c is the most down-regulated miR in the normal and neoplastic stem cell populations compared with the non-stem cell populations [30]. Furthermore, miR-200c plays an integral and active role in the maintenance of differentiated epithelia to antagonize tumorigenesis by silence a cohort of targeted genes and non-coding RNAs involved in regulation of cell differentiation and epithelial homeostasis, including miR-200c [31]. Down-regulation of miR-200c by activated leptin-STAT3-G9a signaling promotes the gain of EMT-CSC traits to expand a subset of highly tumorigenic breast CSCs enriched by the cell surface marker leptin receptor [13].

In contrast, inhibition of STAT3 restores the expression of miR200c, which in turn converts the CSC phenotype to a differentiated epithelial phenotype [13] [31].

Consistently, STAT3 inhibitor treatment significantly suppresses the CSC-like population and abrogates tumor progression of a diet-induced obesity rat model of breast cancer [32].

Together, these studies elucidate critical and sophisticated roles of intrinsic mutation and extrinsic influence (e.g. increased adiposity) in directing EMT-MET (*Mesenchymal Epithelial Transition*) and stemness-differentiation plasticity through regulation of miR-200c expression during tumorigenesis [28] [30]. The results further reveal novel therapeutic implications of reactivation of p53 or inhibition of STAT3 in restoration of miR-200c to eliminate the CSC pool and thereby prevents breast cancer progression / recurrence [29] [31] [33]. miR-200c also targets stem cell factors such as BMI1, and downregulation of miR-200c was shown to be characteristic of breast cancer stem cells and DNA methylation was found to be the cause of the repression in breast cancer stem cell like populations [34].

A natural compound, resveratrol, is increasing the activity of Ago2 and as a result inhibiting breast cancer stem cell-like characteristics by increasing the activity of tumor suppressor miRs including miR-200c [35]. Furthermore, miR microarray analysis revealed that miR-200c is downregulated in breast cancer cells with acquired resistance to cisplatin. It was also found to be downregulated in doxorubicin resistant MCF-7 and BT474 breast cancer cells [36]. It was also associated with trastuzumab resistance, which was found to be reverse by upregulation of miR-200c through the blockage of TGF- β signaling [22] [28].

miR-200c is also associated with increase in radio-sensitivity in breast cancer cells by inhibiting cell proliferation, and by increasing apoptosis and DNA double-strand breaks. TBK1 was found to be a direct target of miR-200c and its down regulation by miR-200c is partially responsible for increased apoptosis [22] [30] [31].

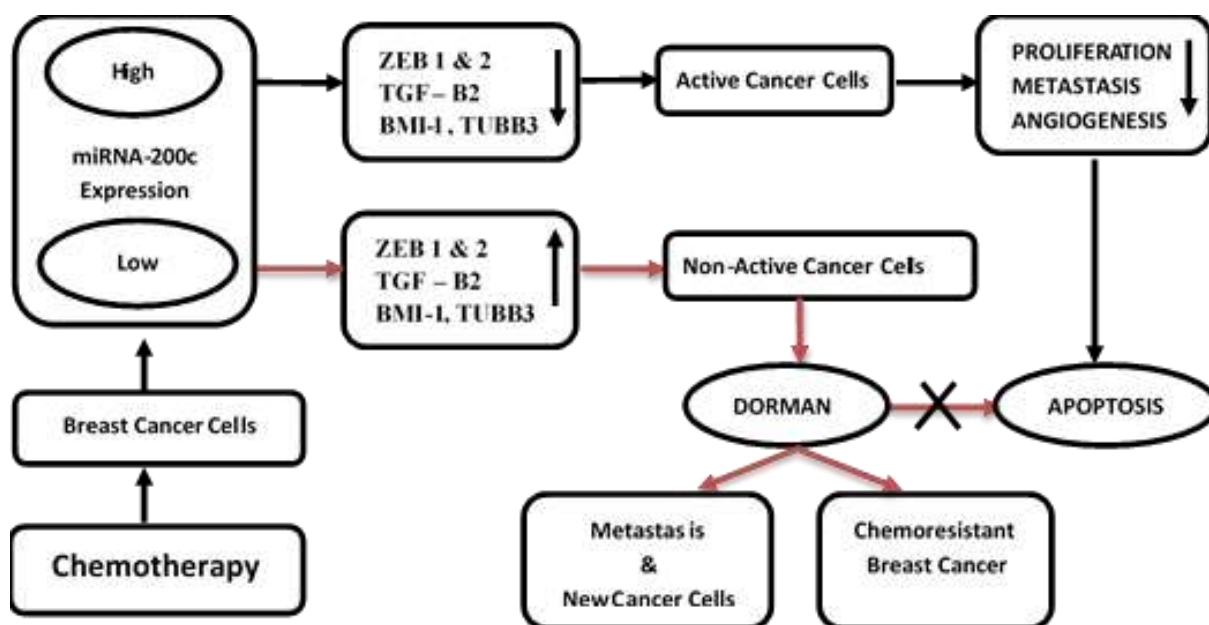


Figure 1. Scheme of the role of miRNA-200c in the Pathogenesis of Chemoresistant Breast Cancer. Redline: Chemoresistant Breast Cancer Pathways.

The Role of miR-200c in Chemoresistant Breast Cancer

Chemoresistant breast cancer is a condition in breast cancer cells that are resistant to chemotherapy and surgery [4] [19]. Breast cancer chemotherapy chemoresistant cause ineffective in inducing apoptosis in cancer cells [6]. This chemoresistant can induce the return of breast cancer although it has been done before surgery and chemotherapy [20]. In the development of breast cancer cells, there are two types of cancer cells that are active proliferation of cancer cells and cancer cells dormant (inactive proliferation) [4] [6] [20].

Breast cancer cells that actively can be targeted chemotherapy, whereas cancer cells dormant can not be a therapeutic target due to not proliferation [19] [20]. This causes breast cancer cells dormant cells. Dormant cells in chemoresistant breast cancer fusiform shape that can metastasize or remain silent on the location [14].

Chemoresistant breast cancer also affected by the missing or reduced regulation of miR-200c. Research from Yohei et al [8], shows down-regulation of miR-200c by increasing TGF- β 2 that form dormant cancer cells Will trigger

chemoresistancy. Supported also by the results of research Zhang Jinsong and Li Ma [17], that decreased expression of miR-200c affect TGF- β 2 in shaping the EMT (Epithelial Mesenchymal Transition) in chemoresistant breast cancer cells. In addition, the loss of miR-200c also because it is not the activation of p53 which will lead to increased regulation ZEB 1 or 2, causing activation of EMT formed dormant cells [22]. The formation of these dormant cells will be occurrence of chemoresistant breast cancer [21] [22].

Decreased miR-200c levels are correlated with clinical stage, local relapse, distant metastasis and poor clinical outcomes. A. Low levels of miR-200c correlated with shorter survival. OS curves for 134 studied patients with high or low miR200c expression. B. DFS curves for 134 studied patients with high or low miR-200c expresión [35].

BMI-1 can induce dormant cells resulting changes dormant cells became fusiform shape [15]. These dormant cells fusiform shape and form will be metastasis of cancer cells [6] [15] [35]. Emphasis on FOG2 can affect a decrease in cell proliferation or division cycle becomes active with an emphasis on cancer cells

[23]. The increase in the activation of dormant cells TUBB3 cause can be chemoresistant due to decreased sensitivity to chemotherapy drugs and metastasis in chemoresistant breast cancer cells dormant [5] [6] [23]. The increase TUBB3 also causes frequent recurrence in breast cancer as well as the formation of new cancer due to metastasis of breast cancer such as liver, lung, brain, and other vital organs in the body [22] [23].

A double-negative feedback loop between ZEB family transcription factors and the miR-200 family was shown to regulate EMT in different cell systems, including breast cancer cells [36]. Moreover, expression of miR-200c was revealed to be activated by p53, resulting in induction of EMT in mammary epithelial cells upon loss of p53 [37]. Loss of p53 was positively correlated with expression of ZEB1 and negatively correlated with expression of miR-200c and E-Cadherin in 106 breast tumor specimens [38] [39].

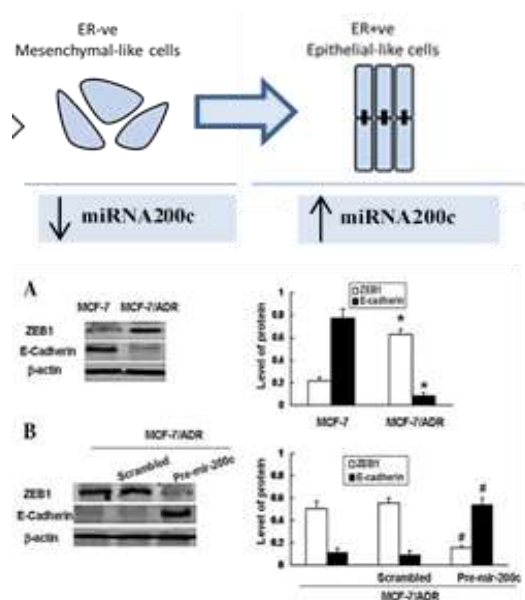


Figure 2. Potential of miRNA-200c in forming MET through ZEB1 or ZEB2 suppression as a therapy for chemoresistant breast cancer cells [8] [11] [25] [36] [40].

miR microarray analysis of 43 primary tumors (10 colon, 10 bladder, 13 breast and 10 lung cancers) and matched lymph node metastases revealed that miR-200c and other miR-200 family members are downregulated in metastases compared to primary tumors [39].

Moreover, miR-200c and other miR-200 family members were shown to be underexpressed in the aggressive claudin-low subtype of breast cancer, which displays an EMT-like gene expression signatura [41]. In contrast, luminal breast cancers, which have a more epithelial-like phenotype and a better clinical prognosis, express high levels of miR-200c [42]. Besides ZEB family, miR-200c can modify metastasis by targeting HMGB1, ZNF217 and a truncated form of VEGFR-1 [13]. miR-200c was also found to be an inhibitor of tumor progression and therapy resistance by targeting KRAS and ZNF217 [43].

Re-expression of the miR-200 family in aggressive breast cancer cells was shown to inhibit experimental lung metastasis and decreased expression of it is associated with lymph node metastases in triple negative breast cancer [11] [44] [45]. In contrast, another study reported that miR-200c is upregulated in breast cancer patients with lymph node metastasis [46] [47]. It was also shown to promote colonization of breast cancer cells [48].

The level of miR-200c was also found to be high in patients with various cancers including breast cancer that develop poly-metastases and it was reasoned that miR-200c is aiding colonization in the late stages of metastasis by reverting EMT [49]. In in vitro assays, miR-200c suppresses migration and invasion of breast cancer cells through various mechanisms, including targeting of ZEB1/ZEB2, PLCG1, myosin and fibronectin [40].

CONCLUSION

Has done numerous studies both in vitro showed that the miR-200c has a unique role of chemoresistant breast cancer. Based on the results of a literature review, miR-200c has the potential to be applied in the treatment of breast cancer management of chemoresistant. Also visible from the benefits of the miR-200c are easily available and have few side effects of drugs in the treatment of chemoresistant breast cancer. Expected with miR-200c can reduce the occurrence of chemoresistant breast cancer. Thus, miR-200c could be therapeutic for the treatment of breast cancer in the future.

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