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Opposite trends of *GAS6* and *GAS6-AS* expressions in breast cancer tissues

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ABSTRACT

Growth arrest-specific gene 6 (GAS6) is a growth factor-like cytokine whose function is related with vitamin K. This protein interacts with receptor tyrosine kinase proteins such as Tyro3, Axl, and TAM Receptor family, therefore affecting the tumorigenic processes via different mechanisms. *GAS6-antisense 1* (*GAS6-AS1*) is a long non-coding RNAs (lncRNAs) that is transcribed from a genomic regions nearby *GAS6*. This lncRNA is also implicated in the pathobiology of cancer. We intended to judge the role of *GAS6* and *GAS6-AS1* in the pathogenesis of breast cancer through appraisal of their expression levels in breast cancer tissues and their paired neighboring non-cancerous samples. Expression of *GAS6* was up-regulated in breast cancer tissues compared with neighboring tissues (Ratio of Mean Expressions = 2.18, *P* value = 4.98E-02). On the other hand, expression of *GAS6-AS1* was down-regulated in breast tumor tissues compared with controls (Ratio of Mean Expressions = 0.37, *P* value = 4.26E-03). There were substantial correlations between expression levels *GAS6* and *GAS6-AS1* in non-cancerous tissues (r = 0.74, *P* value = 1.47e-13) and cancer tissues (r = 0.85, P value = 2.28e-20). Expression of *GAS6-AS* was associated with progesterone receptor status (P value = 1.36E-02). However, expressions of this gene and the sense transcript were not linked with any other clinical or demographic variable. Taken together, *GAS6* and *GAS6-AS1* might partake in the development of breast cancer.

1. Introduction

Growth arrest-specific gene 6 (GAS6) is a growth factor-like cytokine whose function is related with vitamin K. It has a vitamin K-associated gamma-carboxyglutamic domain through which it interacts with phosphatidylserine-comprising proteins (Bellido-Martín and de Frutos, 2008). This function of GAS6 has importance in several physiologic processes such as regulation of vascular smooth muscle cells and mitogenic activity of mesangial cells (Yanagita, 2004). The encoded protein interacts with a number of receptor tyrosine kinase proteins such as Tyro3, Axl, and TAM Receptor family (Tsou et al., 2014). This multifunctional protein contributes in the regulation of numerous processes such as the resolution of inflammatory responses, enhancement of tissue healing and eradication of apoptotic cells (Paolino and Penninger, 2016). Moreover, via interaction with TAM receptors, GAS6 is implicated in the process of cancer evolution and progression (Paolino and Penninger, 2016). This protein can regulate plasticity of tumor cells, angiogenic processes, and activity of immune cells. In the pancreatic cancer, GAS6 is mostly made by the tumor related macrophages and cancer related fibroblasts. Notably, obstruction of GAS6 function in these cells blocks epithelial-to-mesenchymal transition and activate natural killer cells, thus impeding metastatic processes (Ireland et al., 2020). GAS6 has been shown to be over-expressed in ductal carcinoma in situ of breast. However, its expression has been reduced in invasive breast cancer samples (Ibrahim et al., 2020). *GAS6-antisense 1* (*GAS6-AS1*) is a long non-coding RNA (lncRNA) which is transcribed from a genomic regions nearby *GAS6*. Expression of this lncRNA has been deceased in tumor specimens obtained from individuals with non-small

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Table 1
Information about primers used for real time PCR.

Name	Sequence	Primer Length	PCR Product Length
GAS6-F	GTAGCTTCCACTGTTCCT	18	79
GAS6-R	GCGCACTCGTCTATGTCTT	19	
GAS6-AS1-F	GTGGGTACTGCATTCCTACCG	21	131
GAS6-AS1-R	CTCTCCTCTGATGGCAGGAC	20	
B2M-F	AGATGAGTATGCCTGCCGTG	20	105
B2M-R	GCGGCATCTTCAAACCTCCA	20	

cell lung cancer (NSCLC) compared with nearby tissue samples. Besides, down-regulation of this lncRNA has been correlated with lymph node metastasis, high lung cancer stage and poor clinical outcome. Notably, expression of *GAS6-AS1* has been inversely correlated with the expression of the sense transcript (Han et al., 2013). In the present expression assay research, we intended to weigh the role of *GAS6* and *GAS6-AS1* in the development of breast cancer via evaluation of their expression quantities in the breast cancer tissues and their paired adjacent non-cancerous tissues (ANCTs).

2. Material and methods

2.1. Patients

The current study has been performed on tissue sections exsized from 69 breast cancer patients including both tumoral sections and their paired non-cancerous specimens. All patients were Iranian females who were referred to the Farmanieh and Sina hospitals, Tehran, Iran during 2018–2020. The study protocol was permitted by the ethical committee of Shahid Beheshti University of Medical Science (ethical code: IR.SBMU.RETECH.REC.1398.379). In order to exclude confounding variables, patients were selected from those receiving no chemotherapy or radiotherapy. All obtained specimens were conveyed in the liquid nitrogen flask to the Genetics Laboratory and kept in −80 °C till succeeding experimental steps. Medical records were evaluated for obtaining relevant histopathological information.

2.2. Expression assays

RNA was isolated from cancerous and non-cancerous tissues using the RiboEx Total RNA extraction kit (GeneAll, Seoul, South Korea) following the steps stated by the company. Then, approximately 70–80 ng of RNA was converted to cDNA using the ExcelRT™ Reverse Transcription Kit II (SMOBIO, Taiwan). Expressions of *GAS6* and *GAS6-AS* genes in two mentioned sets of specimens were quantified in the ABI step one plus PCR system. Expression levels were normalized to the amounts of *B2M* expression. Reactions were arranged in the RealQ Plus 2× PCR Master Mix (Ampliqon, Odense, Denmark). Information about primers sequences is shown in Table 1.

2.3. Statistical methods

R programming software was used for analyses. Transcript levels of *GAS6* and *GAS6-AS* genes were quantified in relation to the housekeeping gene (HK) using the equation: $\frac{amp_{gene}^{-CT_{gene}}}{amp_{HK}^{-CT_{HK}}}$. Afterwards, the acquired values were log2 transformed. The significance of difference in mean values of expression levels between two sets of samples was evaluated using the paired *t*-test. Correlations between expressions of *GAS6* and *GAS6-AS1* were appraised through the calculation of Spearman correlation coefficients. Receiver operating characteristic (ROC) curve was depicted to assess the diagnostic power of *GAS6* and *GAS6-AS1*. Three predictive machine learning approaches, i.e. Bayesian Generalized Linear Model, Generalized Linear Model, and Linear Discriminant Analysis with 10-fold cross validation were applied to calculate the sensitivity and specificity of each model. The most efficient estimates were obtained using the Bayesian Generalized Linear Model (bayesGLM), therefore, this method was selected to examine the efficiency *GAS6* and *GAS6-AS1* gene for separation of groups. Youden's J statistic was employed to find the optimum threshold. Chi-square test was used to assess the association between clinical variables and transcript levels of *GAS6* and *GAS6-AS*. *P* value <0.05 was regarded as significant.

Table 2
Demographic and clinical data of patients.

Variables	Values (mean ± SD/ Number (%))
Menarche age	13.15 ± 1.56 (10–17)
Menopause age	49.47 ± 5.08 (38–61)
First pregnancy age	21.09 ± 4.69 (14–36)
Breast feeding period (months)	47.85 ± 48.88 (0–240)
Cancer stage	
I	18 (26.1%)
II	22 (31.9%)
III	20 (29%)
IV	5 (7.2%)
Unavailable	4 (5.8%)
Histological grade	
I	12 (17.4%)
II	32 (46.4%)
III	18 (26.1%)
Unavailable	7 (10.1%)
Mitotic rate	
I	23 (33.3%)
II	26 (37.7%)
III	7 (10.1%)
Unavailable	13 (18.8%)
Abortion history	
Positive	57 (82.6%)
Negative	12 (17.4%)
Oral contraceptive intake	
No	35 (50.7%)
Yes	34 (49.3%)
Hormone replacement therapy history	
No	58 (84.1%)
Yes	11 (15.9%)
Estrogen receptor status	
Positive	52 (75.4%)
Negative	13 (18.8%)
Unavailable	4 (5.8%)
Progesterone receptor status	
Positive	48 (69.6%)
Negative	14 (20.3%)
Unavailable	7 (10.1%)
Her2 status	
Positive	13 (18.9%)
Negative	50 (72.5%)
Unavailable	8.69 (7.5%)

3. Results

3.1. Demographic/clinical information

Table 2 summarizes the demographic and clinical information of breast cancer patients.

3.2. Expression assays

Fig. 1 represents expression levels of *GAS6* and *GAS6-AS1* in breast cancer tissues and ANCTs.

Transcript level of *GAS6* was up-regulated in breast cancer tissues

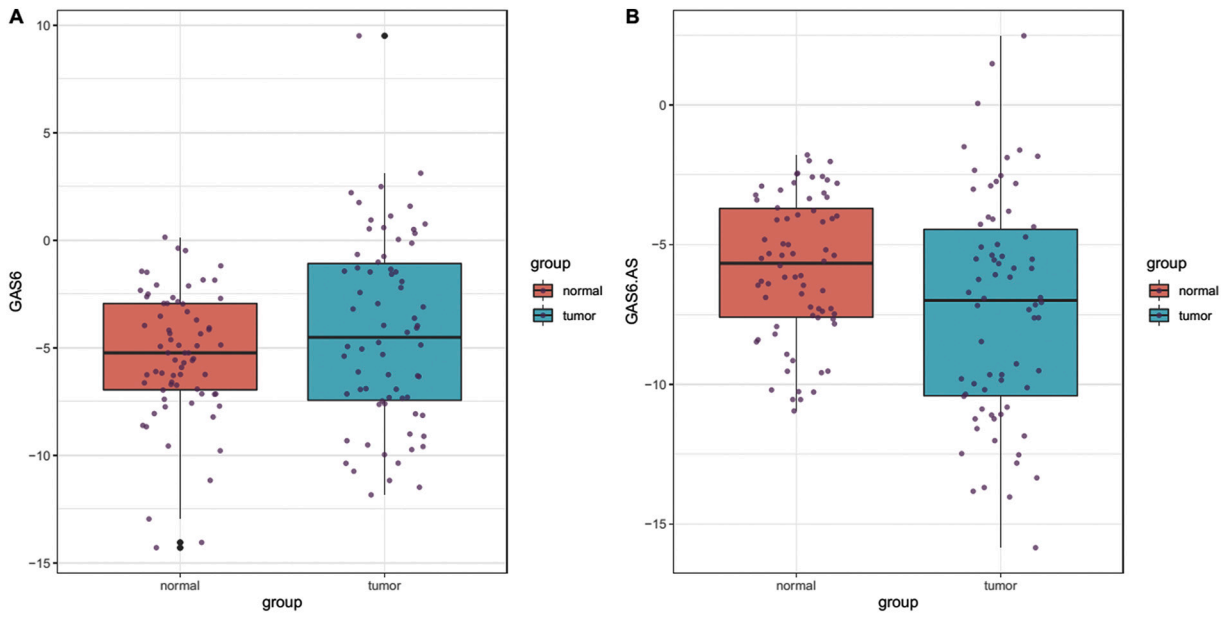

Fig. 1. Expression levels of *GAS6* and *GAS6-AS1* in breast cancer specimens and ANCTs. Median, upper and lower quartile values are shown.

Table 3
Statistics of expression levels of *GAS6* and *GAS6-AS1* in breast cancer tissues compared with ANCTs.

Gene	SE	Ratio of Mean Expressions	*P*-Value	95% CI	
GAS6	0.56	2.18	4.98E-02	0.00	2.24
GAS6-AS1	0.48	0.37	4.26E-03	−2.37	−0.46

compared with ANCTs (Ratio of Mean Expressions = 2.18, *P* value = 4.98E-02). On the other hand, expression of *GAS6-AS1* was deceased in cancer tissues compared with controls (Ratio of Mean Expressions = 0.37, P value = 4.26E-03). Table 3 shows the statistics of expression levels of *GAS6* and *GAS6-AS1* in breast cancer tissues compared with ANCTs.

Expression of *GAS6-AS1* was associated with PR status (P value = 1.36E-02). However, expressions of this gene and the sense transcript were not associated with any other clinical or demographic variable. Table 4 describes the results of association analysis between relative expression levels of *GAS6* and *GAS6-AS1* in breast cancer tissues and ANCTs and clinical features.

There were substantial correlations between expression levels *GAS6* and *GAS6-AS1* in neighboring non-cancerous sections (r = 0.74, P value = 1.47e-13) and cancer tissues (r = 0.85, P value = 2.28e-20). Fig. 2 displays the observed correlations between expression levels of these transcripts in these two sets of samples. (See Fig. 3.)

4. ROC curve analysis

Both *GAS6* and *GAS6-AS1* had high specificity for distinguishing between cancerous and non-cancerous tissues. Yet, their sensitivity was not appropriate. When combining expression levels of both transcripts, the obtained AUC value was increased to 0.80, indicating suitable power of this two-gene panel for the diagnostic purposes. Table 5 summarizes the statistics of ROC curve analysis of *GAS6* and *GAS6-AS* transcripts in distinguishing between cancerous and non-cancerous tissues.

5. Discussion

A number of experiments have assessed expression of natural occurring antisense RNAs and their sense transcripts in diverse cancer types to appraise their functional roles and interactions in this context (Jadaliha et al., 2018; Wang et al., 2018). Meanwhile, *GAS* genes and their antisense RNAs participate in the pathobiology of various human cancers (Goustin et al., 2019; Yu and Li, 2015; Rui et al., 2019). In the present investigation, we measured relative expression of *GAS6* and *GAS6-AS1* in invasive ductal carcinoma samples obtained from female Iranian patients. Notably, expression of *GAS6* was up-regulated in breast cancer tissues compared with ANCTs. GAS6 has been demonstrated to influence cancer progression via different routes. Its functional interactions with diverse receptor tyrosine kinases have endowed it the potential for activation of several cancer-related pathways including PI3K, ERK and NF-κB. Therefore, it can influence cell proliferation and apoptosis, cell adhesion and migration as well as differentiation processes (Wu et al., 2018). GAS6/TAM has necessary roles in the proliferation and migratory ability of tumor cells. Numerous investigations have demonstrated that ablation of Axl and Mer suppresses tumor cell proliferation and activates apoptosis (Song et al., 2011; Zhang et al., 2013). Collectively, GAS6 is involved in the regulation of proliferation, persistence and migratory potential of cancer cells through its attachment with TAM receptors (Wu et al., 2018). However, Ibrahim et al. have reported down-regulation of tumor-originated GAS6 in breast cancer compared with normal samples (Ibrahim et al., 2020). They also reported better survival of patients who had over-expression of this gene (Ibrahim et al., 2020). The main difference between our study and their study is that they only included nine ANCTs, yet we have included this type of control samples from all patients. Therefore, our study provides a more realistic view of *GAS6* expression and a more robust adjustment for confounding variables.

On the other hand, *GAS6-AS1* was under-expressed in cancer tissues compared with control samples. *GAS6-AS1* has been displayed to facilitate gastric cancer progression through enhancing GAS6 expression (Zhang et al., 2019). Although we detected under-expression of this lncRNA in breast cancer tissues, correlation analysis revealed substantial correlations between expression levels *GAS6* and *GAS6-AS1* both in non-cancerous tissues and in cancer tissues. This finding is in line with the suggested role for *GAS6-AS1* in enhancement of GAS6 expression. However, contrary to gastric cancer (Zhang et al., 2019), it seems that *GAS6-AS1* exerts a tumor suppressor role in the breast cancer. Consistent with this hypothesis, Li et al. have reported down-regulation of *GAS6-AS1* as a prognostic marker for outcome of patients with breast cancer (Li et al., 2016). Expression of *GAS6-AS1* has also been associated with

Table 4
Association between expression amounts of *GAS6* and *GAS6-AS1* in breast cancer samples and clinical features (Down-regulated: log2FC ≤ -1; Same expression levels: $-1 <$ log2FC < 1; Up-regulated: log2FC ≥ 1).

		GAS6				*GAS6-AS1*			
		Down- regulated	Same	Up-regulated	P-value	Down-regulated	Same	Up-regulated	P-value
Age					4.04E-01				4.09E-01
	Post-Menopause	28.13%	21.88%	40.63%		40.63%	34.38%	15.63%	
	Pre-Menopause	6.25%	0.00%	3.13%		6.25%	0.00%	3.13%	
Stage					3.01E-01				1.58E-01
	0	6.25%	0.00%	3.13%		6.25%	0.00%	3.13%	
	1	3.03%	9.09%	13.64%		9.09%	9.09%	7.58%	
	2	12.12%	6.06%	13.64%		21.21%	7.58%	3.03%	
	3	12.12%	3.03%	15.15%		15.15%	4.55%	10.61%	
	4	1.52%	1.52%	3.03%		1.52%	3.03%	1.52%	
Histological Grade					7.44E-01				2.47E-01
	0	1.67%	0.00%	0.00%		0.00%	1.67%	0.00%	
	1	3.33%	5.00%	10.00%		8.33%	8.33%	1.67%	
	2	16.67%	8.33%	23.33%		30.00%	8.33%	10.00%	
	3	11.67%	6.67%	13.33%		13.33%	8.33%	10.00%	
Mitotic Rate					4.17E-01				4.24E-01
	0	1.82%	0.00%	0.00%		0.00%	1.82%	0.00%	
	1	10.91%	3.64%	23.64%		25.45%	7.27%	5.45%	
	2	16.36%	12.73%	16.36%		21.82%	10.91%	12.73%	
	3	5.45%	3.64%	5.45%		5.45%	5.45%	3.64%	
Tumor Size					2.29E-01				3.26E-01
	<2	5.00%	6.67%	15.00%		8.33%	10.00%	8.33%	
	2–5	23.33%	13.33%	33.33%		38.33%	16.67%	15.00%	
	>5	3.33%	0.00%	0.00%		3.33%	0.00%	0.00%	
ER Status					1.05E-01				3.00E-01
	Positive	11.48%	1.64%	6.56%		11.48%	1.64%	6.56%	
	Negative	21.31%	16.39%	42.62%		40.98%	22.95%	16.39%	
PR Status					8.51E-01				1.36E-02
	Positive	10.17%	5.08%	11.86%		10.17%	3.39%	13.56%	
	Negative	22.03%	13.56%	37.29%		40.68%	22.03%	10.17%	
Her2 Status					1.65E-01				1.74E-01
	Positive	15.00%	10.00%	13.33%		25.00%	5.00%	8.33%	
	Negative	16.67%	8.33%	36.67%		26.67%	20.00%	15.00%	
Menarche Age					6.41E-01				6.84E-01
	10–12	12.70%	4.76%	14.29%		33.33%	12.70%	15.87%	
	13–15	17.46%	14.29%	30.16%		15.87%	9.52%	6.35%	
	16–18	1.59%	0.00%	4.76%		1.59%	1.59%	3.17%	
Menopause Age					5.24E-01				7.35E-01
	≤50	25.00%	18.75%	28.13%		34.38%	25.00%	12.50%	
	51–55	9.38%	3.13%	9.38%		9.38%	9.38%	3.13%	
	≥ 56	0.00%	0.00%	6.25%		3.13%	0.00%	3.13%	
Breast Feeding Duration					6.11E-01				2.00E-01
	0	7.81%	3.13%	10.94%		14.06%	3.13%	4.69%	
	1–30	1.56%	3.13%	1.56%		9.38%	6.25%	9.38%	
	31–60	10.94%	3.13%	10.94%		9.38%	10.94%	4.69%	
	61–120	4.69%	4.69%	15.63%		14.06%	3.13%	4.69%	
	≥ 121	7.81%	6.25%	7.81%		6.25%	0.00%	0.00%	
Hormone Replacement Therapy					4.26E-01				5.88E-01
	Yes	3.03%	3.03%	10.61%		7.58%	3.03%	6.06%	
	No	30.30%	16.67%	36.36%		45.45%	19.70%	18.18%	

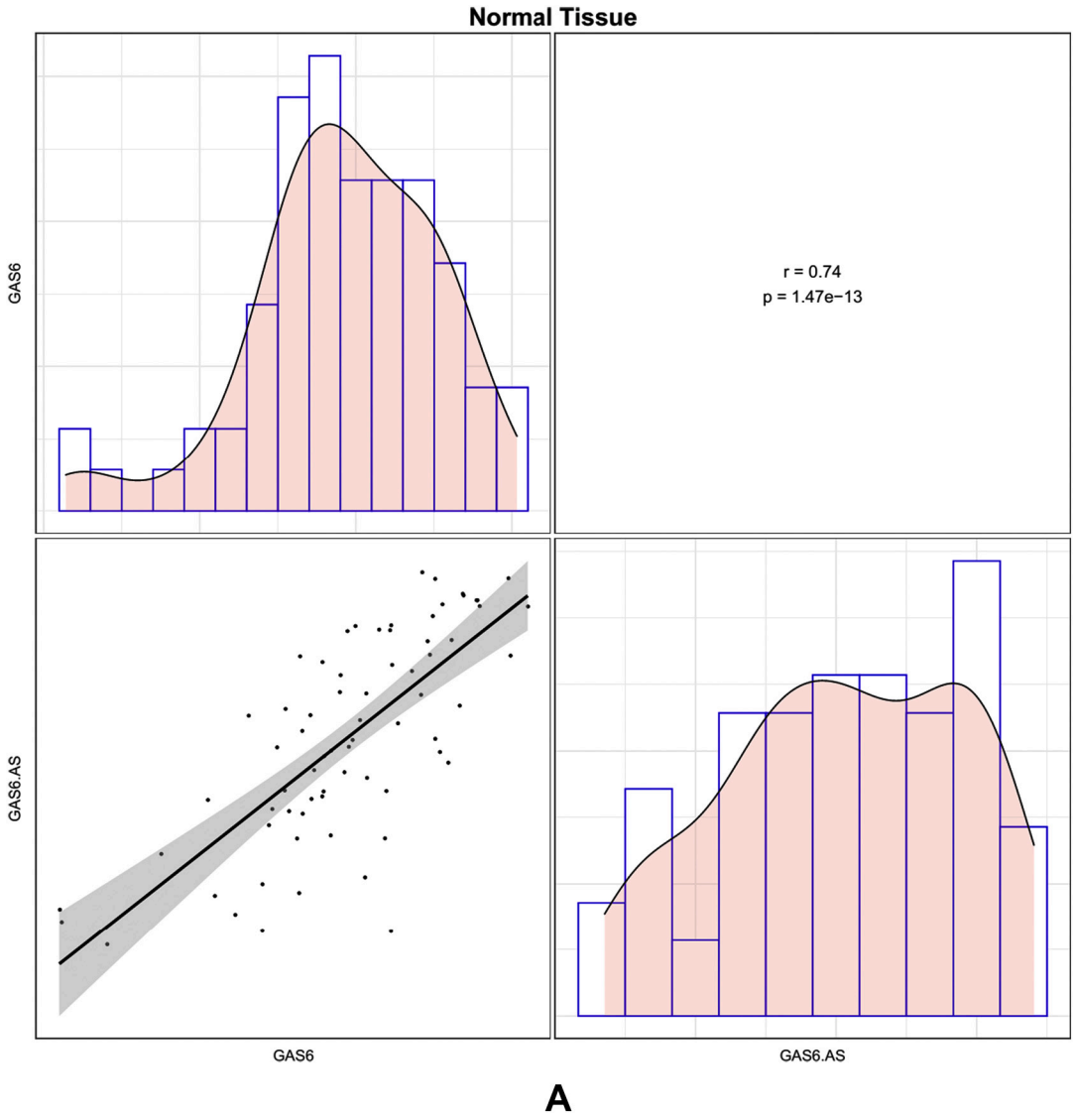

Fig. 2. Correlation between expression levels of *GAS6* and *GAS6-AS1* in non-cancerous tissues (A) and cancer tissues (B). The distributions of transcript levels of genes are shown on the diagonal. The correlation coefficients and *P* values are demonstrated on upper part of the diagonal.

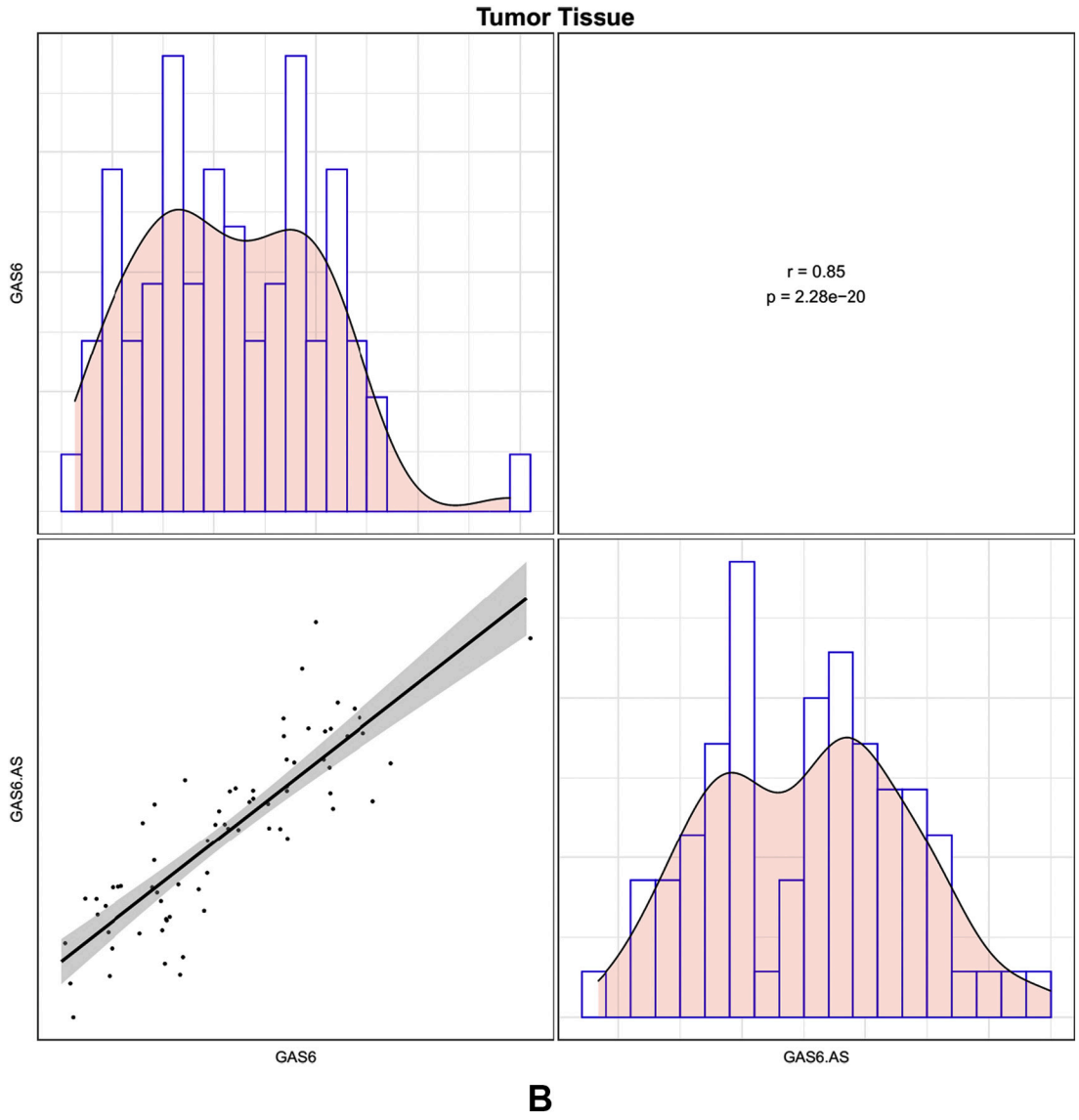

Fig. 2. (*continued*).

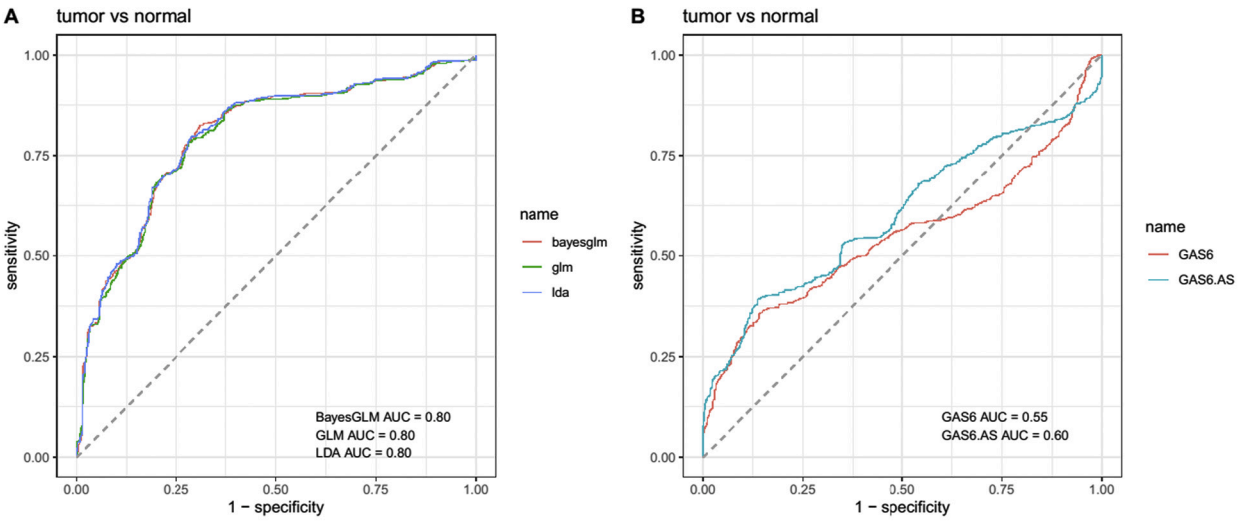

Fig. 3. ROC curves illustrated by three predictive machine learning techniques, i.e. Bayesian Generalized Linear Model, Generalized Linear Model, and Linear Discriminant Analysis (A). ROC curves depicted using the Bayesian Generalized Linear Model (B).

Table 5
Detailed statistics of ROC curve analysis of *GAS6* and *GAS6-AS1* in distinguishing between cancerous and non-cancerous tissues.

Gene	AUC	Sensitivity	Specificity
GAS6	0.55	0.36	0.86
GAS6-AS1	0.60	0.39	0.86
Both	0.80	0.83	0.69

lymph node metastasis and histologic grade in the study conducted by Li et al. Authors have suggested that this lncRNA partake in the evolution and progression of this type of cancer (Li et al., 2016). Such involvement might be through modulation of migratory potential of these cells. Forthcoming functional studies are desired to unravel the mechanism of involvement of this lncRNA in the pathobiology of breast cancer.

Expression of *GAS6-AS1* was associated with PR status. However, expression of this gene and the sense transcript was not associated with any other clinical or demographic variable. Li et al. did not detect association with expression levels of *GAS6-AS1* and PR status (Li et al., 2016). Such discrepancy might reflect the presence of ethnic based heterogeneity.

Both *GAS6* and *GAS6-AS1* had high specificity for distinguishing between cancerous and non-cancerous tissues. Yet, their sensitivity was not appropriate. When combining expression levels of both transcripts, the obtained AUC value was increased to 0.80, indicating suitable power of this panel for the diagnostic purposes. Taken together, *GAS6* and *GAS6-AS1* might participate in the development of breast cancer. Upcoming functional investigations are essential to unravel the molecular route of participation of GAS6 and its antisense in the breast cancer. A limitation of our study is lack of appraisal of association between expression levels of *GAS6/GAS6-AS1* and patients' survival.

Declaration of competing interest

None.

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