Original Paper

Mining Prognostic Significance of MEG3 in Human Breast Cancer Using Bioinformatics Analysis

Xiangrong Cui^{a,b,c} Qin Yi^{a,b,c} Xuan Jing^e Yue Huang^{a,b,c} Jie Tian^d
Chunlan Long^{a,b,c} Zhongping Xiang^{a,b,c} Jianping Liu^f Chunmin Zhang^g
Bin Tan^{a,b,c} Yasha Li^{a,b,c} Jing Zhu^{a,b,c}

^aPediatric Research Institute, Children's Hospital of Chongqing Medical University, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, ^bChina International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing, ^cChongqing Key Laboratory of Pediatrics, Chongqing, ^dCardiovascular Department (Internal Medicine), Children's Hospital of Chongqing Medical University, Chongqing ^eClinical Laboratory, Shanxi Province People's Hospital, Shanxi, ^fClinical Laboratory, The First Affiliated Hospital of Nanchang University, Jiangxi, ^gClinical Laboratory, The Tumor Hospital of Chongqing, Chongqing, China

Key Words

Long non-coding RNAs • MEG3 • Breast carcinoma • Prognosis

Abstract

Background/Aims: Maternally expressed gene 3 (MEG3) is an imprinted gene with maternal expression, which may function as a tumor suppressor by inhibiting angiogenesis. To identify the prognostic value of MEG3 in breast cancer, systematic analysis was performed in this study. **Methods:** To evaluate gene alteration during breast carcinogenesis, we explored MEG3 expression using the Serial Analysis of Gene Expression Genie suite and Oncomine analysis. The prognostic roles of MEG3 in breast cancer were investigated using the PrognScan database. The heat map and methylation status of MEG3 were determined using the UCSC Genome Browser. **Results:** We found that MEG3 was more frequently downregulated in breast cancer than in normal tissues and this correlated with prognosis. However, estrogen receptor and progesterone receptor status were found to be positively correlated with MEG3 expression. Conversely, basal-like status, triple-negative breast cancer status, and Scarff Bloom & Richardson grade criterion were negatively correlated with MEG3 expression. Following data mining in multiple big data databases, we confirmed a positive correlation between MEG3 and heparan sulfate proteoglycan 2 (HSPG2) expression in breast cancer tissues. **Conclusion:** MEG3 could be adopted as a marker to predict the prognosis of breast cancer with HSPG2. However, large-scale and comprehensive research is needed to clarify our results.

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X. Cui, Q. Yi and X. Jing contributed equally to this work.

Jing Zhu

Pediatric Research Institute, Children's Hospital of Chongqing Medical University
Chongqing 400014 (China)
E-Mail 412232858@qq.com

Introduction

Breast cancer remains a leading cause of cancer-related death in women [1-3]. Despite increased screening and improved diagnosis and treatment of breast cancer, prognosis remains poor [4-6]. Therefore, the development of more sensitive and specific biomarkers for the prognosis of patients with breast cancer is urgently needed.

Long non-coding RNAs (lncRNAs) are commonly defined as non-protein coding transcripts longer than 200 nucleotides, many of which are emerging as a critical class of regulatory molecules through a variety of mechanisms involved in regulating fundamental biological processes [7-9]. In tumors, abnormal expression of lncRNAs contributes to the development and progression of cancer by influencing proliferation, apoptosis, autophagy, metastasis, self-renewal, and survival via epigenetic, transcriptional, and post-transcriptional gene regulatory mechanisms [10-12]. Furthermore, aberrant expression of lncRNAs can be detected in circulating cancer cells and in the serum and urine of cancer patients, which suggests that lncRNAs may serve as an effective biomarker for cancer detection and prognosis [13, 14].

Maternally expressed gene 3 (MEG3) is the first lncRNA that has been shown to function as a tumor suppressor and inhibit cell proliferation in numerous human cancer cell lines, and it is expressed in many normal human tissues [15-17]. Loss of MEG3 expression has been identified in many human tumors, including cervical cancer [18], retinoblastoma [19], ovarian carcinoma [20], gastric cancer [21], germ cell tumor [22], and squamous cell carcinoma [23], and such loss is indicative of poor prognosis. MEG3 has also been demonstrated to inhibit cell growth in gliomas by targeting miR-93 and inactivating the PI3K/AKT pathway [24]. Moreover, upregulation of MEG3 can induce autophagy to inhibit tumorigenesis and progression of epithelial ovarian carcinoma by regulating ATG3 activity [20]. Taken together, these findings suggest that MEG3 may not only act as a potential therapeutic target, but also as a novel predictive biomarker of progression and prognosis of cancer.

In this study, we evaluated the significance of MEG3 expression in human breast cancer by using bioinformatics. The study was performed to comprehensively analyze the expression pattern, potential function, and distinct prognostic effect of MEG3 in breast cancer by pooling and analyzing all currently available data.

Materials and Methods

Serial analysis of gene expression (SAGE)

All available published SAGE data were utilized for analysis of lncRNA MEG3 gene expression in normal and malignant human tissues. Digital lncRNA MEG3 gene expression profiles were analyzed and displayed using the SAGE Anatomic Viewer (<http://www.ncbi.nlm.nih.gov/SAGE/>).

Oncomine database analysis

The Oncomine database (<http://www.oncomine.org>) is a web-based data mining platform that incorporates 264 independent datasets and aims to collect, standardize, analyze, and deliver transcriptomic cancer data for biomedical research [25]. lncRNA MEG3 mRNA levels in breast cancer tissues were compared with their matched normal tissues by using online Oncomine analysis tools. The threshold used to obtain the most significant probes of the lncRNA MEG3 for each microarray data included a two-fold difference in expression between cancers and normal tissues with a p-value of less than 1×10^{-4} . Genes co-expressed with MEG3 were analyzed.

UCSC cancer genomics browser analysis

The heat map and correlation between lncRNA MEG3 and HSPG2 in the same patient cohort were verified and analyzed by data mining in TCGA-GBM using the UCSC Xena browser (<http://xena.ucsc.edu/>). Subsequently, the methylation status of lncRNA MEG3 was also examined using the UCSC Xena browser [26-28].

Breast cancer gene-expression miner v4.1

Breast Cancer Gene-Expression Miner v4.1 (bcGenExMiner v4.1), a statistical mining tool of published annotated genomic data, was utilized to assess lncRNA MEG3 expression in breast cancer [29, 30]. Correlations of lncRNA MEG3 and HSPG2 were assessed using the bc-GenExMiner v4.1 correlation module.

Prognoscan

The Prognoscan online database (<http://www.prognoscan.org/>) provides a powerful platform for assessing the biological relationships between gene expression and prognosis in cancer patients [31]. Prognoscan automatically calculates hazard ratios, 95% confidence intervals, and Cox P-values according to the mRNA level (high or low) of a given gene.

Results

lncRNA MEG3 transcript expression and methylation status in human breast cancer

As a long non-coding RNA, the expression profile of MEG3 was identified using the SAGE Digital Gene Expression Display. Our analysis revealed that lncRNA MEG3 expression was lower in brain, breast, kidney, peritoneum, prostate, and lymph node tissues compared with their matched normal tissues (Fig. 1). We also analyzed the expression profile of MEG3 by Oncomine database analysis. Lower expression of MEG3 was identified in human cancers, including hematological malignancies and solid tumors (Fig. 2). Oncomine analysis of cancer vs. normal samples revealed that lncRNA MEG3 expression was significantly lower in invasive breast carcinoma, invasive lobular breast carcinoma, invasive ductal breast carcinoma, male breast carcinoma, invasive ductal and lobular carcinoma, breast carcinoma, medullary breast carcinoma, mucinous breast carcinoma, ductal breast carcinoma in situ, and tubular breast carcinoma (Table 1, Fig. 3) [32, 33]. Comparing the MEG3 expression heatmap and DNA methylation status revealed that its expression might be negatively related with some CpG sites (blank frame) (Fig. 4A). By comparing MEG3 expression in different DNA methylation clusters, we also confirmed that MEG3 expression gradually decreased with increasing DNA methylation (Fig. 4B).

Genetic alternations of MEG3 and clinicopathological parameters in breast cancer patients

In bc-GenExMiner, Welch's t-test was performed to compare the transcription levels of MEG3 among groups of patients, based on different clinicopathological parameters (Table 2). Regarding age, no significant differences were found between the ≤ 51 years and $>$

Fig. 1. Expression profile for MEG3 in human breast cancer using the SAGE digital gene expression display.

Fig. 2. Expression of MEG3 in different types of cancers. This graphic generated by Oncomine indicates the numbers of datasets with statistically significant ($p < 0.01$) mRNA over-expression (red) or down-expression (blue) of MEG3 (different types of cancer vs. corresponding normal tissue). The threshold was designed with the following parameters: p-value of $1E-4$, fold change of 2, and gene ranking of 10%.

Table 1. The significant changes of MEG3 expression in transcription level between different types of breast cancer and normal tissues (ONCOMINE database)

Subtype of breast cancer	p-value	Fold change	Rank (%)	Sample	Reference
Invasive Breast Carcinoma	7.06E-14	-4.726	1%	158	21373875
Invasive Breast Carcinoma	2.00E-30	-5.759	1%	137	TCGA
Invasive Lobular Breast Carcinoma	6.13E-15	-2.964	2%	97	TCGA
Invasive Ductal Breast Carcinoma	1.38E-36	-5.874	2%	440	TCGA
Male Breast Carcinoma	4.02E-8	-5.369	2%	64	TCGA
Invasive Ductal and Lobular Carcinoma	1.09E-5	-3.108	3%	64	TCGA
Invasive Ductal Breast Carcinoma	2.44E-86	-4.565	1%	1700	22522925
Invasive Ductal and Invasive Lobular Breast Carcinoma	8.95E-40	-2.655	2%	234	22522925
Invasive Lobular Breast Carcinoma	6.23E-48	-3.667	2%	292	22522925
Breast Carcinoma	2.15E-10	-3.474	2%	158	22522925
Medullary Breast Carcinoma	2.07E-20	-3.221	2%	176	22522925
Mucinous Breast Carcinoma	1.27E-22	-3.239	3%	190	22522925
Invasive Breast Carcinoma	1.51E-9	-2.802	3%	165	22522925
Tubular Breast Carcinoma	5.81E-29	-3.708	4%	211	22522925
Ductal Breast Carcinoma in Situ	8.18E-5	-5.841	7%	154	22522925

51 years groups (Table 2). HER2 status and nodal status also showed no significant differences between positive and negative status (Table 2, Fig. 5). Estrogen receptor (ER) and progesterone receptor (PR) status were found to be positively correlated with MEG3 expression (Table 2, Fig. 5). Conversely, in breast cancer patients with negative basal-like status, expression of MEG3 was significantly increased compared with positive basal-like status (Table 2, Fig. 5). TNBC is a special type of breast cancer, with ER (-), PR (-), and HER2 (-) type classifications. We found that expression of MEG3 was significantly upregulated in non-TNBC patients (Table 2, Fig. 5). In terms of the Scarff Bloom & Richardson grade status (SBR) criterion, more advanced SBR grade was associated with lower MEG3 mRNA level (Fig. 5). The prognostic value of MEG3 expression was shown using the PrognoScan database,

Fig. 3. MEG3 analysis in breast cancer (Oncomine database). Box plot comparing specific MEG3 expression in normal (left) and cancer tissue (right) generated from Oncomine database. Analysis is shown for invasive breast carcinoma, invasive lobular breast carcinoma, invasive ductal breast carcinoma, male breast carcinoma, invasive ductal and lobular carcinoma, breast carcinoma, medullary breast carcinoma, mucinous breast carcinoma, ductal breast carcinoma in situ, and tubular breast carcinoma.

Fig. 4. A: Heat map of MEG3 expression and DNA methylation status; B: MEG3 expression in different breast cancer DNA methylation clusters. Results generated using the UCSC Xena browser based on data in TCGA.

where higher expression of MEG3 correlated with better overall survival (OS), relapse-free survival (RFS), distant metastasis-free survival (DMFS), and disease-specific survival (DSS) in breast cancer (Table 3, Fig. 6).

Co-expression of MEG3 mRNA

Co-expression of MEG3 was analyzed using OncoPrint (Fig. 7A). The co-expression profile of MEG3 was identified with a large cluster of 3,852 genes across 16 breast carcinomas (Fig. 7A) [34]. Heparan sulfate proteoglycan 2 (HSPG2) is a top correlated gene, which is underexpressed in breast cancer and inhibits chemotherapy resistance of breast cancer cells [35, 36]. Data mining in bc-GenExMiner 4.0 confirmed a positive correlation between MEG3 and HSPG2 expression (Fig. 7B). We confirmed this positive correlation by analyzing breast cancer patient data in the TCGA database using UCSC Xena (<http://xena.ucsc.edu/>) (Fig. 7C-D). These findings suggest that MEG3 might be closely related to the HSPG2 signaling pathway in breast cancer.

Table 2. The relationship between mRNA expression of MEG3 and clinicopathological parameters of breast carcinoma

Variables	No.*	MEG3 mRNA	p-value
Age			
≤ 51	1392	-	0.6770
> 51	2210	-	
Nodal Status			
-	1896	-	0.8459
+	1017	-	
ER			
-	1197	-	0.0001
+	3177	↑	
PR			
-	733	-	<0.0001
+	1173	↑	
HER2			
-	1195	-	0.7568
+	166	-	
Basal-like Status			
Not	3322	↑	<0.0001
Basal-like	908	-	
Triple-negative Status			
Not	3254	↑	0.0056
TNBC	293	-

Fig. 5. Relationship between MEG3 expression and clinicopathological parameters in breast cancer patients. Global significant difference between groups was assessed by Welch's t-test to generate p values, along with Dunnett-Tukey-Kramer test.

Fig. 6. Relationship between MEG3 expression and prognosis in breast cancer patients (PrognScan database). Survival curve analysis with a threshold of $p < 0.05$ (Cox).

Discussion

MEG3 is an imprinted gene within the DLK1-MEG3 locus located at human chromosome 14q32, which is the first lncRNA verified to act as a tumor suppressor and exert its anti-proliferative role through multiple signaling pathways [16, 17, 37, 38]. Wei et al. have revealed that MEG3 can inhibit proliferation and metastasis of gastric cancer via the p53 signaling pathway [39]. Also, MEG3 inhibits proliferation and metastasis of oral squamous cell carcinoma by regulating the WNT/ β -catenin signaling pathway [23]. Overexpression of MEG3

Table 3. The association of MEG3 expression and the survival in breast cancer patients

DATASET	ENDPOINT	PROBE ID	N	COX P-VALUE	HR
GSE19615	Distant Metastasis Free Survival	212732_at	115	0.034625	0.20
GSE12276	Relapse Free Survival	235077_at	204	0.042981	0.88
GSE1456-GPL96	Relapse Free Survival	212732_at	159	0.049868	0.64
GSE1456-GPL97	Relapse Free Survival	226210_s_at	159	0.002372	0.58
GSE1456-GPL97	Disease Specific Survival	226210_s_at	159	0.046592	0.67
GSE1456-GPL97	Overall Survival	226210_s_at	159	0.008029	0.64
GSE3494-GPL96	Disease Specific Survival	210794_s_at	236	0.027159	0.54
GSE3494-GPL97	Disease Specific Survival	226210_s_at	236	0.049525	0.70
GSE4922-GPL96	Disease Free Survival	212732_at	249	0.022086	0.76

Fig. 7. A: MEG3 co-expression of genes analyzed using Oncomine. B: Relationship between MEG3 and HSPG2 in breast cancer analyzed using bc-GenExMiner v4.0; C: Heat map of MEG3 expression and HSPG2 mRNA expression across PAM50 breast cancer subtypes in the TCGA database, determined using UCSC Xena; D: Correlation between MEG3 and HSPG2 mRNA expression in the TCGA database, determined using UCSC Xena.

can promote chemosensitivity of tumor cells through enhancing oxaliplatin-induced cell apoptosis [40]. However, the distinct role of MEG3 expression in the development and metastasis of breast cancer remains largely unknown.

To determine the role of MEG3 in the development, progression, and prognosis of breast cancer, we analyzed the data based on the level of gene expression with clearly defined parameters between cancer and normal tissues. Oncomine analysis revealed that MEG3 expression was significantly decreased in invasive breast carcinoma, invasive lobular breast carcinoma, invasive ductal breast carcinoma, male breast carcinoma, invasive ductal and lobular carcinoma, breast carcinoma, medullary breast carcinoma, mucinous breast carcinoma, ductal breast carcinoma in situ, and tubular breast carcinoma. Meanwhile, ER and PR status were found to be positively correlated with MEG3 expression. Conversely, basal-like status, TNBC status, and SBR criterion were negatively correlated with MEG3 expression. We further investigated the prognostic value of MEG3 in breast cancer using PrognoScan, and the pooled results revealed that low MEG3 expression correlated with shorter OS, RFS, DMFS, and DSS. Together, these findings indicate that decreased expression of MEG3 might be a useful marker of the prognosis of breast cancer.

Through co-expression and correlation analysis, we observed that HSPG2 was positively correlated with MEG3 expression. HSPG2 encodes for the perlecan protein, a large multidomain proteoglycan that cross-links extracellular matrix components and cell-surface molecules, which themselves play essential roles in multiple biological activities [41]. Hu et al. have demonstrated that overexpression of hypomethylated miR-663 might induce chemotherapy resistance in human breast cancer cells through targeting HSPG2 [35]. These previous findings and the present results together provide ample evidence that MEG3 expression might inhibit tumor migration and invasion associated with HSPG2 expression.

Conclusion

In summary, decreased expression of MEG3 was identified in breast cancer compared with matched normal tissues and is associated with the prognosis of breast cancer. HSPG2 could be adopted as a negative marker to predict the prognosis of breast cancer with MEG3. Large-scale and comprehensive studies are needed to confirm our findings and thus promote the clinical utility of MEG3 in the evaluation of breast cancer prognosis.

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Disclosure Statement

The authors declare that no conflict of interest exists.

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