Biglycan as a potential diagnostic and prognostic biomarker in multiple human cancers

SHOU-FENG ZHAO[1], XUE-JING YIN[2], WEN-JU ZHAO[3], LE-CUI LIU[4] and ZHI-PENG WANG[5]

[1]Central Laboratories, Qingdao Municipal Hospital, Qingdao, Shandong 266000; [2]Department of Pharmacy, Qingdao Mental Health Centre; [3]Operating Room, Qingdao Jinhua Gynecology Hospital, Qingdao, Shandong 266235; [4]Neonatal Department, Wulian County People's Hospital, Wulian, Shandong 262300; [5]Marine Science and Engineering College, Qingdao Agricultural University, Qingdao, Shandong 266109, P.R. China

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Abstract. Biglycan (BGN), a key member of the small leucine-rich proteoglycan family, is an important component of the extracellular matrix. Clinical studies have demonstrated that upregulation of BGN is associated with poor prognosis in patients with various types of solid cancer. The present study analyzed the mRNA expression levels of BGN in various types of solid cancer when compared with that in normal tissues via the Oncomine database. The UALCAN, OncoLnc and Kaplan-Meier Plotter databases were additionally used to evaluate the prognostic values of BGN in patients with solid cancer and co-expression gene analysis was conducted using the protein-protein interaction networks of BGN. The present study observed that the mRNA expression levels of BGN were increased in bladder, brain and central nervous system, breast, colorectal, esophageal, gastric, head and neck, lung, ovarian and 28 subtypes of cancer compared with normal tissues. The increased expression of BGN was identified to be associated with a poor outcome in ovarian and gastric cancer. Based on the co-expression network, BGN was identified as the key gene in a 43-gene network. The present findings of increased expression of BGN in solid tumors and its positive association with poor outcome on patient survival indicate that BGN may serve as a prognostic marker and as a target for novel therapeutics for multiple types of cancer.

Introduction

Cancer is considered as one of the four major non-communicable diseases (1). Due to a delay in diagnosis, its poor prognosis and high recurrence rate, cancer is becoming one of the leading causes of mortality worldwide (2,3). Cancer incidence and mortality rates have increased over the last decade. The global cancer burden is estimated to have risen to 18.1 million new cancer cases, and 9.6 million cancer-associated mortalities were reported in 2018 (4), compared with 12.7 million and 7.6 million, respectively, in 2008 (5). Therefore, there is an urgent need to explore novel potential cancer biomarkers that will have beneficial prognostic and therapeutic implications.

Biglycan (BGN; also known as proteoglycan-1 and dermatan sulfate PG-1) is a single-copy gene localized on the long arm of human X chromosome Xq13-qter (6). This gene contains at least two introns and it spans ~6 kb in length (7). BGN is a key member of the small leucine-rich proteoglycan family that resides at the cell surface or in the pericellular space of tissues (8). BGN is typically expressed in the nerve, bone, cartilage, skin and muscles, modulating the morphology, growth, adhesion, bone mineralization, inflammation, migration and differentiation of epithelial cells (9). The upregulation of BGN has been reported in multiple types of solid cancer, including ovarian carcinoma (10), prostate cancer (11), pancreatic cancer (12), gastric cancer (13) and colon cancer (14). Overexpressed BGN has been reported to be associated with the aggressive growth and metastasis of tumors (13,14), and with a worse prognosis for patients with gastric cancer (15) and pancreatic adenocarcinoma (16). These findings suggest that the *BGN* gene may act as either a potential therapeutic target or prognostic biomarker in multiple types of cancer. However, the transcriptional expression and prognostic value of the *BGN* gene in human cancers requires further investigation.

The present study investigated the mRNA expression levels of BGN in human normal and cancer tissues, using the Oncomine database. In addition, the prognostic value of BGN mRNA expression in patients with cancer was also assessed using the UALCAN, OncoLnc and the Kaplan-Meier Plotter databases. Finally, co-expression gene analysis was conducted using the protein-protein interaction (PPI) networks of BGN.

Materials and methods

Analysis of BGN expression in multiple cancers using Oncomine. Oncomine is a cancer microarray database and web-based data-mining platform aimed at facilitating discovery from genome-wide expression analyses, as well as

Correspondence to: Dr Zhi-Peng Wang, Marine Science and Engineering College, Qingdao Agricultural University, 17 Wenhai Road, Jimo, Qingdao, Shandong 266109, P.R. China
E-mail: wangzp@ysfri.ac.cn

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comparing the transcriptome data in multiple types of cancer, respective to normal tissues (17). To date, the Oncomine database contains 19 cancer types, 715 datasets and 86,733 samples, corresponding to ~48 million gene expression measurements. Differential mRNA level analyses of BGN were compared between normal tissues and malignant human tissues in different types of cancer, using the Oncomine database. In the present study, the thresholds were set at 2-fold change, $P<1x10^{-4}$ and the top 10% gene rank.

Analysis using the Kaplan-Meier (KM) plotter, UALCAN and OncoLnc databases. The prognostic significance of the mRNA expression levels of BGN in various types of cancer was evaluated using KM plotter (http://www.kmplot.com), UALCAN (http://ualcan.path.uab.edu) and OncoLnc (http://oncolnc.org). These online databases can be used to assess the effect of gene expression on cancer prognosis. The three databases of KM plotter, OncoLnc and UALCAN contain the same RNA-seq data (from TCGA) for 20 http://www.kmplot.com/analysis/index.php?p=service&cancer=pancancer_rnaseq, 21 (18) and 35 (19) types and subtypes of cancer, respectively. KM plotter also contain the gene chip data [from GEO (breast cancer: GSE12276, GSE16391, GSE12093, GSE11121, GSE9195, GSE7390, GSE6532, GSE5327, GSE4922, GSE3494, GSE2990, GSE2034, GSE1456; ovarian cancer: GSE14764, GSE15622, GSE19829, GSE3149, GSE9891, GSE18520, GSE26712; lung cancer: GSE4573, GSE14814, GSE8894, GSE19188, GSE3141, GSE31210, GSE29013, GSE37745; gastric cancer: GSE44740, GSE51725, GSE13911, GSE43346, and GSE3526)] (20-23) for breast cancer (BC), lung cancer (LC), gastric cancer (GC) and ovarian cancer (OC). Therefore, the prognostic significance of the mRNA expression levels of BGN in various types of carcinomas, including BC, LC, GC and OC was evaluated using RNA-seq data and confirmed by gene chip data. The overall survival rate (OS) in patients with other types and subtypes of carcinomas was estimated using RNA-seq by KM plotter, OncoLnc or UALCAN databases.

The KM plotter is able to assess the effect of 54,675 genes on survival using 10,461 cancer samples. In this database, the types and subtypes of cancer samples were observed from RNA-sequencing (RNA-seq) data while the lung (22), ovarian (21), gastric (23), and breast (20) cancer samples were also analyzed from gene chip microarrays.

Patient samples were divided into two cohorts according to the median expression of the *BGN* gene (high vs. low expression). The present study analyzed the overall survival (OS) in patients using a Kaplan-Meier survival plot. Briefly, the *BGN* gene was uploaded into the respective databases to obtain the Kaplan-Meier survival plots, in which the number-at-risk was presented below the main plot. Affymetrix ID (or RNA-seq ID), log rank P-value and hazard ratio (HR) with 95% confidence intervals were calculated and displayed on the webpage. P<0.05 was considered to indicate a statistically significant difference.

UALCAN, is an interactive web resource for analyzing cancer transcriptome data, built on PERL-common gateway interface with high quality graphics using JavaScript and Cascading Style Sheets. UALCAN was used to construct an algorithm based on The Cancer Genome Atlas (TCGA) level 3 RNA-seq database (https://portal.gdc.cancer.gov/). UALCAN can provide publication quality graphs and plots depicting gene expressions and patient survival information based on gene expression (19). P<0.05 was considered to indicate a statistically significant difference.

OncoLnc is a tool for interactively exploring survival correlations. OncoLnc contains survival data for 8,647 patients from 21 cancer studies performed by TCGA, along with RNA-seq expression for mRNAs and microRNAs from TCGA and long non-coding RNA expressions from MiTranscriptome (β release) (http://www.mitranscriptome.com/). OncoLnc stores precomputed survival analyses, allowing users to quickly explore survival correlations for up to 21 types of cancer in a single click (18). The *BGN* gene was uploaded into the database to obtain the patient survival information. P<0.05 was considered to indicate a statistically significant difference.

Co-expression and PPI network construction. The present study extracted the top 50 co-expressed genes that have similar expression pattern with *BGN* gene, based on Pearson correlation score across all tumor samples from the GEPIA database (http://gepia.cancerpku.cn/index.html). Then, the 11.0 Search Tool for the Retrieval of Interacting Genes/Proteins database (http://string-db.org/), was used to construct a PPI network with these co-expressed genes (24). The PPI pairs were extracted with a combined score of 0.4. Subsequently, the PPI network was visualized using the Cytoscape 3.7.0 software (http://www.cytoscape.org/).

Results

Increased expression of BGN in multiple types of solid cancer. As illustrated in Fig. 1, Oncomine contained a total of 421 research studies for the *BGN* gene. In 78 analyses, *BGN* exhibited statistically significant differences, 5 of which revealed lower mRNA expression levels in solid tumors compared with normal tissues, while 73 analyses indicated the opposite result (Fig. 1). *BGN* gene expression was the most upregulated in bladder, brain and central nervous system (CNS), breast, colorectal, gastric, head and neck, pancreatic cancer and other cancer, followed by esophageal, kidney, liver, ovarian cancer, and lung cancer (Fig. 1). Results in the investigation of *BGN* gene expression have been inconsistent in a number of studies (25-33), including kidney, liver, pancreatic, and prostate cancer. The expression levels of BGN in cervical cancer and melanoma were not significantly changed (Fig. 1). The *BGN* gene expression status in lymphoma, leukemia, sarcoma and myeloma was not analyzed in this study as they are not classified as solid cancers (34).

Solid cancers, in which BGN was reported to be upregulated consistently in different studies, were examined further in the various cancer subtypes using the Oncomine datasets. The data summarized in Table I revealed that there was a significant increase in expression of BGN in BLC, including subtype of IBLCA) (n=53), when compared with that in normal tissues (n=3) in the study by Blaveri *et al* (35). The BGN mRNA expression was significantly elevated in brain and CNS cancer, including subtype of GBM (n=130) when compared with normal tissues (n=30) in the study conducted by Bredel *et al* (36). The mRNA expression of BGN was significantly elevated in BC, including subtypes BRCA, DBC,

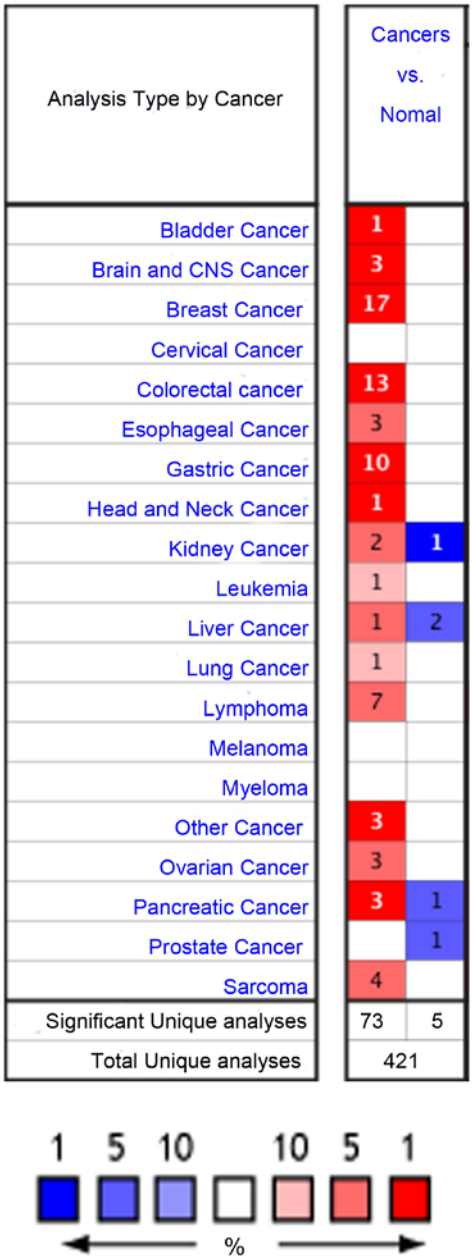

Figure 1. mRNA expression levels of BGN in different types of cancer from the Oncomine database. The schematic reveals the numbers of datasets with statistically significant mRNA overexpression (red) or underexpression (blue) of the target gene. Darker red indicates higher *BGN* expression, Darker blue indicates lower *BGN* expression. The color is determined by the best gene rank percentile for the analyses within the cell. The number in each cell represents the number of analyses that met the thresholds of: Gene, BGN; analysis type, cancer vs. normal; and data type, mRNA. The thresholds were set at 2-fold change, $P<1x10^{-4}$ and the top 10% gene rank. For cervical cancer, melanoma, myeloma and prostate cancer, there was no analysis (white cell) that met the aforementioned thresholds. The gene rank was analyzed using the percentile of target gene in the top of all genes measured in each analysis. BGN, biglycan; CNS, central nervous system.

DCIS, IDBC, IDBCs, IDC, IDC-L, ILBC, ILC, LBC, MBC and TBC (n=2,540) compared with that in normal tissues (n=240), which was performed by Ma *et al* (37), Curtis *et al* (38), Karnoub *et al* (39), Perou *et al* (40), Zhao *et al* (41) and TCGA studies (42,43) The mRNA expression of BGN was also significantly upregulated in CC, including subtypes COAD, CMA, RSA, CeAC and READ (n=463), when compared with that in normal tissues (n=150), which was reported in the studies conducted by Kaiser *et al* (44), Skrzypczak *et al* (45), Graudens *et al* (46), TCGA (47), Gaedcke *et al* (48), and Hong *et al* (49). BGN mRNA expression was also significantly upregulated in EC, including subtype ESCC (n=84), when compared with that in normal tissues (n=80), which was reported in the studies of Su *et al* (50), Hu *et al* (51) and Hao *et al* (52). BGN mRNA expression was also significantly higher in GC, including subtypes ITGA, DGAC and GMA (n=265), when compared with that in normal tissues (n=171), as reported by Chen *et al* (53), Cho *et al* (54), Wang *et al* (55), D'Errico *et al* (56) and Cui *et al* (57). The mRNA expression of BGN was also significantly increased in HNC, including subtype SGACC (n=16) compared with that in normal tissues (n=6) in the study by Frierson *et al* (58). The mRNA expression of BGN was significantly higher in LC, including subtype SCC (n=34) compared with that in normal tissues (n=28) in the study by Talbot *et al* (59). The mRNA expression of BGN was increased significantly in OC, including subtypes SSPC and OSC (n=799) compared with that in normal tissues (n=22), as reported by Welsh *et al* (60), and Bonome *et al* (61), and studies listed in TCGA (62). The mRNA expression of BGN was increased significantly in other types of cancer, including subtype SBCC (n=15) compared with that in normal tissues (n=4), as reported by Riker *et al* (63). Therefore, the expression of BGN was significantly increased in human solid cancers, including 10 types and 28 subtypes of carcinoma. These results indicate that the mRNA expression of BGN is elevated in a wide range of tumors, when compared with that in normal tissues.

High BGN expression and survival outcome in multiple types of solid cancer. The expression of BGN was significantly increased in certain types of human solid cancers, including bladder, brain and CNS, breast, colorectal, gastric, head and neck, esophageal, ovarian, lung and other cancers, however there was no data on the downregulation of the BGN from the database (Table I). The present study used the Kaplan-Meier Plotter, OncoLnc and UALCAN databases to identify the association between survival time and the mRNA levels of BGN in patients with different types and subtypes of solid cancer.

As shown in Table II, *BGN* gene with a significant association with patient survival can be identified in GC and OC ($P<0.05$). There is no significant association of BGN upregulation with patient survival in BC, EC ($P>0.05$), IBC, READ, COAD, and ESCC ($P>0.05$). The survival rate of patients with LC with $P>0.05$ in RNA-seq and $P<0.05$ in microarray analysis requires further investigation. Therefore, high BGN mRNA expression may potentially be associated with the prognosis in patients with BLC, LSCC, and OSC, as the present analyses provided RNA-seq analysis results ($P<0.05$) without microarray analysis confirmation (Table II). The association between BGN mRNA expression and prognosis in patients with other types of cancer and subtypes of cancer requires further investigation as there is no prognostic data in the KM plotter, OncoLnc and UALCAN database (Table III).

As presented in Fig. 2, high expression of BGN was significantly associated with shorter OS time in patients with GC [HR=1.9 (1.56-2.32), $P=1.3x10^{-10}$ in microarry analysis; HR=1.59 (1.13-2.24), $P=6.8x10^{-3}$ in RNA-seq analysis] and

Table I. Significant changes of biglycan mRNA expression between different subtypes of bladder, brain and CNS, breast, colorectal, esophageal, gastric, head and neck, lung, ovarian, other types of cancer and 28 subtypes cancer.

Type of cancer	Cancer Subtype (n)	Normal, n	Fold change	t-test	P-value	Rank, %	(Refs.)
Bladder	Infiltrating Bladder Urothelial Carcinoma (IBLCA) (53)	3	2.391	6.799	$7.02x10^{-7}$	1	(35)
Brain and CNS	Glioblastoma (GBM) (27)	4	3.055	13.066	$6.77x10^{-14}$	1	(36)
	Glioblastoma (GBM) (22)	3	13.32	7.773	$4.92x10^{-5}$	4	
	Glioblastoma (GBM) (81)	23	2.163	7.599	$7.14x10^{-11}$	7	
Breast	Ductal Breast Carcinoma in Situ Stroma (DCIS) (11)	14	13.191	7.155	$2.28x10^{-11}$		(37)
	Invasive Ductal Breast Carcinoma Stroma (IDC) (9)	14	7.232	5.357	$1.27x10^{-6}$	1	
	Invasive Lobular Breast Carcinoma (ILC) (36)	61	3.312	13.142	$1.58x10^{-22}$	1	(42,43)
	Invasive Breast Carcinoma (BRCA) (76)	61	3.131	14.001	$1.22x10^{-27}$	1	
	Male Breast Carcinoma (MBC) (3)	61	4.661	10.406	$3.76x10^{-5}$	4	
	Mixed Lobular and Ductal Breast Carcinoma (IDC-L) (7)	61	2.780	5.576	$8.56x10^{-5}$	4	
	Invasive Ductal Breast Carcinoma (IDC) (389)	61	2.714	14.829	$5.11x10^{-25}$	5	
	Tubular Breast Carcinoma (TBC) (67)	144	3.014	18.174	$4.05x10^{-41}$	1	(38)
	Invasive Lobular Breast Carcinoma (ILBC) (148)	144	3.087	19.715	$8.92x10^{-56}$	1	
	Invasive Ductal and Invasive Lobular Breast Carcinoma (IDC and ILC) (90)	144	2.885	14.973	$4.81x10^{-33}$	1	
	Breast Carcinoma (BC) (14)	144	2.884	5.505	$3.00x10^{-5}$	4	
	Invasive Ductal Breast Carcinoma (IDC) (1556)	144	2.988	26.199	$1.50x10^{-62}$	5	
	Medullary Breast Carcinoma (MBC) (32)	144	2.256	6.302	$1.13x10^{-7}$	9	
	Invasive Ductal Breast Carcinoma Stroma (IDBCs) (7)	15	3.546	6.337	$2.70x10^{-6}$	1	(39)
	Ductal Breast Carcinoma (DBC) (36)	3	3.337	9.550	$7.02x10^{-6}$	2	(40)
	Lobular Breast Carcinoma (LBC) (21)	3	3.337	10.925	$1.22x10^{-7}$	1	(41)
	Invasive Ductal Breast Carcinoma (IDBC) (38)	3	6.756	12.230	$1.80x10^{-6}$	5	
Colorectal	Colon Adenocarcinoma (COAD) (41)	5	3.200	13.125	$1.74x10^{-15}$	1	(44)
	Colon Mucinous Adenocarcinoma (CMA) (13)	5	2.942	9.781	$6.65\ x10^{-8}$	1	
	Rectosigmoid Adenocarcinoma (RSA) (10)	5	3.799	7.377	$4.85x10^{-6}$	2	
	Cecum Adenocarcinoma (CeAC) (17)	5	3.039	6.529	$1.17x10^{-6}$	4	
	Colorectal Carcinoma (CC) (36)	24	4.795	8.671	$3.32x10^{-12}$	1	(45)
	Colorectal Carcinoma (CC) (18)	12	2.563	5.442	$5.94x10^{-6}$	4	(46)
	Colon Carcinoma (cc) (5)	10	7.740	15.965	$3.60x10^{-10}$	2	(45)
	Colon Adenocarcinoma (COAD) (5)	10	4.099	14.219	$6.23x10^{-9}$	2	
	Colon Mucinous Adenocarcinoma (CMA) (101)	22	2.324	11.956	$3.48x10^{-19}$	3	(47)
	Rectal Adenocarcinoma (READ) (22)	22	3.772	10.097	$4.62x10^{-11}$	3	
	Rectal Adenocarcinoma (READ) (60)	22	2.065	8.557	$3.90x10^{-13}$	7	
	Rectal Adenocarcinoma (READ) (65)	65	2.068	11.751	$2.16x10^{-19}$	6	(48)
	Colorectal Carcinoma (CC) (70)	12	3.508	9.208	$4.02x10^{-9}$	7	(49)

Table I. Continued.

Type of cancer	Cancer Subtype (n)	Normal, n	Fold change	t-test	P-value	Rank, %	(Refs.)
Esophageal	Esophageal Squamous Cell Carcinoma (ESCC) (53)	53	2.795	10.666	$3.73x10^{-17}$	2	(50)
	Esophageal Squamous Cell Carcinoma (ESCC) (17)	17	2.964	5.524	$3.47x10^{-6}$	5	(51)
	Esophageal Adenocarcinoma (EA) (14)	10	10.158	8.460	$8.51x10^{-5}$	5	(52)
Gastric	Gastric Intestinal Type Adenocarcinoma(ITGA) (62)	29	4.852	18.317	$4.31x10^{-32}$	1	(53)
	Diffuse Gastric Adenocarcinoma (DGAC) (13)	29	6.483	23.103	$1.13x10^{-17}$	1	
	Gastric mixed Adenocarcinoma (GMA) (8)	29	9.700	11.684	$1.63x10^{-6}$	1	
	Diffuse Gastric Adenocarcinoma (DGAC) (31)	19	3.287	8.446	$2.38x10^{-11}$	1	(54)
	Gastric Intestinal Type Adenocarcinoma (ITGA) (20)	19	3.038	6.251	$4.01x10^{-7}$	1	
	Gastric Cancer (GC) (15)	12	5.721	5.853	$2.49x10^{-6}$	1	(55)
	Diffuse Gastric Adenocarcinoma (DGAC) (6)	31	6.207	5.794	$9.36x10^{-5}$	2	(56)
	Gastric Mixed Adenocarcinoma (GMA) (4)	31	9.737	8.460	$1.49x10^{-5}$	3	
	Gastric Intestinal Type Adenocarcinoma (ITGA) (26)	31	4.413	7.512	$2.59x10^{-9}$	5	
	Gastric Cancer (GC) (80)	80	3.226	5.032	$6.55x10^{-7}$	2	(57)
Head and neck	Salivary Gland Adenoid Cystic Carcinoma (SGACC) (16)	6	4.703	11.107	$5.90x10^{-10}$	1	(58)
Lung	Squamous Cell Carcinoma (SCC) (34)	28	2.177	5.194	$1.45x10^{-6}$	10	(59)
Ovarian	Ovarian Serous Surface Papillary Carcinoma (SSPC) (28)	4	36.947	7.443	$2.62x10^{-8}$	2	(60)
	Ovarian Carcinoma (OC) (185)	10	3.105	10.018	$9.77x10^{-9}$	7	(61)
	Ovarian Serous Cystadenocarcinoma (OSC) (586)	8	2.706	8.141	$2.09x10^{-5}$	10	(62)
Other cancer	Skin Basal Cell Carcinoma (SBCC) (15)	4	5.312	11.144	$1.81\ x10^{-9}$	1	(63)

Cancer samples were compared with normal tissues. CNS, central nervous system; TCGA, The Cancer Genome Atlas; IBLCA Infiltrating Bladder Urothelial Carcinoma.

Table II. Overall survival of patients with different types of cancer with overexpressed *BGN* gene.

Cancer types	RNA-seq P-value (database)	gene chip P-value (database)
Breast cancer	0.2556[a]	0.7210[a]
Esophageal adenocarcinoma	0.0965[a]	N/A
Lung cancer	0.3010[a]	0.0002[a]
Gastric cancer	0.0068[a]	$1.3x10^{-10}$[a]
Ovarian cancer	0.0093[a]	0.0004[a]
Bladder cancer	0.0025[a]	N/A

Calculated using [a]Kaplan-Meier Plotter databases with RNA-seq data and gene chip data. BGN, biglycan; N/A, not applicable.

Table III. Overall survival of patients with different subtypes of cancer with overexpressed *BGN* gene.

Cancer subtype	RNA-seq P-value (database)	gene chip P-value (database)
Lung squamous cell carcinoma	0.0111[a]	N/A
Ovarian serous cystadenocarcinoma	0.0290[c]	N/A
Breast invasive carcinoma	0.9400[c]	N/A
Colon adenocarcinoma	0.0963[b]	N/A
Rectum adenocarcinoma	0.1776[a]	N/A
Esophageal Squamous Cell Carcinoma	0.2707[a]	N/A

Calculated using [a]Kaplan-Meier Plotter databases, [b]OncoLnc and [c]UALCAN with RNA-seq data. BGN, biglycan; N/A, not applicable.

OC [HR=1.28 (1.11-1.47), $P=4.4x10^{-4}$ in microarry analysis; HR=1.45 (1.09-1.93), $P=9.3x10^{-3}$ in RNA-seq analysis].

In summary, high BGN mRNA expression in gastric cancer and ovarian cancer was significantly associated with poor overall survival. High BGN mRNA expression was indicated to be associated with poor clinical outcome in the prognosis of patients with bladder cancer, lung squamous cell carcinoma, and ovarian serous cystadenocarcinoma. However, the association between BGN mRNA upregulation and prognosis in patients with other types and subtypes of cancer requires further examination.

PPI network construction. The GEPIA database was used to download the top 50 co-expressed genes, then the PPI was generated (Fig. 3). In the network, BGN directly interacted with 42 neighboring genes, including *ANTXR1*, *AEBP1*, *CDH11*, *CTHRC1*, *EFEMP2*, *FAP*, *LEPRE1*, *LRRC15*, *LUM*, *MMP14*, *MRC2*, *MXRA5*, *OLFML2B*, *PCOLCE*, *PDGFRB*, *PXDN*, *SERPINH1*, *SFRP2*, *SPARC*, *SULF1*, *TGFβ3*, *THBS2*, *THY1*, genes of the disintegrin and metalloproteinase gene

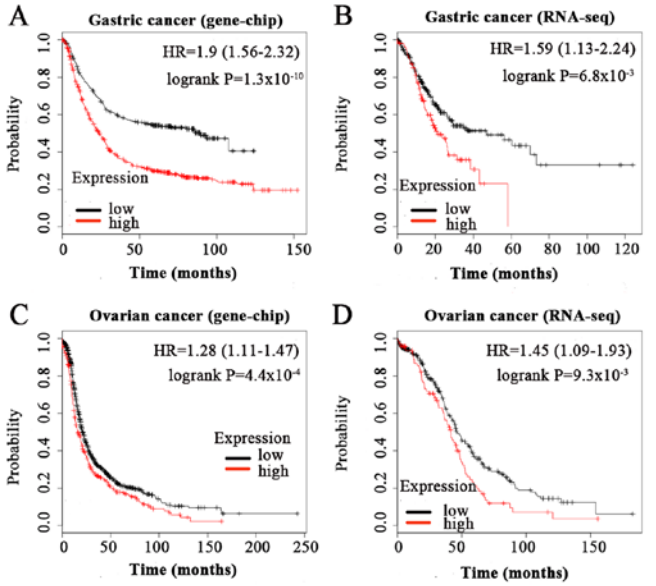

Figure 2. OS curves of patients with different types of cancer divided by BGN expression. High expression levels of the *BGN* gene exhibited a significant association with lower OS time in patients with (A) gastric cancer (gene chip data), (B) gastric cancer (RNA-seq data), (C) ovarian cancer (gene chip data), (D) ovarian cancer (RNA-seq data). The plots were generated using the KM plotter database. The red lines indicate patients with *BGN* gene expression above the median value, and the black lines indicate patients with *BGN* gene expression below the median value. OS, overall survival; *BGN*, biglycan; HR, hazard ratio.

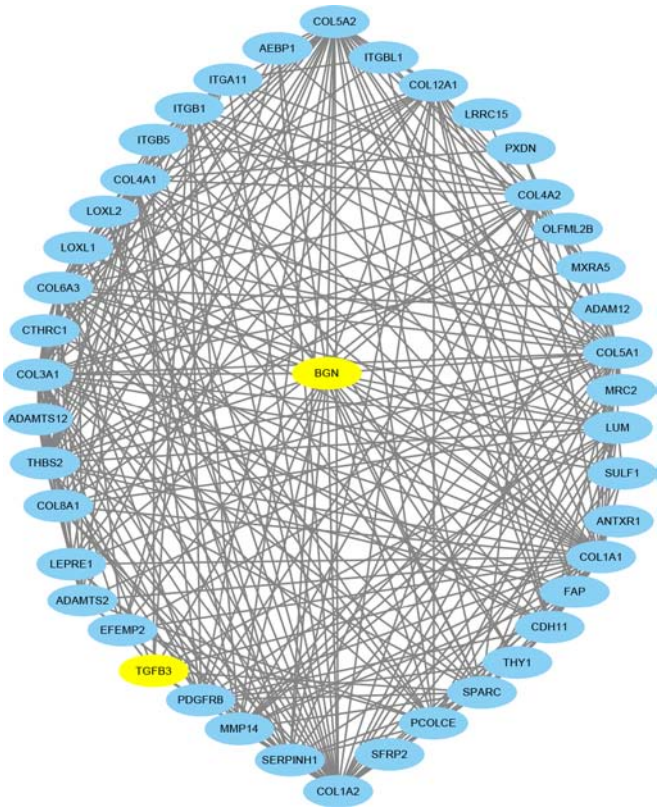

Figure 3. PPI network for BGN and its potential interacting proteins. Genes that were co-expressed in cancer together with BGN were extracted from the GEPIA database, and then a PPI network was established using the STRING database and visualized using the Cytoscape software. TGFβ3 was highlighted in yellow because it may play an important role to regulate the expression of BGN. PPI, protein-protein interactions; BGN, biglycan; TGFβ3, transforming growth factor β3.

family, collagen family genes, the integrin subunit gene family and lastly the lysyl oxidase-like gene family, which jointly regulate the occurrence and development of human tumors. Jointly genes with similar expression patterns are likely to have related functions (64). For example, enrichment indicates that *BGN*-coexpressed genes are at least partially biologically connected in developing multiple cancers (65). The basic interaction between the neighboring genes is the 'functional association'. The two proteins that both contribute jointly to a specific biological function can interact specifically without touching at all, such as when a transcription factor helps to regulate the expression and production of another protein, or when two enzymes exchange a specific substrate via diffusion. The exact molecular mechanisms in cancer associated with BGN remain unclear (66). BGN upregulation has been implicated in the inflammatory response triggered by transforming growth factor β (TGF-β) (8,67,68). In the PPI network, TGF-β3 may play an important role to regulate the expression of BGN, however, the influence of TGF-β3 needs to be further investigated.

Discussion

In the present study, the mRNA expression levels of BGN were systematically analyzed, and the results indicated that BGN was upregulated in various types of cancerous tissues, when compared with that in normal tissues. Previous studies have demonstrated that significantly increased levels of BGN are frequently detected in the clinical samples of patients with gastric (13), breast (69), colorectal (70), lung (71), ovarian (10) and pancreatic cancer (16). In addition, high expression of BGN in patients with solid cancer is significantly associated with poor outcome (15). Solid cancer include BLC, brain and CNS cancer, BC, cervical cancer, CC, EC, GC, HNC, kidney cancer, liver cancer, LC, melanoma, OC, pancreatic cancer, prostate cancer (72). Consistent with these studies, the present analyses demonstrated that BGN expression levels were increased in the majority of cancers, such as bladder, brain and central nervous system, breast, colorectal, esophageal, gastric, head and neck, lung, ovarian, and 28 subtype cancers, when compared with that in normal tissues. In addition, the current prognosis analyses revealed that high tissue BGN expression predicts worse survival in GC and OC. High BGN mRNA expression was associated with poor overall survival in patients with BLC, LSCC, and OSC. Therefore, BGN may be employed as either a novel prognostic biomarker or as a promising therapeutic target for human carcinomas, which is consistent with the findings of previous reports (15,73). The 43 genes with similar expression patterns are likely to have related functions in the aggressive growth and metastasis of cancers (64). In the PPI network, the genes of *AEBP1, MMP14, OLFML2B, PDGFRB, SERPINE1, SPARC, SFRP2, COL1A2, COL6A3, THBS2, COL5A2, COL11A1, FAP, MXRA5* and *THY1* were upregulated in solid cancer tissues, and significantly associated with the overall survival of patients with cancer (74-82). Some genes in the PPI network, including *AEBP1, OLFML2B, PDGFRB, SERPINE1, COL1A2, COL6A3,* and *THBS2* have been reported to be associated with metastasis, invasion and migration in cancer cells (74,76,80,83,84). The enrichment of BGN-coexpressed genes indicates that the proteins are at least partially biologically connected as a group (64). However, a detailed understanding of the mechanism associated with the function of BGN is currently lacking; therefore, further functional studies are warranted in the future. In addition, the BGN protein expression levels or the signaling pathways potentially involved require further investigation. Finally, studies utilizing larger cohorts, specific cancers, or larger prospective studies also need to be conducted in order to validate the prognostic values of BGN.

In summary, the present study comprehensively analyzed the mRNA expression levels and prognostic value of BGN in the most common types of cancer, and the results indicated that BGN exhibited significantly high expression levels in cancer tissues compared with normal tissues in multiple types of cancer. The present findings indicated that BGN may serve as a promising prognostic biomarker and therapeutic target for patients with BLCA and STAD.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SFZ conceived and designed the study. XJY, WJZ, LCL and ZPW made substantial contributions to the design of the current study, acquisition of data, interpretation of data and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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