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Original Research

Expression patterns of LncRNA-GAS5 and its target APOBEC3C gene through miR-103 in breast cancer patients

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Abstract: Early diagnosis of breast cancer can increase the survivability of the patients and the patient's quality of life. There is growing evidence demonstrating the active role of LncRNA-GAS5 and miR-103 in cancer biology. APOBEC enzymes are important players in immunity and may contribute to carcinogenesis. Mutation and expression alteration in the APOBEC gene family was found to have a strong correlation with breast cancer risk. This study aimed to evaluate the expression level of lncRNA-GAS5 and its target APOBEC3C in women with breast cancer through expression evaluation of miR-103. Moreover, the interaction between lncRNA-GAS5 and miR-103 was studied. In the present study, forty paired tumor and normal samples classified based on breast cancer subtypes and clinical features of patients were analyzed using gene expression studies. Immunohistochemical analysis of the gene products was performed to classify tumors. The RNA samples were extracted from breast tissue. Real-time PCR was conducted for APOBEC3C and Lnc-RNA GAS5 expression. In addition, miR-103a miScript Primer Assay was utilized for the expression of miR-103-5p. It was revealed that the expression level of APOBEC3C and lncRNA-GAS5 were significantly down-regulated; however, the miRNA-103 expression level was significantly up-regulated. GAS5 expression was positively correlated with APOBEC3C expression and negatively correlated with miR-103 expression. In conclusion, we observed down-regulation of APOBEC3C and LncRNA-GAS5 and up-regulation of miRNA 103 in breast cancer patients. The expression of GAS5 may provide a new potential treatment target for breast cancer. To clarify the role of these molecules in the cellular signaling pathways, further studies are required.

Key words: Breast cancer; APOBEC3C; lncRNA-GAS5; miR-103; Expression analysis.

Introduction

Breast cancer is a leading debilitating and the most common cancer affecting females worldwide that shortens the life span of patients and increases mortality rate (1). Based on histopathological features of the cancer cells, breast cancer can be categorized into different types: Carcinomas, the most common breast cancers type, that occur at the epithelial cells of the breast, and adenocarcinoma that mainly occurs in glandular tissue (2). Females with a family background of breast cancer roughly have two folds increased risk of developing breast cancer compared to women without such a history (3).

Early diagnosis of metastatic cells by molecular methods and/or by radiologic screening will increase the survivability of the patients and increase the patient's quality of life by reducing the toxicity of the prescribed drugs (1,2). Diagnosis at the molecular level targets the basic mechanisms associated with disease development, hence, controlling or destroying these targets is the goal of practitioners and research scientists (1,2). The intriguing part of cancer development is, the time manner fashion, a clone arises from the already differentiated cell due to somatic mutation, somehow, escapes from the immune surveillance mechanisms starting to cell division and proliferation and metastasis, acting like pseudo embryonic totipotent cells which lack differentiation potentials. But this is not always the case, as scattered differentiated tissue fragments can also be found within the proliferated mass (1).

Recently, long non-coding RNAs (lncRNAs), with the ability to control many of the main cellular processes, have gained much attention (4). Several evidences suggested that the lncRNAs abnormal expression may play a crucial role in cancer biology, owing to their function either as proto-oncogenes (e.g., HOTAIR) or as tumor suppressor genes (e.g., GAS5 growth arrest-specific transcript 5) (4,5). Thymoma cell line GAS5 ability to suppress apoptosis has been identified through functional screening in mouse (5). Moreover, many related studies have reported the presence and aberrational expression of GAS5 in several cancers including breast cancer, hepatocellular carcinoma, gastric cancer, bladder cancer and non-small cell lung cancer (NSCLC) (4). However, GAS5's expression and mechanism of function in breast carcinoma have been poorly defined.

In addition, numerous miRNAs have been proven to enhance tumorigenesis through the down-regulation of target genes. Amongst, the miR103 has been found

stimulating breast cancer by changing target gene expression (4,5). Wang et al introduced miR-103 as a potential clinical marker for breast cancer and provided valuable knowledge about the patients ' clinicopathological characteristics. Chen et al, discovered that the bioinformatics study prediction showed the competitive suppression of lncRNA-GAS5 on miR-103 expression (4).

The gene APOBEC3C is a member of the cytidine deaminase genes family. This is one of seven relevant genes or pseudogenes observed on chromosome 22 in a cluster believed to arise from gene duplication. Cluster members encode proteins that are functionally and structurally linked to the cytidine deaminase APOBEC1 editing C to U RNA. The proteins are believed to be RNA editing enzymes and to have functions in the growth or regulation of the cell cycle. The APOBEC gene family was previously identified to perform important functions in the restriction of viruses (6). Recently, mutation and expression alteration in the APOBEC gene family was found to have a strong correlation with breast cancer risk (7); though its regulation is still unclear.

The present study was conducted to evaluate the expression level of lncRNA-GAS5 and its target APOBEC3C in women with breast cancer through expression evaluation of miR-103. Moreover, the interaction between lncRNA-GAS5 and miR-103 was also studied. Furthermore, the interaction between miR-103 and APOBEC3C was predicted computationally. Depending on these findings, we planned for the first time to investigate the potential involvement of GAS5 in breast carcinogenesis and to expose any interaction between GAS5 and APOBEC3C, miR-103 molecules.

Materials and Methods

Specimen collection

The subjects were taken at Hiwa Hospital, Sulaymaniyah, Iraq. A sample of 80 individuals was evaluated. The study provided 40 matched normal and tumor samples of patients categorized by the breast cancer types and the patients ' clinical characteristics including average age and grade. Breast tissue samples were kept in RNA stabilizer solution until further study.

All participants received informed permission, and the study was accepted by the local ethics committee, with an approval number of 02.04.2017/137.

Immunohistochemical analysis

The immunohistochemical experiment of the gene products estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was performed to classify tumors. Immunohistochemical staining was conducted for the antigens using commercial monoclonal antibodies in compliance with the instructions of the manufacturer. Positive staining in C10 percent of tumor cells for ER and PR were described as nuclear staining. HER-2 positivity was dependent on tumor cell proportion, and membrane staining intensity HER-2 immunostaining has been marked positive when high (+++) membrane staining was identified in at least 10% of tumor cells, while 0-++ staining cases were considered negative. Protein expression was managed to score based on the current guidelines of the American Society of Clinical Oncology / American Pathologists ' College (ASCO / CAP).

RNA extraction and cDNA conversion

The RNA samples were extracted from breast tissue using the extraction kit (Bioneer, ExiPrepTM Tissue Full RNA package, Korea) based on the instruction of the manufacturer. Biophotometer (Eppendorf, Germany) was used to quantify and qualify the total concentration of RNA. Then, Ipsogen RT Kit (Qiagen, GmbH, Hilden, Germany) was used to convert APOBEC3C gene expression level mRNA extracted for cDNA measurement. In addition, miScript II RT Kit (Qiagen GmbH, Hilden, Germany) was employed to obtain cDNA of non-coding RNA isolated for mir-103 and Lnc-RNA GAS5 expression analysis. In thermal cycling processes, cDNA was obtained using Mastercycler pro PCR System (Eppendorf, German). Since the quality and quantity of total RNA for all samples were not equal, a variable amount of total RNA was utilized for every individual sample.

Expression analysis

Real-time PCR was conducted using IQ5 RT-PCR device (Biorad, USA) for APOBEC3C expression with both RT2 SYBR Green ROX FAST Mastermix (Qiagen GmbH, Hilden, Germany) and miScript SYBR Green PCR Kit (Qiagen GmbH, Hilden, Germany) for miR-122-5p. The pairs of primers designed for APOBEC3C were used as a housekeeping gene when evaluating exon-exon junction, Lnc-RNA GAS5 and GPDH (Table 1). In addition, miR-103a miScript Primer Assay (Qiagen GmbH, Hilden, Germany) was utilized for the expression of miR-103-5p and RNU6B 13 miScript Primer Assay (Qiagen GmbH, Hilden, Germany) was used as the internal normalization control.

Table 1. Primer sequences, PCR product size of three targets region of APOBEC3C/Exp*, APOBEC3C*/Mut and lncRNA-GAS5 genes, along with their optimum annealing temperature.

primer name	Sequence 5'to 3'	Optimal annealing temperature	PCR product Size
APOBEC3C			
F. Primer	AACCTATGGGAAGCCAACGA	54.2 °C	179 bp
R. Primer	GGAGACAGTATGTCGTCGCA		
LncRNAGAS5			
F. Primer	TGGTTCTGCTCCTGGTAACG	55.3 °C	185 bp
R. Primer	AGGATAACAGGTCTGCCTGC		

Results

Expression result

The mRNA expression rate of the APOBEC3C gene for 40 cancer patients was studied for both normal and cancerous tissues. Every patient's expression level was distinct when compared among normal controls and tumors, as depicted in Figure 1.

APOBEC3C gene expression rate was studied for 40 pairs; tumor, along with its normal control samples. The level of an expression was evaluated by RT-qPCR. It's been founded that the expression quantity of the APOBEC3C gene in tumor samples mRNA, was significantly reduced (down-regulated) compared to normal tissues sample (p= 0.0001, T-test; p > 0.05). Figure 2 reveals the results of mRNA expression in both control and tumors.

The expression levels of 40 cancer patients from normal tissues and tumors were received with LncRNA-GAS5. Each patient's expression showed a distinct pattern as seen in Figure 3.

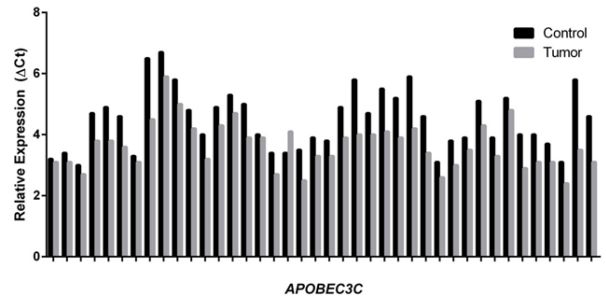

Figure 1. The expression rate of mRNA for both normal controls and tumors according to ΔC_T of *APOBEC3C* gene. The level of mRNA expression in cancerous tissues was decreased compared with normal controls.

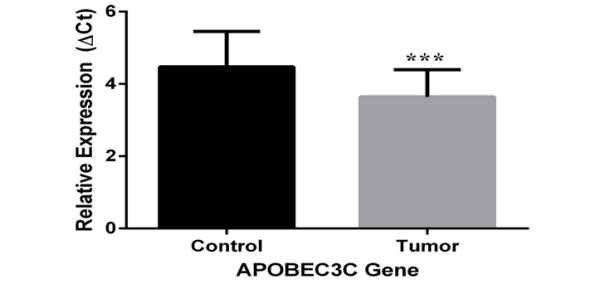

Figure 2. The quantitative rate of mRNA expression of *APOBEC3C* gene for both normal controls and tumors (p=0,0001). The average mean of control samples = 4.473 and tumor = 3.645.a

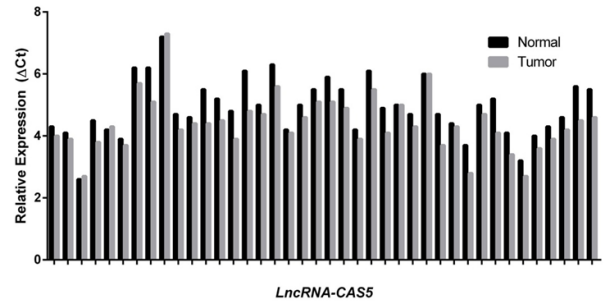

Figure 3. The expression rate of mRNA for both normal controls and tumors according to ΔC_T of LncRNA-GAS5. The level of mRNA expression in cancerous tissues was decreased compared with normal controls.

LncRNA-GAS5 expression was studied for 40 pairs; tumor and its normal counterpart using RT-qPCR. In tumor samples, the quantity of RNA expression for GAS5 was significantly declined compared to the normal sample (p= 0.001, T-test; p > 0.05). Figure 4 shows the statistical results of the GAS5 expression rate for both normal controls and tumors.

The miRNA 103 expression level of 40 patients with cancer was collected from normal tissues and tumors. - Patient's expression level was distinct, the relation of normal controls to tumors is shown in Figure 5.

The miRNA 103 expression was studied for 40 pairs including tumor and normal control samples using RT-qPCR. The MiRNA 103 in tumor tissues has over-expressed (up-regulated) compared to normal tissue samples (p= 0.0001, T-test; p > 0.05). Figure 6 shows the statistical results for MiRNA 103 expression of both normal controls along with cancerous tissues.

In order to determine the impact of lncRNA-GAS5 on breast cancer, the relative expression of lncRNA-GAS5 was evaluated in breast cancer patients' tissues

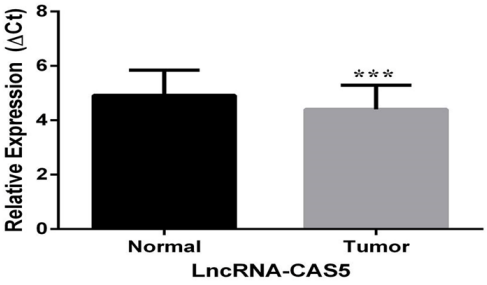

Figure 4. The quantitative rate of mRNA expression of the GAS5 gene for both normal controls and tumors (p=0,001). The average mean of control samples = 4.918 and tumor = 4.403.

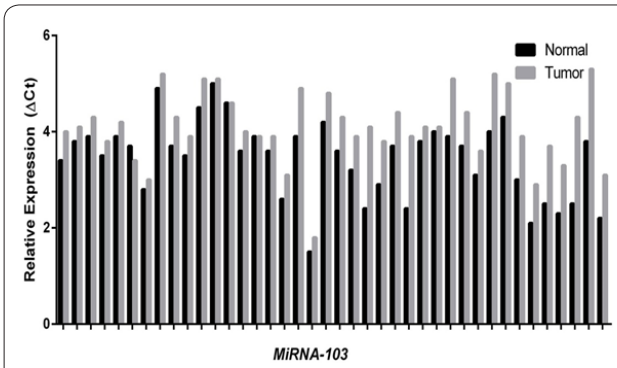

Figure 5. The expression level of each normal control and tumor according to ΔC_T of MiRNA 103. The level of mRNA expression in cancerous tissues was increased according to normal controls.

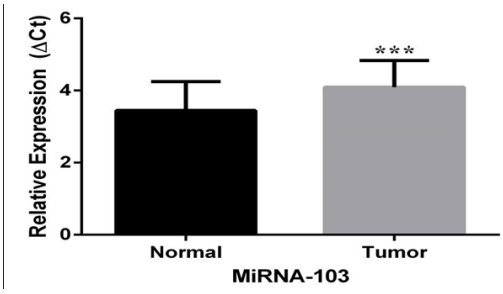

Figure 6. The quantitative expression level of miRNA 103 for both normal controls and tumors (p=0,0001). The average mean of control samples = 3.448 and tumor = 4.095.

and health controls with qRT-PCR. Among breast cancer patients, a lower level of expression of lncRNA-GAS5 was found compared to that of healthy controls. Moreover, APOBEC3C expression was found in the tissue of patients with breast cancer and healthy controls. APOBEC3C expression has also been down-regulated in tissues of patients with breast cancer. Correlation analysis was conducted to investigate the probable relation between APOBEC3C and GAS5 expression in breast cancer. According to the results, the expression of GAS5 was positively correlated with that of APOBEC3C, as presented in Figure 7.

GAS5 was predicted to be able to bind to miR-103 based on the current online tool for bioinformatics analysis (Figure 8a). In this study, the presence of miR-103 in the tissue of patients with breast cancer and healthy controls was also analyzed. The results revealed that miR-103 was significantly up-regulated in patients with breast cancer tissue. Furthermore, correlation analysis showed a negative correlation between the GAS5 and miR-103 expression (Figure 8).

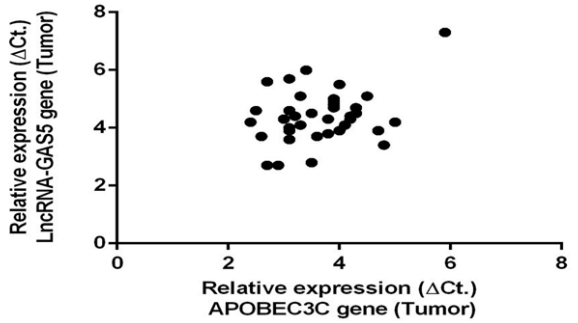

Figure 7. Correlation analysis of the expression of LncRNA-GAS5 and *APOBE3C* gene in breast cancer patients.

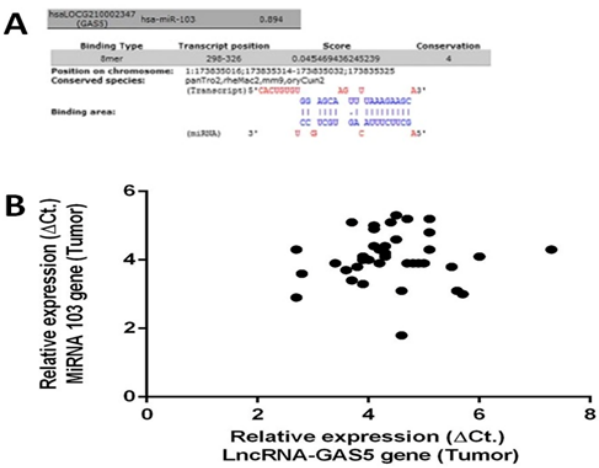

Figure 8. LncRNA-GAS5 suppressed the expression of miR-103. **a**) Bioinformatics analysis of the combination of LncRNA-GAS5 and miR-103. **b**) Correlation analysis of the expression of LncRNA-GAS5 and miR-103 in breast cancer patients.

Discussion

We have analyzed the expression level of lncRNA-GAS5 and its target APOBEC3C in breast cancer patients through expression evaluation of miR-103 using RT-qPCR. Lately, the interaction between lncRNA-GAS5 and miR-103 was studied. In addition, the coding region of mRNA of APOBEC3C sequence was screened to finding possible mutation via a genetic analyzer. As the most common cancer in women, breast cancer is a complex and heterogeneous tumor that arises from the breast tissue and becomes malignant (8,9). Most molecular studies of breast cancer have concentrated on just one or two high characteristic platforms; expression of mRNA profile or DNA copy number analysis sequencing (10).

The environment of protein-coding reflects just one side of the coin and considerable attempts and advances have been made through the years to recognize new reasons and principles in breast cancer biology. Different non-coding RNAs (miRNAs) were found to be active in the signaling pathway for the target gene and breast cancer (3). For instance, other miRNAs implicitly influenced specific target signaling through regulated other genes; oncomiRs miR-221/222 supported breast cancer proliferation through suppressing p53 up-regulated cell death expression modulator (3). In breast cancer, MiR 21 antagonizes the p53 process by preventing the expression of p53 regulated genes. Another miRNA group targets directly the p53 mRNA and negatively regulates the p53 expression such as miR 125b, miR 375 and miR 504. As already described, numerous studies have shown that non-coding RNAs are consistently upregulated in different cancers. Meanwhile, multiple lncRNAs were defined with different patterns of expression in breast cancer tissue as opposed to healthy breast tissue (3). For example, Yang et al have presented over 1300 lncRNAs that reveal significantly aberrational patterns of expression in the HER-2-enriched breast cancer subtype using next-generation sequencing (3,9). Similarly, Shen et al. (11) found that in triple-negative breast cancer (TNBC), more than 1750 lncRNAs were expressed differentially. These findings show undesirable patterns of expression of lncRNAs that perform a significant and often overestimated role in carcinogenesis of breast cancer.

APOBEC family consists of a total of 11 genes in the human genome (12,13) and is believed to encode the cytosine deaminases dependent on Zn2 + DNA. Out of 11 members, seven enzyme editing apolipoprotein B mRNA, catalytic polypeptide-like 3 genes (APOBEC3A, APOBEC3B, APOBEC3C, APOBEC3D, APOBEC3F, APOBEC3G, and APOBEC3H) lie tandemly on chromosome 22 (14,15). The remaining four members are positioned on other chromosomes including APOBEC1, APOBEC2, APOBEC4 and activation-induced deaminase activity (AICDA) (16). The proteins of the APOBEC family illustrate various groups of DNA cytosine deaminase domains and different tissue expression profiles, implying that they could have various biological processes. The APOBEC proteins demonstrate various functions in restricting replication of viruses and suppressing retrotransposition of LINE-1. Latest studies have found increased APOBEC3B expression in several tumors. Furthermore, the high correlation in cancer specimens of somatic base-substitution mutation with APOBEC3B mRNA levels has involved APOBEC3B as an enzymatic source that induces somatic mutations (C-to-T) (17). However, the differentiated mutational patterns and genomic modifications have also been described in breast cancer subtypes, implying the mutagenesis induced by APOBEC and the family expression of APOBEC that varying in cancer subtypes.

In our study, the APOBEC3C gene expression on the level of mRNA was significantly dropped (down-regulated) as shown in Figures 1 and 2 ($p > 0.05$). Yanfeng et al, (17) also reported down-regulation of APOBEC3C expression. Extensive research on expression profiling has indicated differential gene expression patterns between histologic subtypes of breast cancer. Evaluation of the gene expression has demonstrated several specific diagnostic markers. Our expression analyses suggested that APOBEC3C expression patterns were correlated with breast cancer tissues and clinical outcomes, providing an additional implication that other APOBEC family member genes may contribute to expression aberrant and clinical outcomes in breast cancer subtypes.

Epigenetic factors; DNA hyper-methylation, histone modification and non-coding RNA, represent the major factors causing a change in mRNA expression of genes. DNA hyper-methylation especially at the promoter region is one of the main factors that lead to low expression genes. Zhang et al determined the epigenetic profile of activation and inactivation of APOBEC family members in breast cancer cell lines. The authors reported that the APOBEC3C gene showed lower expression than normal breast cell lines while other APOBEC members were not expressed or down-regulated in breast cancer cell lines. In their study, activated 74 epigenetic markers, involving H3K4me3 and H3K27ac and H3K36me3, were observed in the APOBEC3 genes, in both ER+; and ER- breast cancer cell lines. In addition, all other APOBEC family members revealed DNA hyper-methylation at their promoters in the ER- cell line, which might contribute to their no expression or down-regulation. Moreover, the authors found that DNA methylation and modification in histone could regulate gene expression patterns in APOBEC family members in breast cancer cell lines. Also, the microenvironment of cell lines affected the expression level of the gene as Leonard et al. (17) showed that APOBEC3B mRNA expression has differentiated commonly in ovarian cancers. However, compared to normal ovarian tissue as control was significantly up-regulated in addition, lower levels for APOBEC3C down-regulated in ovarian cancers were observed in the tumor than normal ovaries, or they are poorly expressed in cells that eventually grow into tumors. This aspect is also impacted through shifts in the microenvironment during tumor progression (18). In addition, non-coding RNAs are also considered to serve a vital role in cell cycle maintenance and programmed cell death; they can either function as genes for tumor suppressors, while others are classified as oncogenes (11). They control target gene expression by transcriptional prevention or post-transcription suppressing.

As presented in Figures 3 and 4, the expression level of LncRNA-GAS5 was decreased (down-regulated) T-test showed statistically high significance; $p > 0,05$. GAS5's function in human cancers has been reported first in breast cancer. Mourtada-Maarabouni et al reported that GAS5 is down-regulated in tissues with breast cancer (19). GAS5 is usually down-regulated in different cancers, and lower levels of expression can often be suggestive of poor prognosis in cancer patients (20,21). In addition, GAS5 advocates cell division and/or apoptosis in distinct types of cells such as breast cancer cells, and its importance as a tumor suppressor is concluded by breast tumor growth inhibition). Li et al. (22) discovered that GAS5 levels in trastuzumab-resistant SKBR-3/Tr cells and trastuzumab-treated patients with breast cancer tissue is reduced. Knockdown of GAS5 risen in vivo cell proliferation and tumor growth, as well as low GAS5 levels associated with histological grade and advanced TNM stage. That demonstrates that trastuzumab decreases GAS5 and can act as a tumor suppressor in trastuzumab-resistant breast cancer (11,20). Our reducing result in GAS5 expression level is compatible with previous studies.

Numerous microRNAs (miRNAs) have recently been proposed to enhance tumorigenesis or metabolic diseases through down-regulating the target gene expression (23). Among them, miR103 had been identified to stimulate colorectal cancer via gene expression down-regulation (4). Boren et al. and Chung et al. first defined, for miR-103, the abnormal over-expression of miR-103 in endometrial cancer (24,25). In addition, Dongqi Yu et al discovered that miR-103 induced the development and invasion of endometrial cancer cell lines by post-transcriptionally decreasing the tumor suppressor expression TIMP-3 (26). In this study, the expression level of miR-103 was significantly increased (up-regulated) as shown in Figures 5 and 6 ($p > 0,05$). Our result accords with to those reported by Jeremy et al., who found that up-regulated expression of miR-103a-3p in breast cancer patients. According to previous studies, MiR-103's function in cancer supports that miR-103 works as an oncomiR instead of a tumor suppressor. MiR-103's high expression in response to breast cancer was associated with metastasis, tumor progression and poor outcome (27). On the other hand, one breast cancer study showed that miR-103 prevents the development of stem cells in triple-negative breast cancer.

Throughout this study, we found down-regulation of GAS5 in breast cancer cells, as is the case for APOBEC3C. The online bioinformatics prediction recently indicated that GAS5 can bind to miR-103. The miR-103 expression on the level of mRNA was significantly reduced or enhanced by transfecting GAS5 plasmid or si-GAS5 into cancer cells, respectively (4). We observed that miR-103 may be able to reduce APOBEC3C mRNA levels during decreased GAS5 expression in breast cancer cells.

In this study, coding sequence regions of the APOBEC3C gene were investigated by nucleotide sequencing analysis. However, no mutation was observed in this coding region, a result that agrees with previous studies. Yanfeng et al observed a negative correlation between the number of mutations per tumor exome and expression levels of APOBEC3C (17).

Further study is needed to examine genome-wide association studies to identify candidate genes (28) and polymorphism (29, 30) in different populations.

In conclusion, we found a significant reduction of both APOBEC3C and LncRNA-GAS5 expression and significantly increased expression of miRNA 103 in breast cancer patients. We found a positive correlation between APOBEC3C and LncRNA-GAS5 in breast cancers cells. Manipulation of the expression of the GAS5 may provide a new potential treatment target for the therapy of breast cancer. To clarify the interaction

among the tumors in the breast and the biomarkers; further research is warranted.

Acknowledgments
None

Interest conflict
The authors declare no conflict of interest.

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