REVIEW; MEDICAL BIOTECHNOLOGY

Expression and function of miR-155 in breast cancer

Jing Liu*a, WenHui Huan*a, HaiXia Yangb and Ying Luoa

aLab of Molecular Genetics of Aging and Tumor, Faculty of Medicine, Kunming University of Science and Technology, Kunming, Yunnan, P.R. China; bOutpatient Department, Municipal Authorities Clinics of Jinan, Jinan, Shandong, P.R. China

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A major problem in the treatment of breast cancer at present is the lack of more sensitive and specific tumour biomarkers. MicroRNAs (miRNAs) were first discovered as important regulators of development in Caenorhabditis elegans, and their functions have been widely investigated. miR-155 is an oncogenic miRNA which has been explored mainly in leukaemia but is also known to play an important role in the progression of breast cancer. There is an accumulating body of evidence about additional roles of miR-155 in the development of breast cancer. In this mini-review, we provide an overview and update of miR-155 expression and its roles in breast cancer. We also attempt to summarize the current understanding of miR-155 regulation networks and speculate on the potential of miR-155 as a putative accessory parameter for diagnosis of breast cancer.

Keywords: miR-155; breast cancer; oncogenic miRNA; target genes

Introduction

MicroRNAs (miRNAs) are small (22–25 nt) non-coding single-stranded RNAs that control the expression of target genes by suppressing translation or inducing the cleavage of target mRNAs.[1,2] miRNAs have been reported to be involved in the control of gene expression and to provide a broad regulatory role in various biological processes, including cancer development, cellular differentiation, proliferation, apoptosis and metabolism.[3–5]. Breast cancer is the most frequently diagnosed cancer with high mortality in females.[6] The incidence of mortality from breast cancer is associated with differences in reproductive and hormonal factors.[7] A major problem in the treatment of breast cancer at present is the lack of more sensitive and specific tumour biomarkers. In the clinic, there are only two markers that are well established and used in breast cancer diagnostics. One is estrogen receptor, the indication of endocrine therapy, and the other is epidermal growth factor receptor-2 (HER-2), which predicts the response to trastuzumab.[8] New biomarkers that can complement and improve the current methods for breast cancer diagnostics are urgently needed. MiRNAs were first discovered as important regulators of development in Caenorhabditis elegans and their functions have been widely investigated. miRNAs, such as miR-155,[9] may be suggested as novel potential diagnostic targets in cancer diagnostics. miR-155, which was first described by Clurman and Hayward in 1989 and reported to be involved in the progression of lymphoma [10], now has more than 400 predicted gene targets,[11] including over 100 confirmed ones. In the light of the sustained upregulation of miR-155 in breast cancer patients, we may hypothesize that miR-155 could be a diagnostic biomarker for breast cancer.

MiRNA and breast cancer

Recent advances in phenotyping and molecular profiling of human cancer have greatly enhanced the molecular mechanisms and diagnosis of breast cancer.[12] However, several problems, including unpredictable risk and resistance to drug treatment, still prevail in the management of breast cancer patients. In the process of carcinogenesis and cancer development, a multitude of transcription factors regulate the expression of miRNAs. At the same time, miRNAs function as regulators of target-gene expression involved in the cancer processes, which suggests that miRNAs could be considered potential biomarkers and therapeutic targets. As miRNAs were first identified as tumour suppressors, several miRNAs, such as miR-21 and miR-155, were revealed to exhibit oncogenic activity in the following years.[13,14] For review, see [15]. Half of the mature human miRNAs have been shown to be associated with cancer genes (reviewed in [16]). For example, miR-196 and miR-10a are located in homeobox clusters which are involved in the development of breast cancer.[17] These studies underline the

*Corresponding author. Email: jingliu1437@163.com

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importance and potential use of miRNAs as breast cancer classifiers and therapeutic targets.

**Biosynthesis of miR-155**

In humans, miR-155 is encoded by gene MIR155HG (also termed the B cell integration cluster, or BIC locus), which is located on chromosome 21. The primary miRNA molecule ( pri-miR-155 ) is processed from the BIC gene RNA transcript. The pri-miR-155 molecule is first cleaved to be a precursor ( pre-miR-155 ) by the Drosha and Pasha miRNA microprocessor in the nucleus. Then, pre-miR-155 is exported to the cytoplasm and transformed to mature miR-155 by the RNase III Dice (reviewed in [18]).

Finally, mature miR-155 is incorporated into a miRNA-induced silencing complex, which binds to the sequences in the 3’-untranslated regions (3’-UTRs) of target mRNAs, including those for some key regulatory proteins such as Ras homolog family member A (RhoA), forkhead box O3A (FOXO3a) and suppressor of cytokine signalling 1 (SOCS1).[19,20] These genes in breast cancer can induce an increase in epithelial to mesenchymal cell transition, cell plasticity, cell survival, growth, chemo-resistance and radio-resistance.[19,20]

**Expression of miR-155 in breast cancer**

Several studies suggest that the expression of miR-155 is upregulated in breast cancer (Table 1). The high level of miR-155 is associated with tumour subtype and high mortality.[34] For example, a study on 29 miRNAs that are deregulated in breast cancer showed that only miR-155 is significantly upregulated,[7] suggesting that miR-155 plays an important role in breast cancer. In another larger study, serum miR-155 was also significantly increased in breast cancer patients compared with healthy ones.[30] A further study also indicated that the level of miR-155 is increased in breast cancer and suggested its potential clinical prognostic value. Higher miR-155 expression in breast cancer has been shown to be significantly associated with higher tumour grade, advanced tumour stage and lymph node metastasis, suggesting its potential as a clinical prognostic value.[35] For a review on circulating miRNAs as biomarkers in breast cancer, see [35].

**Regulation of miR-155 expression in breast cancer**

Breast cancer 1 (BRCA1) is the most remarkable finding related to the role of miR-155 in breast cancer. BRCA1 is encoded by the human breast cancer susceptibility gene BRCA1 and is involved in DNA repair and cell cycle progression.[36] Mutations of BRCA1 are related to increased risk of breast cancer.[37] In a recent study, overexpression of miR-155 in BRCA1 wild-type cells showed a similar phenotype to the mutant, indicating that BRCA1 functions in the control of miR-155.[38] In addition, BRCA1 controls miR-155 expression by regulating the transcription of pri-miR-155.[38] A clinical study demonstrated that miR-155 levels are upregulated in human breast tumours with BRCA1 mutation.[38] This suggests that miR-155 is closely related to BRCA1 and can reinforce the important roles of miR-155 in breast cancer development.

In microarray analyses, the miR-155 promoter has been shown to harbour the binding sequence of some transcription factors which were reported changed in breast cancer, such as FOXO3a, PBX1 and Sp1.[39–41]

| Country | Ethnicity | Samples | Source of controls | Genotyping method | Cases/control | Expression | Year | Reference |
|---------|-----------|---------|-------------------|-------------------|---------------|------------|------|-----------|
| Canada  | Caucasian | Tissues | Healthy people    | TaqMan® density arrays | 34/6          | Up         | 2009 | Hui et al. [21] |
| Germany | Caucasian | Serum   | Healthy people    | Real-time PCR      | 59/29         | Up         | 2010 | Roth et al. [22] |
| China   | Asian     | Tissues | Pericancerous tissues | MicroRNA microarray | 68/40         | Up         | 2010 | Wang et al. [24] |
| China   | Asian     | Tissues | Pericancerous tissues | Real-time PCR      | 45/45         | Up         | 2010 | Zhu et al. [25] |
| China   | Asian     | Tissues | Pericancerous tissues | Real-time PCR      | 45/45         | Up         | 2011 | Zheng et al. [26] |
| China   | Asian     | Serum   | Healthy people    | Real-time PCR      | 20/10         | Up         | 2012 | Liu et al. [27] |
| China   | Asian     | Tissues | Pericancerous tissues | Real-time PCR      | 92/92         | Up         | 2012 | Chen et al. [28] |
| China   | Asian     | Tissues/ | Pericancerous tissues | Real-time PCR      | 67/6767/70    | Up         | 2012 | Lu et al. [29] |
| China   | Asian     | Serum   | Healthy people    | Real-time PCR      | 103/55        | Up         | 2012 | Sun et al. [30] |
| Egypt   | Egyptian  | Tissues | Pericancerous tissues | Real-time PCR      | 40/40         | Up         | 2012 | Hafez et al. [31] |
| Italy   | Caucasian | Tissues | Healthy people    | MicroRNA microarray | 76/34         | Up         | 2005 | Iorio et al. [7] |
| Italy   | Caucasian | Tissues | Healthy people    | MicroRNA microarray | 363/177       | Up         | 2006 | Volinia et al. [32] |
| UK      | Caucasian | Tissues | Healthy people    | MicroRNA microarray | 93/5          | Up         | 2007 | Blenviron et al. [33] |

Note: PCR: Polymerase chain reaction.
indicates that the expression level of miR-155 could be considered one of the typical changes in breast cancer.

**Target genes of miR-155**

The main function of miRNAs is to inhibit their target mRNAs by binding to the 3'UTR of mRNAs and consequently affecting the corresponding cellular processes. Therefore, understanding the role of miR-155 in breast cancer requires the identification of critical miR-155 targets.

Using TargetScan (http://www.targetscan.org/), 440 conserved targets of miR-155 in human genes were identified. Some miR-155 target genes, such as those encoding SOCS1 and FOXO3a, have a confirmed role in breast cancer development. SOCS1 expression is inversely correlated with miR-155 in breast cancer cell lines as well as in a subset of primary breast tumours.[9] Overexpression of miR-155 in breast cancer cells induces the activation of transcription 3 (STAT3) through the Janus-activated kinase pathway, and stimulation of breast cancer cells by the inflammatory cytokines IFN-γ, interleukin-6 and lipopolysaccharide, suggesting that miR-155 may serve as a bridge between inflammation and cancer.[9] FOXO3a is a transcription factor which plays a crucial role in apoptosis and cell growth by regulation of a number of apoptosis/cell growth associated genes, and miR-155 can directly interact with the 3'UTR of FOXO3a and block FOXO3a translation.[19,42,43]

Moreover, a number of target genes of miR-155 are involved in cancer-related pathways such as cell growth and survival (CCND1, GAB3), cell migration and invasion (PAK2, RAB6A), cell adhesion junction (ANKRD6, SMAD2), apoptosis and proliferation.[18,44–46] It is, thus, suggested that miR-155 also affects the development of breast cancer.

Although the knowledge about the expression and function of miR-155 in breast cancer may still be not complete, there appears to be accumulating evidence that miR-155 could be considered a potential therapeutic target and/or, hypothetically, a diagnostic biomarker in breast cancer. Such potential uses of miR-155, however, need further exploration.

**Conclusions**

The present mini-review attempted to summarize, although perhaps not completely comprehensively, the available data on miR-155 expression and function in breast cancer. MiR-155 has been identified as an onco- genic miRNA. It is involved in the control of several signalling pathways, such as cell growth and survival, cell migration and invasion, cell adhesion junction, apoptosis and proliferation. The role of miR-155 in the regulation of human breast cancer suggests great potential for diagnostic and therapeutic strategies in breast cancer. Moreover, much of the underlying roles of miR-155 in breast cancer are still largely unknown and the topic requires further exploration. Further studies of miRNA targets and functions in breast cancer will be required to uncover the relationship between miRNA regulation and breast cancer mechanisms.

**Disclosure statement**

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**References**

[1] Ambros V. MicroRNA pathways in flies and worms: growth, death, fat, stress, and timing. Cell. 2003;113 (6):673–676.
[2] Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136(2):215–233.
[3] Ambros V. The functions of animal microRNAs. Nature. 2004;431(7006):350–355.
[4] Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. Science. 2004;303(5654):83–86.
[5] Xu P, Guo M, Hay BA. MicroRNAs and the regulation of cell death. Trends Genet. 2004;20(12):617–624.
[6] Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.
[7] Iorio MV, Ferracin M, Liu CG, et al. MicroRNA gene expression deregulation in human breast cancer. Cancer Res. 2005;65(16):7065–7070.
[8] Early Breast Cancer Trialists’ Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687–1717.
[9] Jiang S, Zhang HW, Lu MH, et al. MicroRNA-155 functions as an OncomiR in breast cancer by targeting the suppressor of cytokine signaling 1 gene. Cancer Res. 2010;70 (8):3119–3127.
[10] Clurman BE, Hayward WS. Multiple proto-oncogene activations in avian leukosis virus-induced lymphomas: evidence for stage-specific events. Mol Cell Biol. 1989;9 (6):2657–2664.
[11] Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell. 2005;120 (1):15–20.
[12] Heneghan HM, Miller N, Lowery AJ, et al. MicroRNAs as novel biomarkers for breast cancer. J Oncol. 2009;2009:950201.
[13] Volinia S, Galasso M, Costinean S, et al. Reprogramming of miRNA networks in cancer and leukemia. Genome Res. 2010;20(5):589–599.

[14] Costinean S, Zanesi N, Pekarsky Y, et al. Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. Proc Natl Acad Sci USA. 2006;103(18):7024–7029.

[15] Ling H, Fabbri M, Calin GA. MicroRNAs and other non-coding RNAs as targets for anticancer drug development. Nat Rev Drug Discov. 2013;12(11):847–865.

[16] Esquela-Kersch A, Slack FJ. Oncomirs — microRNAs with a role in cancer. Nat Rev Cancer. 2006;6(4):259–269.

[17] Makiya K, Hamada J, Takada M, et al. Aberrant expression of HOX genes in human invasive breast carcinoma. Oncol Rep. 2005;13(4):673–679.

[18] Yang W, Lee DY, Ben-David Y. The roles of microRNAs in tumorigenesis and angiogenesis. Int J Physiol Pathophysiol Pharmacol. 2011;3(2):140–155.

[19] Kong W, He L, Coppola M, et al. MicroRNA-155 regulates cell survival, and chemosensitivity by targeting FOXO3a in breast cancer. J Biol Chem. 2010;285(23):17869–17879.

[20] O’Day E, Lal A. MicroRNAs and their target gene networks in breast cancer. Cancer Res. 2010;70(2):201.

[21] Hui AB, Shi W, Boutros PC, et al. Robust global microRNA profiling with formalin-fixed paraffin-embedded breast cancer tissues. Lab Invest. 2009;89(5):597–606.

[22] Roth C, Rack B, Muller V, et al. Circulating microRNAs as blood-based markers for patients with primary and metastatic breast cancer. Breast Cancer Res. 2010;12(6):R90.

[23] Yan LX, Huang XF, Shao Q, et al. MicroRNA miR-21 overexpression in human breast cancer is associated with advanced clinical stage, lymph node metastasis and patient prognosis. RNA. 2008;14(11):2348–2360.

[24] Wang F, Zheng Z, Guo J, et al. Correlation and quantitation of microRNA aberrant expression in tissues and sera from patients with breast tumor. Gynecol Oncol. 2010;119(3):586–593.

[25] Zhu J, Hu XQ, Guo GL, et al. Expression and its clinical significance of miR-155 in human primary breast cancer. Zhonghua Hu Xi Ke Za Zhi. 2010;48(3):205–208. Chinese.

[26] Zheng SR, Guo GL, Zhang W, et al. Clinical significance of miR-155 expression in breast cancer and effects of miR-155 ASO on cell viability and apoptosis. Oncol Rep. 2012;27(4):1149–1155.

[27] Liu J, Mao Q, Liu Y, et al. Analysis of miR-205 and miR-155 expression in the blood of breast cancer patients. Chin J Cancer Res. 2013;25(1):46–54.

[28] Chen J, Wang BC, Tang JH. Clinical significance of microRNA-155 expression in human breast cancer. J Surg Oncol. 2012;106(3):260–266.

[29] Lu Z, Ye Y, Jiao D, et al. miR-155 and miR-31 are differentially expressed in breast cancer patients and are correlated with the estrogen receptor and progesterone receptor status. Oncol Lett. 2012;4(5):1027–1032.

[30] Sun Y, Wang M, Lin G, et al. Serum microRNA-155 as a potential biomarker to track disease in breast cancer. PLoS One. 2012;7(10):e47003.

[31] Haefez MM, Hassan ZK, Zeki AR, et al. MicroRNAs and metastasis-related gene expression in Egyptian breast cancer patients. Asian Pac J Cancer Prev. 2012;13(2):591–598.

[32] Volinia S, Calin GA, Liu CG, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. Proc Natl Acad Sci USA. 2006;103(7):2257–2261.

[33] Blenkiron C, Goldstein LD, Thorne NP, et al. MicroRNA expression profiling of human breast cancer identifies new markers of tumor subtype. Genome Biol. 2007;8(10):R214.

[34] Mattiske S, Suetani RJ, Neilsen PM, et al. The oncogenic role of miR-155 in breast cancer. Cancer Epidemiol Biomarkers Prev. 2012;21(8):1236–1243.

[35] Cortez MA, Welsh JW, Calin GA. Circulating microRNAs as noninvasive biomarkers in breast cancer. Recent Results Cancer Res. 2012;195:151–161.

[36] O’Donovan PJ, Livingston DM. BRCA1 and BRCA2: breast/ovarian cancer susceptibility gene products and participants in DNA double-strand break repair. Carcinogenesis. 2010;31(6):961–967.

[37] Szabo CI, King MC. Inherited breast and ovarian cancer. Hum Mol Genet. 1995;4(5):1811–1817.

[38] Chang S, Wang RH, Akagi K, et al. Tumor suppressor BRCA1 epigenetically controls oncogenic microRNA-155. Nat Med. 2011;17(10):1275–1282.

[39] Magmani L, Ballantyne EB, Zhang X, et al. PBX1 genomic pioneer function drives ERalpha signaling underlying progression in breast cancer. PLoS Genet. 2011;7(11):e1002368.

[40] Yue L, Li L, Liu F, et al. The oncoprotein HBXIP activates transcriptional coregulatory protein LMO4 via Sp1 to promote proliferation of breast cancer cells. Carcinogenesis. 2013;34(4):927–935.

[41] Zou Y, Tsai WB, Cheng CJ, et al. Forkhead box transcription factor FOXO3a suppresses estrogen-dependent breast cancer cell proliferation and tumorigenesis. Breast Cancer Res. 2008;10(1):R21.

[42] Sunters A, Fernandez de Mattos S, Stahl M, et al. FoxO3a transcriptional regulation of Bim controls apoptosis in paclitaxel-treated breast cancer cell lines. J Biol Chem. 2003;278(50):49795–49805.

[43] Tran H, Brunet A, Grenier JM, et al. DNA repair pathway stimulated by the forkhead transcription factor FOXO3a through the Gadd45 protein. Science. 2002;296(5567):530–534.

[44] Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc. 2009;4(1):44–57.

[45] Huang da W, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. Nucleic Acids Res. 2009;37(1):1–13.

[46] Kong W, Yang H, He L, et al. MicroRNA-155 is regulated by the transforming growth factor beta/Smad pathway and contributes to epithelial cell plasticity by targeting RhoA. Mol Cell Biol. 2008;28(22):6773–6784.