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Research Article

The Roles of BTG1 mRNA Expression in Cancers: A Bioinformatics Analysis

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Abstract

Background: BTG1 (B-cell translocation gene 1) might suppress proliferation and cell cycle progression, and induce differentiation, apoptosis, and anti-inflammation. This study aimed to clarify the clinicopathological and prognostic significances of BTG1 mRNA expression in cancers.

Methods: We performed a bioinformatics analysis of BTG1 mRNA expression through Oncomine, TCGA and Kaplan-Meier plotter databases up to July 1, 2017.

Results: Oncomine data showed that BTG1 expression was lower in gastric cancer than normal mucosa, but versa for pulmonary squamous cell carcinoma, breast invasive ductal cancer and ovarian cancer ($p<0.05$). In term of TCGA, BTG1 expression was positively correlated with dedifferentiation, histological grading, and poor prognosis of gastric cancer ($p<0.05$) and TNM staging of ovarian cancer ($p<0.05$), but negatively associated with lymph node metastasis, TNM staging and adverse prognosis of breast cancer ($p<0.05$). BTG1 expression was higher in pulmonary squamous cell carcinoma than adenocarcinoma ($p<0.05$). Younger age, lymph node metastasis, TNM staging and BTG1 hypoexpression was independent factors for worse prognosis of the breast cancer patients ($p<0.05$). According to Kaplan-Meier plotter, BTG1 expression was negatively correlated with favorable prognosis of the gastric, lung or ovarian cancer patients, but the converse was true for breast cancer patients.

Conclusion: BTG1 expression might be employed as a potential marker to indicate carcinogenesis and subsequent progression, even prognosis.

Keywords: BTG1, Bioinformatics analysis, Carcinogenesis, Aggressiveness, Prognosis

Introduction

BTG1 (B-cell translocation gene 1) is reported to suppress cell proliferation and cell cycle progression and induce cell differentiation due to its interaction with the myogenic factor MyoD [1], protein arginine methyltransferase 1 [2], and human carbon catabolite repressor protein-associative factor 1 [3]. *BTG1* has also been reported to enhance Hoxb9-induced transcription to suppress proliferation in HeLa cells [4]. Additionally, *BTG1* mediates apoptotic induction, which is evidenced by *BTG1* overexpression in apoptotic cells [5] and the contribution of *BTG1* to anti-sense Bcl-2- induced cytotoxic effects [6]. *Liu et al.* [7] found that *BTG1* potentiated apoptosis and suppressed proliferation in renal cell carcinoma by interacting with PRMT1. *BTG1* could reverse the miR-22-induced inhibition of autophagy [8] and miR-4295 significantly promoted proliferation, colony formation, and migration of bladder cancer cell via directly targeting *BTG1* [9]. MiRNA-511 promotes the proliferation of human hepatoma cells and miRNA 301A promotes colitis-associated cancer development by inhibiting *BTG1* [10,11]. *BTG1* functioned as a direct target of miR-330-3p, and miR-27a-3p in hepatocellular carcinoma and ovarian cancer cells, and thereby weakened cell viability, migration, and invasion, and promoted cell apoptosis [12,13]. *BTG1* was shown to prevented antigen from inducing molecular features of in vitro allergic reactions as a direct target of miR-183-5p. In atopic dermatitis, NF-κB overexpression and activation was shown to promote the transcription of miR-183-5p by binding to its promoter [14].

Su et al. [15] reported that *BTG1* overexpression triggered G1/S phase cell cycle arrest and increased apoptosis in HCT-116 cells via the ERK/MEK signaling pathway. *Zhu et al.* [16] reported

that *BTG1* enhanced the radiation sensitivity of human breast cancer by inducing cell cycle arrest, the formation of reactive oxygen species, chromosomal aberrations, and apoptosis via inhibition of the PI3K/Akt signaling pathway. *BTG1* overexpression was also found to suppress proliferation, tumor growth and lung metastasis, induce differentiation, autophagy, and apoptosis, and mediate chemosensitivity in colorectal and gastric cancer cells [17,18]. In combination of these data, it is suggested that *BTG1* may function as a tumor suppressor. In the present study, we aimed to clarify the clinicopathological and prognostic significances of *BTG1* mRNA expression in cancers by a bioinformatics analysis of high-throughput cDNA array and RNA sequencing uding online Oncomine, TCGA and Kaplan-Meier plotter.

Materials and Methods

Oncomine Database Analysis

The individual gene expression level of *BTG1* mRNA was analyzed using Oncomine *(*www.oncomine.org*)*, a cancer microarray database and web-based data mining platform for a new discovery from genome-wide expression analyses. We compared the differences in *BTG1* mRNA level between normal tissue and cancer. All data were log-transformed, median centered per array, and standard deviation normalized to one per array.

TCGA Database Analysis

The expression data (RNA-seqV2) and clinicopathological data of gastric (n=392), lung (n=865), breast (n=1093) and ovarian (n=304) cancer patients were downloaded from the Cancer Genome Atlas *(TCGA,* https://cancergenome.nih.gov/) database by TCGA-assembler in R software [19]. We integrated the raw data, analyzed *BTG1* expression in the cancers, and compared it with clinicopathological and prognostic data of the cancer patients. The means were compared with student t test. Kaplan-Meier survival plots were generated with survival curves compared by log-rank statistic. Cox's proportional hazards model was employed for multivariate analysis. Two-sided $p<0.05$ was considered as statistically significant. SPSS 17.0 software was employed to analyze all data.

Kaplan-Meier Plotter Analysis

The prognostic significance of *BTG1* mRNA was also analyzed in gastric, lung, breast and ovarian cancers using Kaplan-Meier plotter *(*http://kmplot.com*)* [20].

Results and Discussion

The Clinicopathological and Prognostic Significances of BTG1 mRNA Expression in Gastric Cancer

According to Wang's database, we found that *BTG1* mRNA expression was lower in gastric cancer than normal tissues (Figure 1A, $p<0.05$). In TCGA data, *BTG1* expression was positively correlated with dedifferentiation, histological grading, and poor prognosis of gastric cancer (Figure 1B, $p<0.05$). According to Kaplan-Meier plotter, a higher *BTG1* expression was negatively correlated with overall and progression-free survival rates of all cancer patients, male or perforating cancer patients and the patients receiving 5-FU-based adjuvant (Figure 1C, Figure 1D &Table 1, $p<0.05$). As shown in Table 1, stage II and IV, T2, N3, intestinal- and mixed-type, or Her2-positive cancer patients with high *BTG1* expression showed a shorter overall survival time than those with its low expression ($p<0.05$). It was similar for progression-free survival in female, male, or poorly differentiated cancer patients ($p<0.05$). Negative association between *BTG1* expression and overall prognosis was observed in the cancer patients only receiving surgical operation (Table 1, $p<0.05$).

Table 1: The prognostic significance of BTG1 mRNA in gastric cancer.

Clinicopathological Features	Overall Survival		Progression-Free Survival	
	Hazard Ratio	p-value	Hazard Ratio	p-Value
Sex				
Female	0.69 (0.45 – 1.07)	0.098	0.65 (0.43 – 0.99)	0.045
Male	1.65 (1.22 – 2.24)	0.001	1.45 (1.08 – 1.94)	0.012
T				
2	1.65 (1.08 – 2.53)	0.019	1.44 (0.9 – 2.32)	0.13
3	0.75 (0.51 – 1.08)	0.12	-	-
4	0.54 (0.2 – 1.48)	0.23	-	-
N				
0	1.98 (0.84 – 4.67)	0.11	1.68 (0.72 – 3.91)	0.22
1--3	1.29 (0.99 – 1.69)	0.062	1.24 (0.92 – 1.67)	0.16
1	1.49 (0.98 – 2.27)	0.063	1.33 (0.89 – 1.98)	0.16
2	0.72 (0.46 – 1.13)	0.15	0.79 (0.51 – 1.21)	0.28

3	2.07 (1.16 – 3.71)	0.013	1.71 (0.97 – 3.01)	0.061
M				
0	-	-	1.28 (0.94 – 1.75)	0.12
1	1.37 (0.99 – 1.91)	0.058	1.63 (0.85 – 3.13)	0.14
TNM Staging				
I	1.67 (0.54 – 5.18)	0.37	0.5 (0.16 – 1.57)	0.23
II	2.5 (1.05 – 5.97)	0.032	1.89 (0.84 – 4.26)	0.12
III	0.81 (0.56 – 1.19)	0.28	0.74 (0.48 – 1.13)	0.16
IV	1.73 (1.14 – 2.65)	0.0099	1.38 (0.92 – 2.08)	0.11
Differentiation				
Well-Differentiated	-	-	-	-
Moderately Differentiated	0.62 (0.32 – 1.21)	0.16	0.66 (0.35 – 1.24)	0.2
Poorly Differentiated	0.61 (0.37 – 1.01)	0.05	0.59 (0.37 – 0.94)	0.026
Lauren's Classification				
Intestinal Type	1.49 (1.03 – 2.13)	0.031	1.38 (0.95 – 2.02)	0.092
Diffuse Type	1.18 (0.82 – 1.68)	0.38	0.81 (0.56 – 1.18)	0.27
Mixed Type	3.52 (1.11 – 11.15)	0.023	0.5 (0.18 – 1.35)	0.16
Her2 Positivity				
-	1.27 (0.97 – 1.66)	0.078	1.23 (0.91 – 1.65)	0.18
+	1.73 (1.11 – 2.71)	0.015	1.42 (0.89 – 2.27)	0.14
Perforation				
-	0.57 (0.38 – 0.86)	0.0059	0.61 (0.42 – 0.9)	0.011
Treatment				
Surgery Alone	1.56 (1.13 – 2.14)	0.0063	1.31 (0.96 – 1.77)	0.083
5-FU-Based Adjuvant	0.21 (0.06 – 0.71)	0.0058	0.16 (0.05 – 0.55)	0.00095
Another Adjuvant	0.6 (0.25 – 1.47)	0.26	1.54 (0.69 – 3.44)	0.29

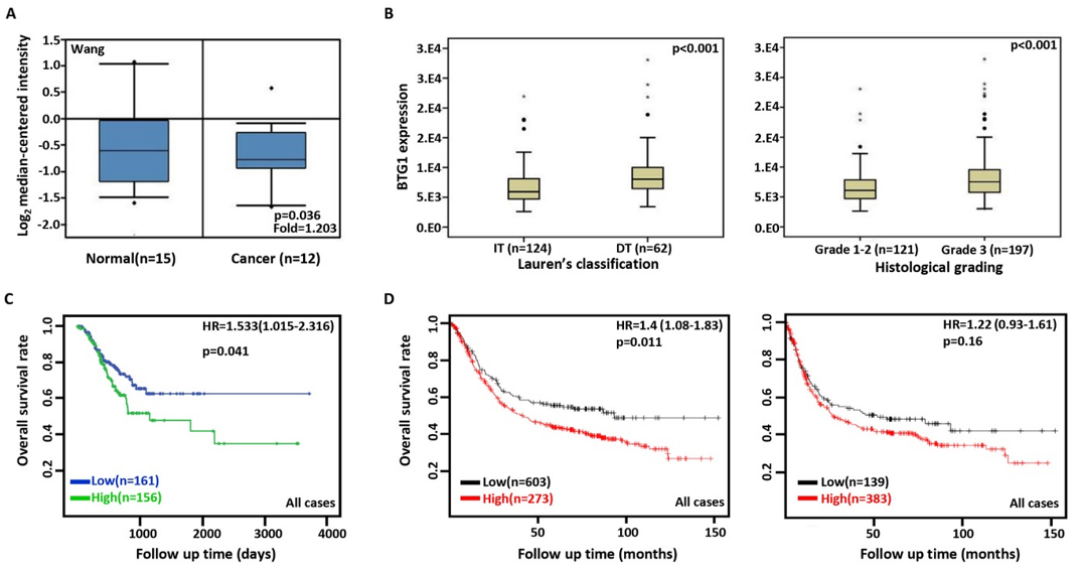

Figure 1: The clinicopathological and prognostic significances of *BTG1* mRNA expression in gastric cancer.

Wang's dataset was used for bioinformatics analysis to explore *BTG1* expression in gastric cancer. A lower *BTG1* expression was detectable in gastric cancer than that in normal mucosa (A, $p<0.05$). TCGA database showed that *BTG1* was less expressed in intestinal-type (IT) than diffuse-type (DT) ones, and in Grade 1-2 than Grade 3 carcinomas (B, $p<0.05$). *BTG1* expression was negatively correlated with overall survival rate of the cancer patients (C, $p<0.05$). It was the same for the overall and progression-free survival rates of the patients with gastric cancer according to the data from Kaplan-Meier plotter (D, $p<0.05$). HR, hazard ratio.

The Clinicopathological and Prognostic Significances of BTG1 mRNA Expression in Lung Cancer

Then, we used Talbot's and Hou's datasets to perform bioinformatics analysis and found that *BTG1* expression was higher in squamous cell carcinoma than normal tissue (Figure 2A, p<0.05). In TCGA data, *BTG1* expression was higher in squamous cell carcinoma than adenocarcinoma, in male than female cancer patients, and in elder than younger cancer patients (Figure 2B, p<0.05). According to Kaplan-Meier plotter, we found that a higher *BTG1* expression was negatively correlated with the overall rate of all, male, or grade 2 cancer patients (Figure 2C, p<0.05).

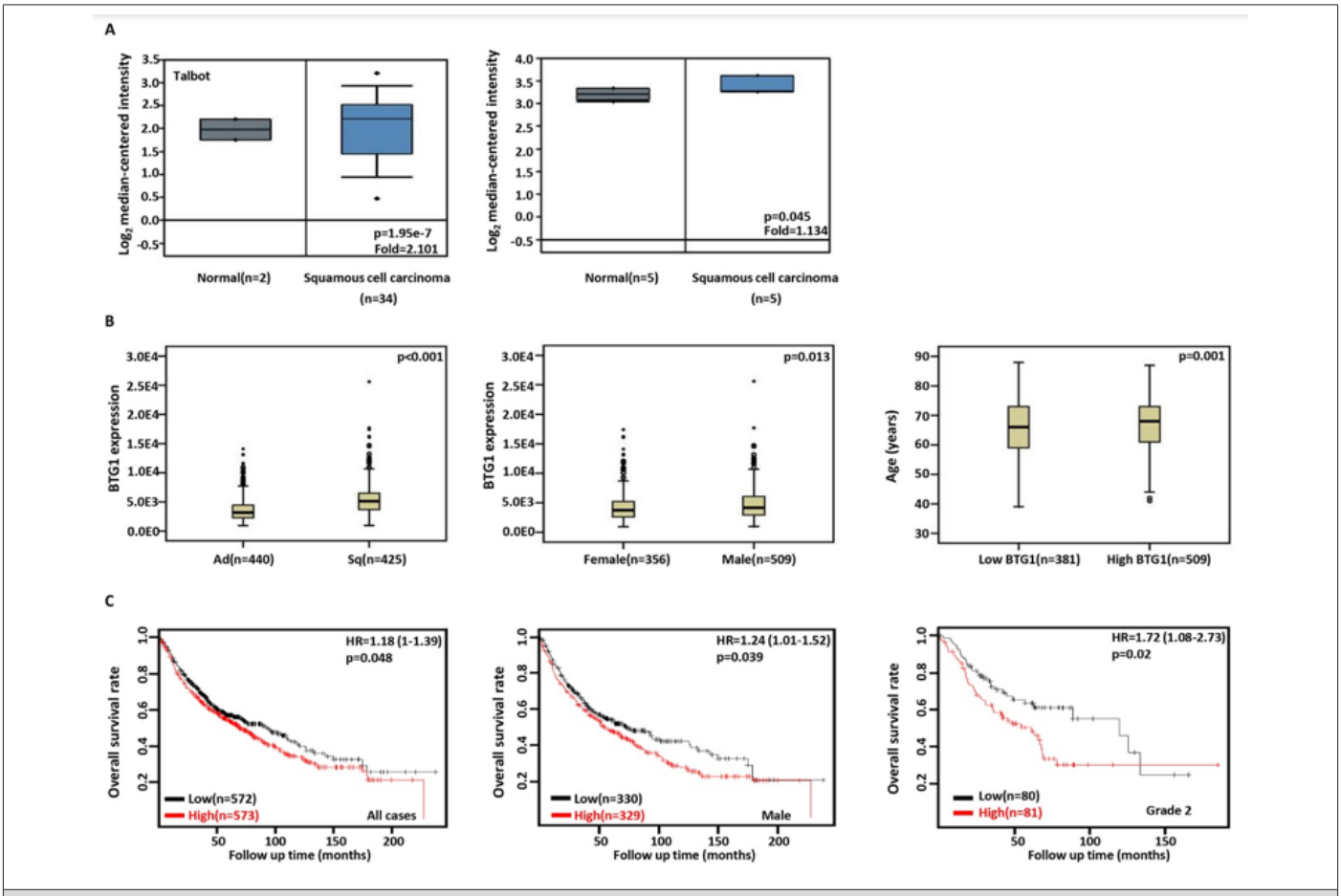

Figure 2: The clinicopathological and prognostic significances of *BTG1* mRNA expression in lung cancer.

Talbot's and Hou's datasets were employed for bioinformatics analysis to analyze *BTG1* expression during lung carcinogenesis. *BTG1* expression was up regulated in squamous cell carcinoma, compared with normal tissue (A, *p*<0.05). In TCGA database, *BTG1* expression was compared with histological subtyping, gender, and age of the cancer patients (B). The correlation between *BTG1* expression and overall or post-progression survival rate of the patients with lung cancer was analysis using KM plotter (C). HR, hazard ratio.

The Clinicopathological and Prognostic Significances of BTG1 mRNA Expression in Breast Cancer

BTG1 was more expressed in breast invasive ductal cancer than normal tissues according to Karnoub's database (Figure 3A, p<0.05). TCGA database showed that *BTG1* expression was negatively associated with lymph node metastasis, TNM staging and adverse prognosis of breast cancer (Figure 3B&3C, p<0.05). Cox's risk proportional analysis showed that younger age, lymph node metastasis, TNM staging and *BTG1* hypoexpression were independent factors for worse prognosis of the patients with breast cancer (Table 2, p<0.05). According to Kaplan-Meier plotter, a higher *BTG1* expression was positively correlated with overall survival rates of all or luminal-B cancer patients (Figure 3D, p<0.05). Her2-negative and luminal-B cancer patients with high *BTG1* expression showed a long distant- metastasis-free survival time than those with its low expression (p<0.05, data not shown). There appeared a positive relationship between *BTG1* expression and the progression-free survival rate of the cancer patients without chemotherapy or margin invasion (p<0.05, data not shown). The overall survival rate of the patient with ER-negative, Grade-3, or luminal-B cancer was higher in the group of high *BTG1* expression than its low expression (p<0.05, data not shown).

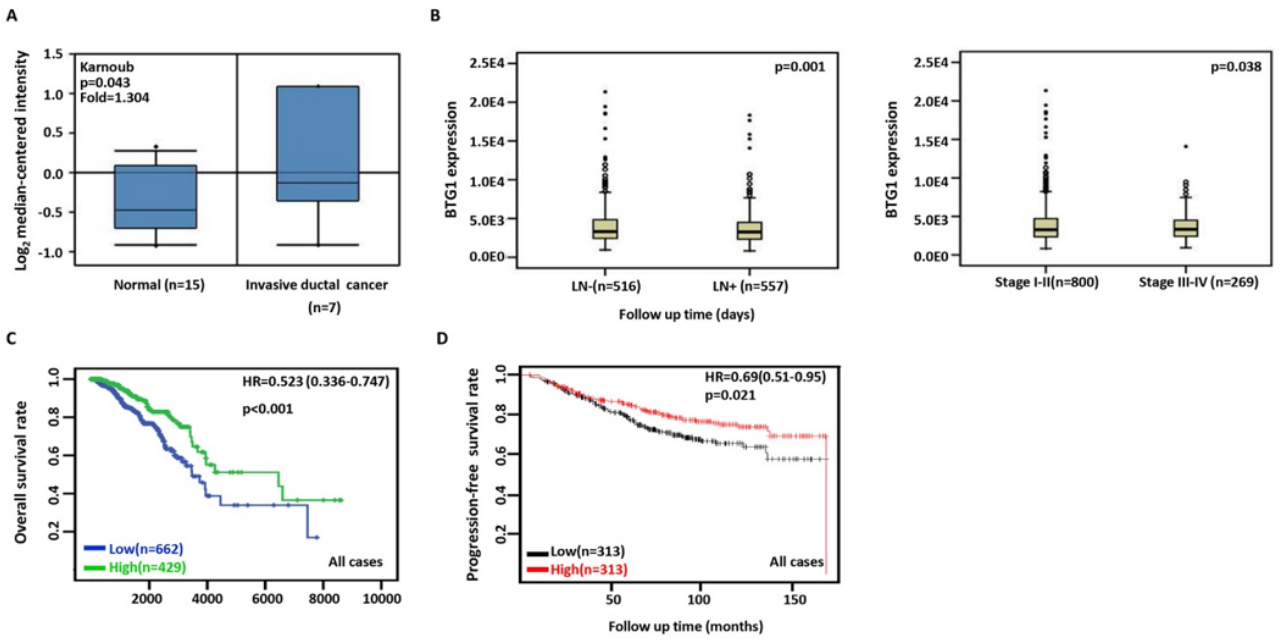

Figure 3: The clinicopathological and prognostic significances of *BTG1* mRNA expression in breast cancer.

According to Karnoub's data, *BTG1* overexpression was detectable in breast invasive ductal cancer, compared with normal breast tissue (A, $p<0.05$). TCGA database showed a higher *BTG1* expression was negatively correlated with lymph node metastasis and TNM staging of breast cancer (B, $p<0.05$). The overall survival rate of the cancer patients was higher in high than low *BTG1* expression groups according to TCGA database (C, $p<0.001$) and KM plotter (D, $p<0.05$). HR, hazard ratio.

Table 2: Multivariate analysis of hazard factors of the prognosis of the patients with breast cancer.

Clinicopathological Features	Hazard Ratio (95% CI)	p-value
Age (<60/≧60years)	2.175 (1.467-3.226)	<0.001
Gender (Female/Male)	0.589 (0.081-4.266)	0.6
Stage T (T1-2/T3-4)	0.713 (.401-1.269)	0.25
Lymph Node Metastasis (-/+)	1.761 (1.066-2.911)	0.027
TNM Staging (I-II/III-IV)	2.341 (1.343-4.083)	0.003
Histological Classification (Ad/Sq)	1.090 (0.650-1.828)	0.744
BTG1 mRNA Expression (Low/High)	0.503 (0.329-0.770)	0.002

Note*: Ad, Adenocarcinoma; Sq, Squamous Cell Carcinoma.

The Clinicopathological and Prognostic Significances of *BTG1* mRNA Expression in Ovarian Cancer

Then, we used Bonome's and Hendrix's datasets to perform bioinformatics analysis and found that *BTG1* expression was higher in ovarian cancers or mucinous adenocarcinoma than normal tissues (Figure 4A, p<0.05). In TCGA data, *BTG1* expression was higher in stage III-IV than I-II cancers (Figure 4B, p<0.05). According to Kaplan-Meier plotter, a higher *BTG1* expression was negatively correlated with the overall survival rates of Dubulk suboptimal and p53-mutanttant cancer patients (Figure 4C, p<0.05). Stage I+II, II, II+III, III, and III+IV cancer patients with high *BTG1* expression showed a short progression-free survival time than those with its low expression (Figure 4C, p<0.05). There appeared a negative relationship between *BTG1* expression and the overall survival rate of the cancer patients with paclitaxel treatment (Figure 4D, p<0.05).

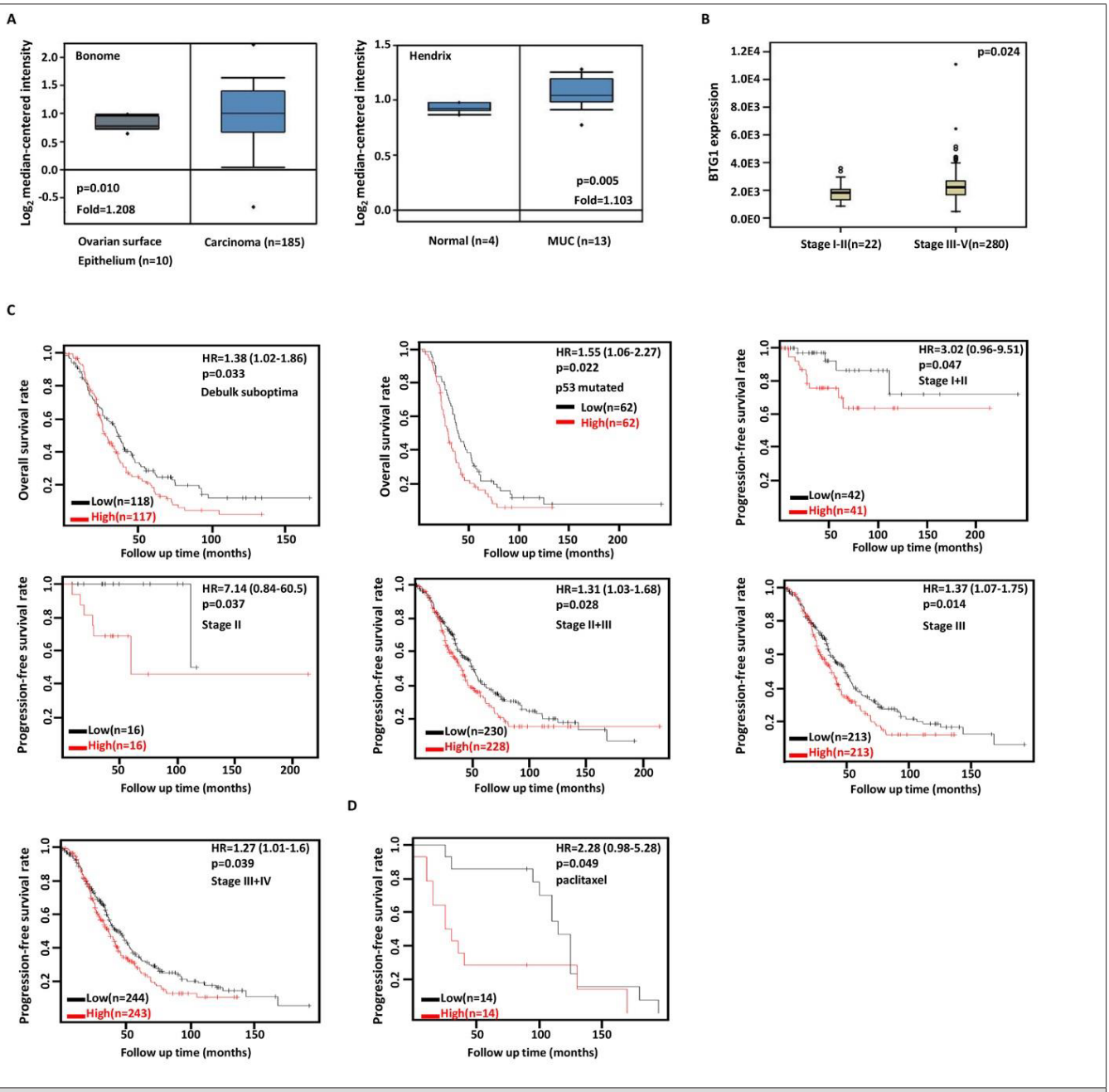

Figure 4: The clinicopathological and prognostic significances of *BTG1* mRNA expression in ovarian cancer

Bonome's and Hendrix's datasets were employed for bioinformatics analysis to observe *BTG1* expression in ovarian cancer. A lower *BTG1* expression was detectable in ovary than that in ovarian carcinoma or mucinous adenocarcinoma (MUC) respectively (A, $p<0.05$). TCGA database showed that *BTG1* was more expressed in stage III-IV than I-II cancer (B, $p<0.05$). The correlation between expression and overall, or post-progression survival rate of the patients with ovarian cancer, even stratified by different clinicopathological parameters (C, $p<0.05$). HR, hazard ratio.

Conclusion

BTG1 overexpression suppressed proliferation, migration and invasion, and induced apoptosis and cell cycle arrest of hepatocellular, thyroid, nasopharyngeal, esophageal, breast, and non-small cell lung cancer cells with down-regulated expression of Cyclin D1, Bcl-2, and MMP-9 [21-26]. In ovarian cancer, *BTG1* expression caused lower growth rate, high cisplatin sensitivity, G1 arrest, apoptosis, and decreased migration and invasion by down-regulating the expression of PI3K, PKB, Bcl-xL, survivin, VEGF, and MMP-2 [27]. The chemosensitivity of *BTG1* transfectants to paclitaxel, cisplatin, MG132 or SAHA was positively correlated with its apoptotic induction of colorectal cancer cells [18]. *BTG1* overexpression suppressed tumor growth and lung metastasis of gastric and colorectal cancer cells by inhibiting proliferation and enhancing autophagy and apoptosis in xenograft models [17,18]. Taken together, *BTG1* should be used as a molecular target for cancer gene therapy. *Jung et al.* [28] found that *BTG1* expression

was lower in colorectal cancer than control, and in metastatic than primary cancer, due to the hypermethylation of *BTG1* promoter. *BTG1* expression was decreased in hepatocellular, thyroid, nasopharyngeal, esophageal, breast, colorectal, and non-small cell lung cancers, and negatively associated with aggressive behaviors [20-26]. Decreased *BTG1* expression in gastric cancer was positively correlated with depth of invasion, lymphatic and venous invasion, lymph node metastasis, TNM staging and worse prognosis [16], but the lower *BTG1* expression in ovarian cancer was positively correlated with FIGO staging [25]. Here, it was found that *BTG1* expression was lower in gastric cancer than normal mucosa in line with both Kanda's and our reports [17,29], but versa for pulmonary squamous cell carcinoma, breast invasive ductal cancer, and ovarian cancer, different from the other results [24-26]. Reportedly, the downregulated *BTG1* expression is positively correlated with its promoter methylation in colorectal, gastric, and ovarian cancers [17,29 &30]. Moreover, *BTG1* expression was positively correlated with dedifferentiation and histological grading and of gastric cancer, and TNM staging of ovarian cancer, but negatively associated with lymph node metastasis and TNM staging of breast cancer. *BTG1* expression was higher in pulmonary squmaous cell carcinoma than adenocarcinoma, which provided another evidence that squamous cell carcinoma but not adenocarcinoma showed higher *BTG1* expression than normal tissue. These findings suggested that aberrant *BTG1* expression was positively correlated with carcinogenesis, histogenesis and subsequent progression. The paradoxical data in our and other data may be due to sample selection, different methodologies, and tissue specificity. *Kanda et al.* [29] reported that downregulation of *BTG1* mRNA in gastric cancer was positively associated with shorter disease-specific and recurrence-free survival of the patients with gastric cancer as an independent prognostic factor. *BTG1* expression was adversely linked to poor prognosis of the patients with hepatocellular, thyroid, nasopharyngeal, esophageal, breast, or non-small cell lung cancer [22-26]. According to Kaplan-Meier plotter, we found that *BTG1* expression was negatively correlated with favorable prognosis of the gastric, lung or ovarian cancer patients, but versa for breast cancer patients. The correlation between *BTG1* expression and prognosis of the cancer patients did not parallel with the alteration in *BTG1* expression in cancer tissues. Additionally, TCGA data showed the same results about the prognostic significance of *BTG1* expression to KM plotters in gastric and breast cancers although KM plotter is based on cDNA array and TCGA experiment on RNA sequencing. The tissue specificity might account for the phenomenon about the relationship between *BTG1* expression and prognosis.

In conclusion, aberrant *BTG1* mRNA expression was closely linked to carcinogenesis, cancer aggressiveness, and worse prognosis of the cancer patients in a tissue-specific manner. The limitation of this study is not to verify the results from Oncomine, TCGA and KM plotter datasets using real-time RT-PCR, even after laser capture dissection.

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Conflict of Interest

The authors have declared that no competing interests exist.

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