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The role of oncomiRs in the pathogenesis of breast cancer: A review

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ABSTRACT

Intoduction: The discovery of MicroRNAs (miRNAs), an extensive family of small nonprotein-coding RNAs, provided an exciting era in cancer research and recent findings have prompted us to revise the traditional concept of cancer. Deregulated miRNAs expression influences biological events leading to cancer such as proliferation, differentiation, metastasis and apoptosis. The expression of oncogenic miRNAs (oncomiRs) is markedly upregulated in various types of malignancy. Increased level of oncomiRs suppresses the expression of tumor-suppressor genes which involved in cell proliferation, DNA repair, apoptosis and metastasis. Here, we reviewed the current literatures to elucidate mechanisms by which upregulated oncomiRs expression contribute in pathogenesis of breast cancer. Better understanding of these mechanisms will surely open new avenues for early detection of breast cancer, as well as for the development of novel prevention and treatment strategies.

Key words: MicroRNAs, Oncogenic miRNAs, OncomiRs, Breast cancer

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Introduction:

Breast cancer, accounting for 23 % of the total cancer cases, is the most common malignancy among women [1, 2]. According to Cancer Facts and Figures, by the American Cancer Society, in 2015, 231,840 estimated new cases of breast cancer will be diagnosed, and 40,290 deaths will occur [3]. In spite of remarkable progressions in detection, diagnosis and treatment strategies, breast cancer still ranks 2nd as the leading cause of cancer-related deaths in women in the United State [3]. In the last decades, widespread researches have been conducted to disclose the molecular mechanisms which involved in development and progression of breast cancer. Although, these investigations have been unearthed more clues of the breast cancer nature which may be lead us towards treatment of cancer and introduce anticancer drugs, the most puzzling facets of breast cancer are still remained enigmatic.

To date, various oncogene and tumor suppressor genes have been identified that play fundamental roles in transforming healthy breast cells into tumor cells [4, 5]. Recently, a class of short, non-coding~22-23 nucleotide RNAs, microRNAs (miRNAs), has been identified that brought a new insight into the pathogenesis of breast cancer [6]. MiRNAs delicately regulate the expression of protein-coding genes at the post-transcriptional level through targeting mRNAs in a sequence-specific manner by triggering translational repression or, more commonly, degradation of the mRNAs [7, 8]. MiRNAs negatively regulate their targets in one of two ways depending on the degree of complementarity between the miRNA and the target [9]. The perfect or nearly perfect complementarity between miRNA and target results in mRNA degradation, while incomplete complementarity causes translation repression [8, 9]. Up to now, more than 700 human miRNAs have been published in the miRBase database (http://www.microrna.sanger.ac.uk/sequences/) [10]. It has been suggested that miRNA account for 1-5 % of the human genome and fine-tune more than onethird of protein-coding genes in mammals [10]. The miRNA binding sites were mapped to 3′ UTR (46 %), coding region (50 %) and 5′ UTR (4 %) of the target mRNAs [9, 10]. Transcripts targeted by miRNAs are involved in a wide variety of biological processes such as chromatin structure remodeling, genome rearrangement, DNA repair, cell cycle progression and cell programmed death [11]. Over the past several years it has become clear that altered miRNA expression contributes to development and progression of various human malignancies especially breast cancer [12, 13].

The aim of this review is briefly to describe miRNA biogenesis and focused on mechanistic role of oncogenic miRNAs deregulation in pathogenesis of breast cancer.

MiRNAs and cancer

Owing to the critical role of miRNAs in various biological processes, it is therefore not surprising that altered miRNAs expression contributes to development and progression of cancers. The first evidence of link between miRNAs and cancer derived from studies on chronic lymphocytic leukemia (CLL),

OncomiRs and breast cancer

Upregulation of oncomiRs promote tumor development and progression by negatively inhibiting tumor suppressor genes and/or genes that regulate cell proliferation or programed cell death. The following miRNAs have been shown to function as oncogenes in breast cancer (see Table 1).

Table 1: Oncogenic miRNAs in breast cancer

OncomiRs	Suggested targets	Reference
miR-21	Programmed cell death 4 (PDCD4)	[25]
	Tropomyosin 1 (TPM1)	[27]
	Tissue inhibitor of metalloproteases 3 (TIMP3)	[28]
miR-27a	Zinc Finger and BTB Domain Containing 10 (ZBTB10)	[32]
mir-10b	Homeobox protein Hox-D10 (HOXD10) E-cadherin	[38] [37, 39]
miR-155	Suppressor of cytokine signaling 1 (SOCS1)	[47]
	Signal transducer and activator of transcription 3 (STAT3) RhoA	[47] [48]
miR-17-5p	HMG box-containing protein 1 (HBP1)	[49]
	Programmed cell death 4 (PDCD4)	[50]
	Phosphatase and tensin homolog (PTEN)	[50]

particularly in an attempt to identify tumor suppress at chromosome 13q14 that frequently deleted in CLL [15]. Thanks to highthroughput profiling techniques, the aberrant miRNA expression profiles have subsequently been documented in various types of malignancies [16-19]. Although, miRNAs have been revealed to be both down- as well as up-regulated in cancerous cells as compared with non-neoplastic tissues, it is widely believed that the miRNAome globally downregulated during cell transformation and tumorigenesis [13]. The aberrant expression of miRNAome may be stems from chromosomal instability, epigenetic alterations, genomic mutations, polymorphisms and altered expression or function of the miRNA biogenesis machinery components in tumor cells [20, 21]. The predicted targets for the differently expressed miRNAs suggest that miRNAs could serve functionally as ‘‘oncogenes’’ or ‘‘tumour suppressor’’ genes [13, 20].

MiRNAs and breast cancer

In breast cancer, at least thirty miRNAs have been identified that play different roles in oncogenesis, tumor-suppression and metastasis. Accordingly, these miRNAs subdivided in two main categories: oncogenic (oncomiR) and tumor-suppressor (mirsupp) miRNAs [22, 23]. It should be noted that some miRNAs may have dual functions as both tumor suppressors and oncogenes, depending on tumor type [13, 20]. Here, we focused on mechanistic role of oncogenic miRNAs deregulation in pathogenesis of breast cancer.

miR-21:

One well-established oncomiR found in breast cancer is miR-21. Yan et al. reported that overexpression of miR-21 is correlated with advanced tumor stage, lymph node metastasis, and poor survival of the patients in breast cancer [24].

MiR-21 promotes cell transformation by translational repression of the tumor suppressor programmed cell death 4 (Pdcd4) gene [25]. In breast cancer, Her2/neu-positive cells represent a downregulation of Pdcd4 by overexpression of miR21 [26]. The tumor suppressor gene tropomyosin 1 (TPM1), as a target of miR-21, plays fundamental role in cell migration. Zhu et al. found that suppression of mir-21 in metastatic breast cancer MDA-MB-231 cells significantly reduced invasion and metastasis [27]. Song et al. revealed that tissue inhibitor of metalloproteases 3 (Timp3) expression is inversely correlated with miR-21 in breast cancer. Therefore, upregulation of miR-21 could promote invasion in breast cancer cells [28].

miR-27a

MiR-27a regulates cell growth and division in a dose-dependent manner and the expression of miR27a is markedly upregulated in breast cancer [29, 30]. Upregulated expression of miR-27a promotes tumor growth and metastasis, and is associated with poor overall survival in patients with breast cancer [30, 31]. In breast cancer, miR-27a also play vital role in the apoptotic response and cell cycle checkpoints through negative impact at the G1 to S phase transition [32- 34]. High miR-27a expression in breast cancer cells contributes to overexpression of transcription factor specificity protein by directly suppressing Zinc Finger and BTB Domain Containing 10 (ZBTB10) expression [32]. ZBTB10 mediated inhibition of the vascular endothelial growth factor (VEGF) and survivin expression which involved in angiogenesis and metastasis of breast cancer [35]. Surprisingly, VEGF promotes the transcription of miR-27a by enhancing RUNX1 binding to miR-27a promoter [36]. Tang et al concluded that miR-27a induces angiogenesis by mediating endothelial differentiation of breast cancer stem like cells [36].

mir-10b

It has been reported that the overexpression of miR-10b positively correlated with tumor size, pathological grading, clinical staging, lymph node metastasis, Her2-positivity and tumor proliferation in breast cancer [37]. Ma et al. demonstrated that high miR-10b expression initiates invasion and metastasis in breast cancer cells [38]. The miR-10b gene is a target for the transcription factor Twist, which is highly expressed in metastatic breast cancer cells. The miR-10b induced by Twist suppresses translation of the mRNA encoding HOXD10, which in turn led to increased expression of the prometastatic RhoA/RhoC gene, Rho kinase activation and tumour cell invasion [38]. Epithelialmesenchymal transition (EMT), an important process in the tumor metastasis, is determined by the loss of cell-cell adhesions, and is induced by transforming growth factor-β (TGF-β) [39]. TGF-β1 increases the expression of miR-10b, which modulates breast cancer metastasis through Ecadherin downregulation [37, 39].

miR-155

A growing list of reports demonstrated that miR155 is upregulated in human breast cancer, and is associated with higher tumour grade, advanced tumour stage, lymph node metastasis, and high mortality rate[40- 43]. The expression of miR-155 is upregulated in human breast tumors with BRCA1 mutation [41]. Chang et al. found that BRCA1epigenetically controls miR-155 expression through binding of BRCA1 protein and histone deacetylase (HDAC) to the miR-155 promoter [41]. In addition, the promoter region of miR-155 has binding sites for FOXO3a, PBX1 and Sp1 transcription factors which were reported dysregulated in breast cancer [44- 46]. Suppressor of cytokine signaling 1 (SOCS1) gene has recently been identified as a target of miR-155, which led to an induction of proliferation in breast cancer cells [47]. Jiang et al. reported that upregulation of miR155 activates signal transducer and activator of transcription 3 (STAT3) via Janus-activated kinase (JAK) pathway, and acts as a critical factor in the tumorigenesis in breast cancer cells [47]. A study has shown that TGF-β promotes miR-155 expression through Smad4, and downregulated expression of miR-155 suppressed TGF-β-induced EMT, as well as cell migration and invasion by targeting RhoA [48].

miR-17-5p

MiR-17-5p, a members of the miR-17-92 cluster, plays a key role in breast cancer cell invasion and migration by suppressing HMG

box-containing protein 1 (HBP1) and subsequent activation of Wnt/β-catenin pathway [49]. It has been reported that the tumor suppressor proteins programmed cell death 4 (PDCD4) and phosphatase and tensin homolog (PTEN) are downregulated in triple negative breast cancer (TNBC). Upregulation of miR-17-5p inhibit ribosomal translation of tumor suppressor gene mRNAs PDCD4 and PTEN in TNBC [50].

Conclusion:

As discussed earlier, oncomiRs affect the genesis and progression of breast cancer when overexpressed. Therefore, breast cancer carcinogenesis can be controlled by manipulating of oncomiRs. Development of miRNA-based drugs that target specific oncomiRs can be considered as a potential therapeutic approach. However, there is still a significant gap between basic research on miRNAs and clinical application. Hence, further in-depth investigations are required to provide more precise elucidation of the roles, mechanisms, and therapeutic utility of this miRNAs in breast cancer.

Disclosure statement:

No potential conflict of interest was reported by the authors.

Ethical issues

None to disclosure

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