Distinct prognostic value of mRNA expression of guanylate-binding protein genes in skin cutaneous melanoma

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Abstract. The purpose of the present study was to assess if guanylate-binding protein (GBP) mRNAs could be prognostic biomarkers for patients with skin cutaneous melanoma (SKCM). The prognostic value of *GBP* mRNA expression in patients with SKCM was investigated by analyzing gene expression data in 459 SKCM patients. The data were extracted from the OncoLnc database of The Cancer Genome Atlas. A high expression of *GBP1, GBP2, GBP3, GBP4* and *GBP5* were correlated with favorable overall survival (OS) in the SKCM patients followed for over 30 years. In addition, a high expression of *GBP6* mRNA was not correlated with OS in the SKCM patients. A joint effects analysis showed that the co-incidence of the high expression of *GBP1-5* was correlated with favorable overall survival in SKCM patients. Our findings suggest that *GBP1-5* mRNAs in SKCM are associated with favorable prognosis and may be potential prognostic biomarkers. The combination of *GBP1-5* could improve the sensitivity for predicting OS in SKCM patients.

Introduction

Skin cutaneous melanoma (SKCM) is one of the most aggressive malignancies; tumors of millimeters are lethal. SKCM accounts for 91% of new cases of skin cancers and results in 74% of skin-related deaths (1). The incidence of SKCM has continued to increase in recent years, and it tends to affect younger people (1,2). The 5-year and 10-year relative survival rates for persons with SKCM are 92 and 89%, respectively. The primary treatment for SKCM is surgery combined with chemotherapy, immunotherapy and radiation (3). Effective prognosis markers may aid in therapeutic treatment for SKCM patients (4). Previous studies have shown that many genes, including *AURKB, CCNE1, CDCA8, CDK4, CENPO, GINS2, H2AFZ, LIG1, PKMYT1, PLK1, PTTG1, SKA1, TUBA1B, TUBA1C, TYMS* (5), and *EZH2* (6), are associated with poor prognosis in SKCM. However, the association between *GBP* genes and the prognosis of SKCM has not been reported.

Guanylate-binding protein (GBP) belongs to the superfamily of INF-inducible guanosine triphosphate hydrolases (GTPases) (7,8). Up to now, seven human *GBP* genes, including *guanylate-binding protein 1* (*GBP1*), *guanylate-binding protein 2* (*GBP2*), *guanylate-binding protein 3* (*GBP3*), *guanylate-binding protein 4* (*GBP4*), *guanylate-binding protein 5* (*GBP5*), *guanylate-binding protein family member 6* (*GBP6*) and *guanylate-binding protein 7* (*GBP7*), have been reported (9-11). GBPs, such as *GBP1* and *GBP2*, have antiviral and antimicrobial activities in host defense (12) and could act as protective factors in host defense, controlling infection and autoimmunity (13).

The roles of *GBP* genes in cancers are complicated. Studies showed that some *GBP* family members were expressed in colorectal cancer (CRC) (14-17), breast cancer (18,19), oral squamous cell carcinoma (OSCC) (20), esophageal squamous cell carcinomas (SCC) (21), cutaneous T-cell lymphoma (22), prostate cancer (23), and Kaposi's sarcoma (24,25). *GBP1* was upregulated in CRC (15) and OSCC (20), modulated the migration and invasion of OSCC cell *in vitro* (20), and inhibited the growth of highly malignant TS/A mammary carcinoma cells (19) and CRC tumors (14,15,17) *in vivo*. The high expression of *GBP1* was associated with high overall pathological stage in OSCC tissue. *GBP2* was related to T-cell infiltration in breast cancer (18).

The expression of *GBP* mRNAs is highly induced by interferon-γ (IFN-γ) in many cells including fibroblasts, B cells, T cells, and some tumor cells (15,24,26). *GBP* was also associated with the prognosis of many

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Abbreviations: GBP, guanylate-binding protein; OS, overall survival; SKCM, skin cutaneous melanoma

Key words: guanylate-binding protein, mRNA, correlation, prognosis

cancers (14,16-21,23,25). In addition, *GBP1* plays dual roles in different tumor cells. Upregulated *GBP1* mediated the anti-tumorigenic effects of IFN-γ and correlated with better OS in CRC (15,17). However, overexpressed *GBP1* was significantly associated with poorer prognosis in OSCC patients (20). A high expression of *GBP2* with a favorable prognosis was found in patients with node-negative breast carcinomas (18). However, the prognostic value of individual *GBP* in SKCM remains elusive. The present study investigated the prognostic value of individual *GBP* mRNA and made a joint effects analysis in 459 SKCM patients using OncoLnc data generated from The Cancer Genome Atlas (TCGA; https://cancergenome.nih.gov/, accessed March 1, 2017) database (27). Our results indicated that a high mRNA expression of individual *GBP1-5* genes and a high co-expression of these gene mRNAs were correlated with high OS, suggesting that these genes may be potential prognosis biomarkers in SKCM patients.

Materials and methods

Data preparation. TCGA survival data of SKCM was extracted from OncoLnc (http://www.oncolnc.org/, accessed March 3, 2017) (27), including the patients' ID in TCGA, sex, age at diagnosis, events, median survival, survival time, death status, and *GBP* members' mRNA expression regarding 459 SKCM patients. Briefly, 7 *GBP* sub-members (*GBP1, GBP2, GBP3, GBP4, GBP5, GBP6,* and *GBP7*) were entered into the database (http://www.oncolnc.org/, accessed by March 3, 2017). The patients were sorted into a percentile of 50:50 by the expression of every *GBP* sub-member, and then SKCM patients' survival data information was obtained.

The Metabolic gEne RApid Visualizer (MERAV: http://merav.wi.mit.edu/SearchByGenes.html, accessed March 1, 2017) (28) was used to make a boxplot of *GBP* sub-members' expression levels in normal tissue and primary tumors of skin cancer. After *GBP* genes and the selected tissue type were submitted on the website, boxplots were made and displayed. The unit for mRNA expression is counted in downloaded TCGA data.

Correlation and bioinformatics analysis. The Pearson correlation coefficient was used to assess the co-expression of *GBP* genes. The relative expression levels of *GBP* genes in multiple normal tissues were determined with the GTEx Portal (http://www.gtexportal.org/home/, accessed April 25, 2017) (29). A gene function prediction website (GeneMANIA: http://genemania.org/, accessed March 15, 2017) (30) was also used to construct the gene-gene interaction networks. The Database for Annotation, Visualization, and Integrated Discovery (DAVID) v.6.7 (https://david.ncifcrf.gov/tools.jsp, accessed April 3, 2017) (31,32) was used to annotate input genes, classify gene functions, identify gene conversions, and carry out Gene Ontology (GO) term analysis (32). $P<0.05$ and a false discovery rate (FDR) <0.05 were considered to indicate a statistically significant difference.

Survival analysis. A Kaplan-Meier estimator with a log-rank test was used to evaluate the correlation of six mRNAs with patient survival. Hazard ratios (HR) and 95% confidence intervals (CI) were used to assess the relative risk of SKCM survival.

Joint effects analysis. A joint effects analysis was performed based on the survival analysis results. Patients were regrouped based on the combined *GBP* mRNA expression and OS scores, which were calculated by summarizing all of the points given to *GBP1-5* in a patient when 1 point was assigned to genes of high expression with favorable OS and 0 points were assigned to genes of low expression with poor OS.

Statistical analysis. Statistical analyses were carried out using SPSS v.22.0 software (IBM, Chicago, IL, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

mRNA expression of GBP genes in human normal skin and skin cancer tissues. The *GBP* family is composed of seven members. Among the seven *GBP* genes, only *GBP7* was not found in www.oncolnc.org, likely due to its low expression (33). In human skin tissue, *GBP2* and *GBP6* were expressed at high levels, whereas the remaining *GBP* genes (*GBP1*, *GBP3*, *GBP4* and *GBP5*) were expressed at low levels (Fig. 1A-F; Fig. 1A, *GBP1*; Fig. 1B, *GBP2*; Fig. 1C, *GBP3*; Fig. 1D, *GBP4*; Fig. 1E, *GBP5*; Fig. 1F, *GBP6*).

The boxplots of the *GBP* family generated from MERAV shows differences in the expression levels of *GBP* genes between normal skin tissue and primary skin tumor. The expressions of *GBP1*, *GBP4* and *GBP5* in normal skin tissue were higher than skin cancer. Moreover, the expressions of *GBP2*, *GBP3* and *GBP6* in skin cancer were higher than in normal skin tissue (Fig. 2).

Functions and correlation of the mRNA expression of GBP genes in human tissues. A co-expression analysis (Fig. 3) showed that *GBP1, GBP2, GBP3, GBP4* and *GBP5* were co-expressed in human tissues. *GBP3* was in the *NFATC2* pathway, *GBP2* was in the *IFI35*, *IRF9* and *XAF1* pathways, and GBP2 was predicted in the *IRF1* pathway. The correlation of individual *GBP* family gene mRNA expression was tested using the Pearson correlation coefficient (Table I). With the exception of *GBP6*, the mRNA expression of all other *GBP* family genes was significantly ($R=0.550$-0.842, $P<0.001$) positively correlated (Table I). A GO term analysis using DAVID revealed that *GBP* genes were significantly associated with the biological process of immune response, as well as the molecular functions of GTPases activity and guanosine triphosphate (GTP) binding (Table II).

Survival analysis. The prognostic value of the *GBP* family gene mRNA expression was assessed with SPSS. A high expression of *GBP1-5* was significantly ($P<0.001$) associated with a favorable OS in SKCM patients (Fig. 4A-E). *GBP6* expression did not show a significant correlation with OS in SKCM patients ($P=0.401925$, $HR=1.121$, 95% CI=0.8580-1.465) (Fig. 4F).

Joint effects analysis. A joint effects analysis was used to determine the combined effect of the *GBP* gene mRNA

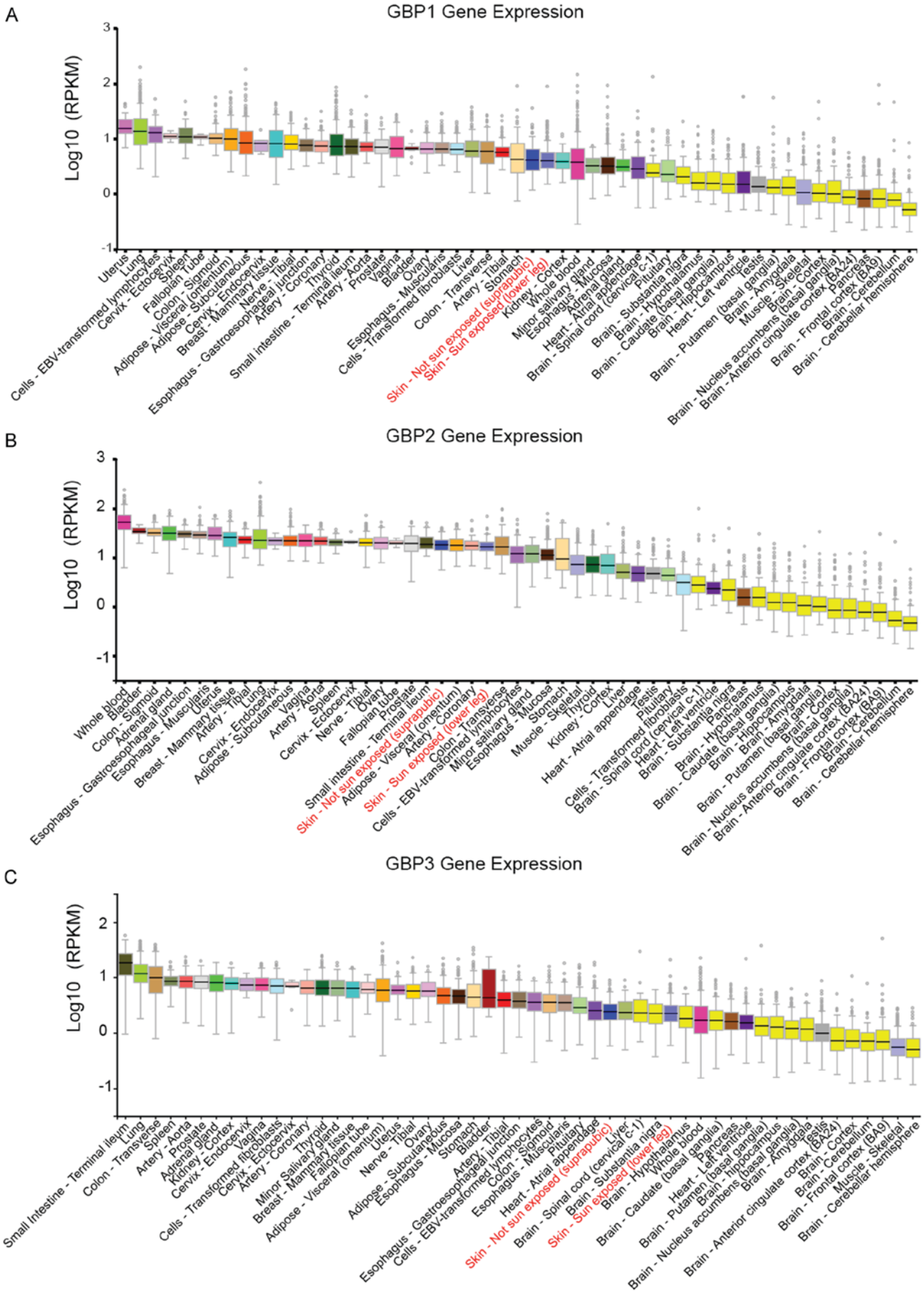

Figure 1. *GBP* genes in multiple normal tissues in the GTEx Portal database. The expression of *GBP* genes in normal skin tissue was highlighted in red. (A) *GBP1* gene expression in multiple normal tissues; (B) *GBP2* gene expression in multiple normal tissues; (C) *GBP3* gene expression in multiple normal tissues. GBP, guanylate-binding protein.

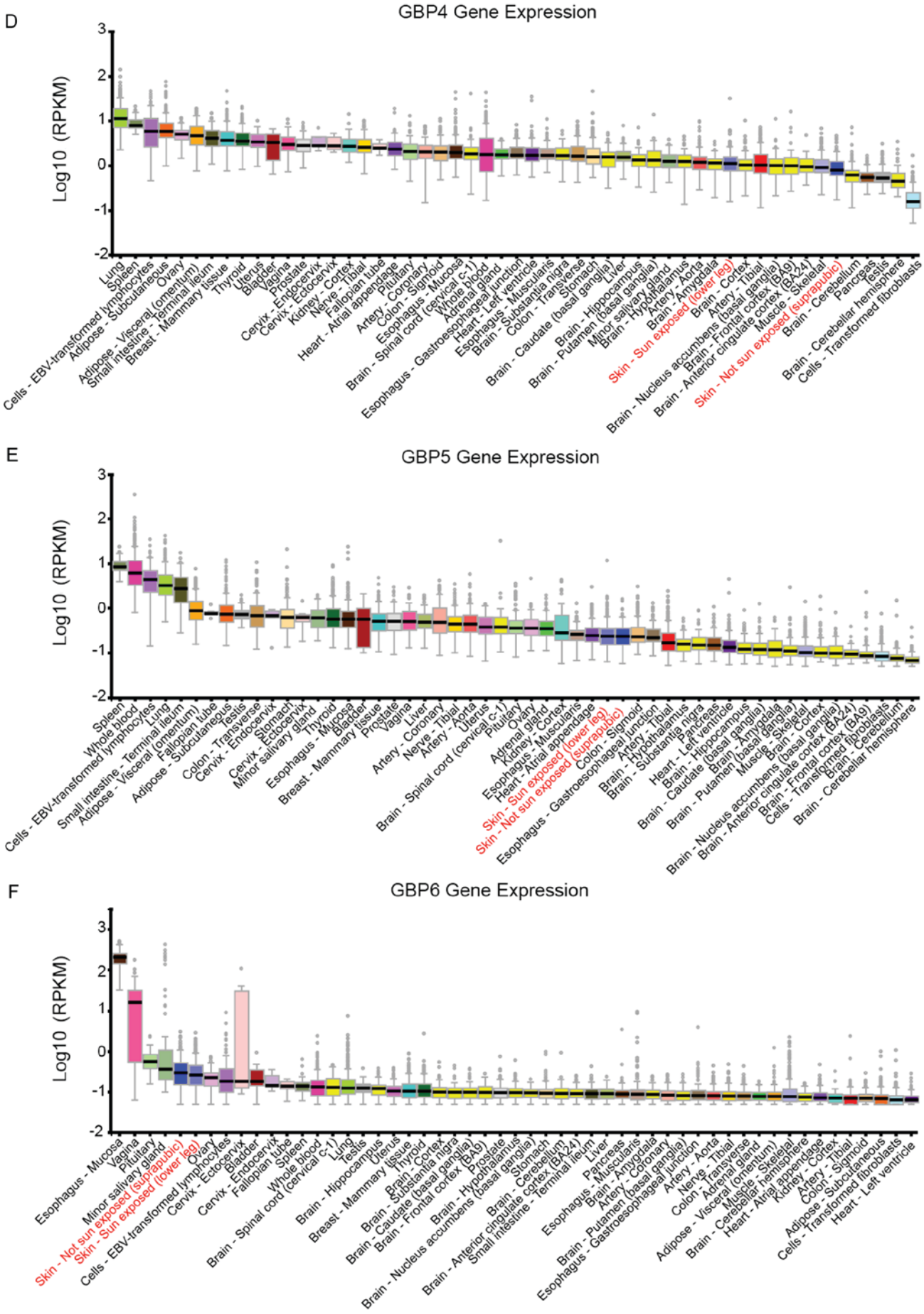

Figure 1. Continued. (D) GBP4 gene expression in multiple normal tissues; (E) GBP5 gene expression in multiple normal tissues; (F) GBP6 gene expression in multiple normal tissues. GBP, guanylate-binding protein.

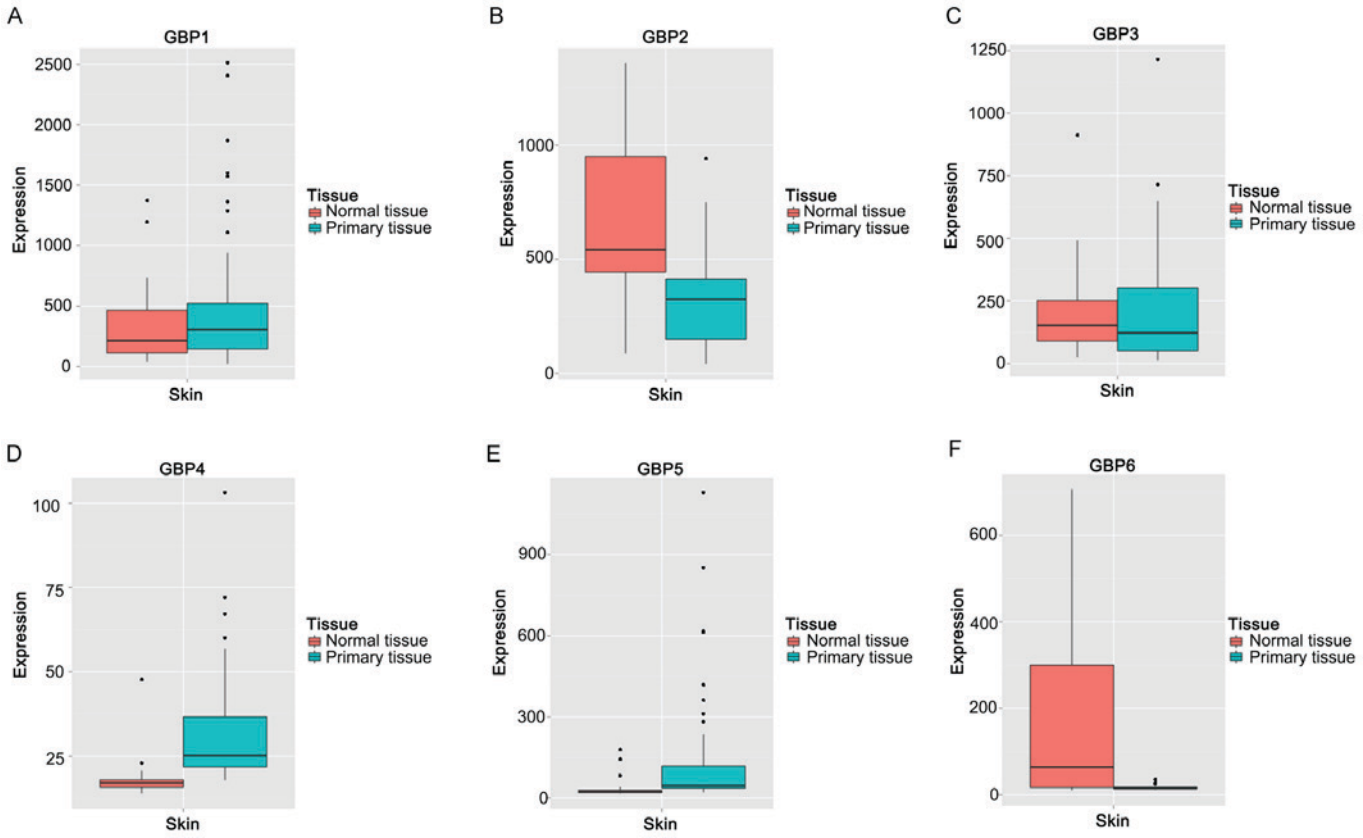

Figure 2. The MERAV boxplots of *GBP* family expression in skin normal tissue and primary tumor. (A) Boxplot for *GBP1* expression; (B) boxplot for *GBP2* expression; (C) boxplot for *GBP3* expression; (D) boxplot for *GBP4* expression; (E) boxplot for *GBP5* expression; (F) boxplot for *GBP6* expression. MERAV, Metabolic gEne RApid Visualizer; GBP, guanylate-binding protein.

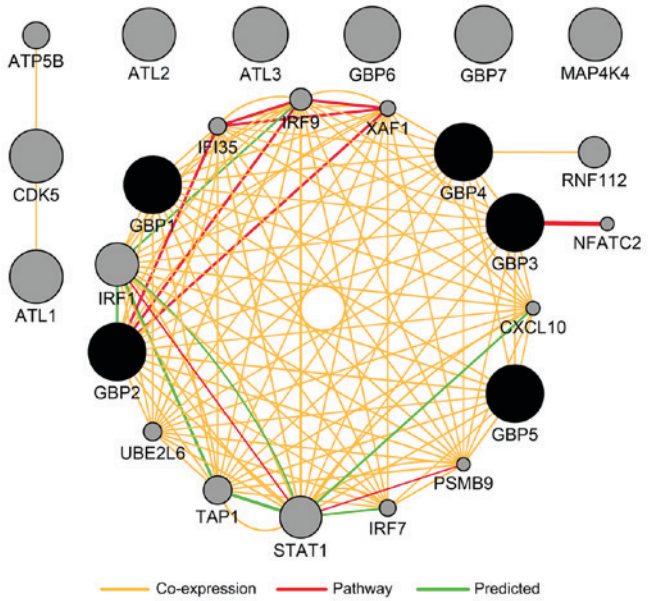

Figure 3. Co-expression/pathway/predication analysis of *GBP1*, *GBP2*, *GBP3*, *GBP4* and *GBP5* according to human expression data in GeneMANIA. GBP, guanylate-binding protein.

co-expression on the OS of SKCM patients. Patients were divided into 6 groups: Group 1 (0 points group, n=136), group 2 (1 point group, n=60), group 3 (2 points group, n=32), group 4 (3 points group, n=39), group 5 (4 points group, n=47) and group 6 (5 points group, n=141) (detailed grouping information is shown in Table III). Kaplan-Meier estimator with a log-rank test was used to evaluate the prognostic value of these 6 groups. The co-overexpression of *GBP1-5* in Group 6 (141 from 455) was found to be more highly correlated with a favorable OS than the co-overexpression of fewer *GBP*

Table I. Co-expression of GBP family at mRNA level.

	GBP1		*GBP2*		*GBP3*		*GBP4*		*GBP5*		*GBP6*	
Genes	R	P-value	R	P-value	R	P-value	R	P-value	R	P-value	R	P-value
GBP1	-	-	0.842	<0.001	0.743	<0.001	0.670	<0.001	0.702	<0.001	0.000	0.995
GBP2	0.842	<0.001	-	-	0.685	<0.001	0.643	<0.001	0.654	<0.001	0.047	0.313
GBP3	0.743	<0.001	0.685	<0.001	-	-	0.550	<0.001	0.594	<0.001	0.022	0.636
GBP4	0.670	<0.001	0.643	<0.001	0.550	<0.001	-	-	0.768	<0.001	-0.013	0.776
GBP5	0.702	<0.001	0.654	<0.001	0.594	<0.001	0.768	<0.001	-	-	0.001	0.990
GBP6	0.000	0.995	0.047	0.313	0.022	0.636	-0.013	0.776	0.001	0.990	-	-

The correlations of gene mRNA expression in *GBP* families were tested using the Pearson correlation coefficient. R, Pearson correlation coefficient; *GBP*, guanylate-binding protein.

Table II. Analysis of enriched GO terms for *GBP* genes carried out using DAVID.

Category	Term	Genes	P-value	FDR
Molecular function	GTPase activity	6	$1.08x10^{-09}$	$5.58x10^{-07}$
	GTP binding	6	$1.88x10^{-08}$	$9.70x10^{-06}$
	Guanylate nucleotide binding	6	$2.15x10^{-08}$	$1.11x10^{-05}$
	Guanylate ribonucleotide binding	6	$2.15x10^{-08}$	$1.11x10^{-05}$
	Ribonucleotide binding	6	$5.63x10^{-05}$	0.029018
	Purine ribonucleotide binding	6	$5.63x10^{-05}$	0.029018
	Purine nucleotide binding	6	$7.01x10^{-05}$	0.03611
	Nucleotide binding	6	$1.54x10^{-04}$	0.079382
Biological process	Immune response	6	$3.40x10^{-07}$	$7.69x10^{-05}$
Cellular component	Internal side of plasma membrane	3	0.001798	-
	Plasma membrane part	3	0.078854	-
	Plasma membrane	3	0.210327	-

GBP, guanylate-binding protein; GO Gene Ontology; DAVID, Database for Annotation, Visualization, and Integrated Discovery; GTPases, guanosine triphosphates. GTP, guanosine triphosphate; FDR, false discovery rate.

genes in other groups (P<0.0001). In contrast, the expression of *GBPs* was homogeneously low in Group 1 (136 from 455), which was found to be more highly correlated with poor OS than the other groups (P<0.0001) (Fig. 5).

Discussion

In the present study, the data for the *GBP* gene mRNA expression and survival of SKCM patients were extracted from OncoLnc, analyzed to predict the function of *GBP* genes, and assessed for the potential of the mRNA expression of *GBP* genes to be used as prognosis biomarkers. Our analysis revealed that GBPs may be responsible for host defense, GTP binding and GTP hydrolysis. The correlation between the *GBP* gene mRNA levels and OS suggested that *GBP* mRNA may be good prognosis biomarkers for SKCM patients.

Our bioinformatics analysis revealed that the most meaningful molecular functions of GBP were GTPase activity, GTP binding, guanylate nucleotide binding, guanylate ribonucleotide binding, ribonucleotide binding, purine ribonucleotide binding, purine nucleotide binding, and nucleotide binding, which is in agreement with the observations that GBP belongs to the superfamily of INF-inducible GTPases including four sub-families: GBPs, immunity-related GTPases, very large inducible GTPase and myxovirus resistance proteins (7,8). The probable involvement of GBPs in the biological process of immunity deduced by our analysis is in agreement with the observations that GBPs, such as GBP1 and GBP2, have antiviral and antimicrobial activities in host defense (12) and that GBPs could act as protective factors in host defense, controlling infection and autoimmunity (13). The predicted immunity roles of *GBP* genes are also in agreement with the finding that upregulated *GBP1* in CRC inhibits tumor growth (14,15,17) and that *GBP2* was associated with T-cell infiltration in breast cancer (18).

In the present study, the Kaplan-Meier curves show that a high expression of *GBP1-5* was found to be correlated with favorable OS in all SKCM patients. The correlation between a

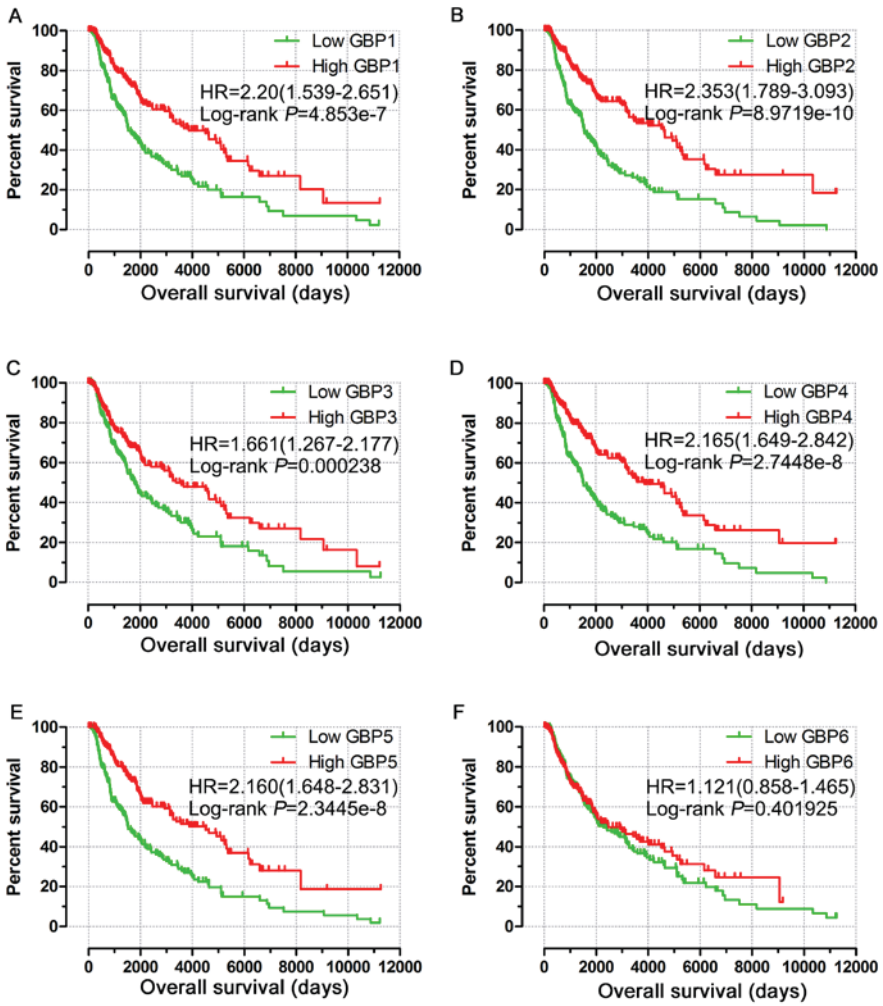

Figure 4. The prognostic value of *GBP* expression. (A) survival curves are plotted for all SKCM patients of *GBP1* (n=458); (B) survival curves are plotted for all SKCM patients of *GBP2* (n=458); (C) survival curves are plotted for all SKCM patients of *GBP3* (n=458); (D) survival curves are plotted for all SKCM patients of *GBP4* (n=458); (E) survival curves are plotted for all SKCM patients of *GBP5* (n=458); (F) survival curves are plotted for all SKCM patients of *GBP6* (n=458). Data were analyzed using SPSS. GBP, guanylate-binding protein; SKCM, skin cutaneous melanoma.

high expression of *GBP1* and favorable OS in SKCM patients is in accordance with its correlation with high survival in CRC (17) but contrary to its correlation with poor survival in OSCC (20). These results indicated that *GBP1* could play different roles in different cancers. The correlation of a high expression of *GBP2* with a favorable OS in SKCM observed in the present study and in node-negative breast carcinomas (18) suggests that *GBP2* may share the same mechanism in both SKCM and node-negative breast carcinomas. Though the expression of *GBP6* in skin tumor tissue was more than its expression in normal tissue, no correlation between prognosis value with high expression of *GBP6* or low expression of *GBP6* was found. It is unclear why the high expression of downregulated *GBP1*, *GBP4* and *GBP5*, as well as upregulated *GBP2* and *GBP3* showed the same correlation with a favorable OS in skin cancer. No survival information on *GBP7* in SKCM patients is available, likely due to its low expression in normal skin tissue and SKCM, which makes it difficult to assess its correlation with prognosis outcomes.

The joint effects analysis showed that the co-expression of *GBP1-5* all at high levels was correlated with a favorable OS in SKCM patients. In contrast, the co-expression of

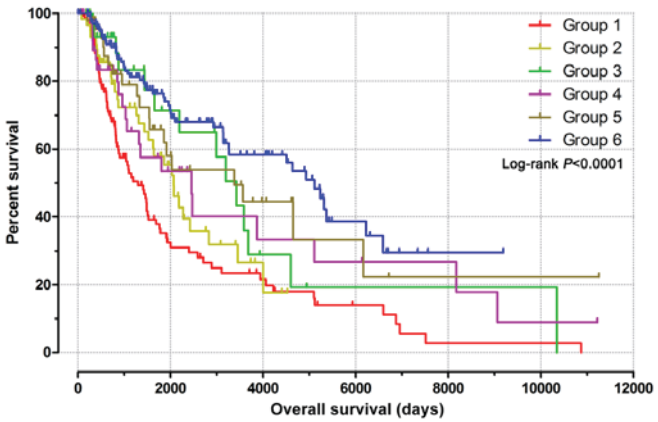

Figure 5. The result of the joint effects analysis. OS stratified by 5 *GBP* genes expression levels. Group 1 (0 points group, n=136), Group 2 (1 point group, n=60), Group 3 (2 points group, n=32), Group 4 (3 points group, n=39), Group 5 (4 points group, n=47) and Group 6 (5 points group, n=141). GBP, guanylate-binding protein.

GBP1-5 at low levels was correlated with poor OS in SKCM patients. There was a tendency for GBP genes with higher

Table III. Grouping information for the combination among *GBP* genes.

Group	Points	Composition
1	0	Low *GBP1*+Low *GBP2*+Low *GBP3*+Low *GBP4*+Low *GBP5*
2	1	High *GBP1*+Low *GBP2*+Low *GBP3*+Low *GBP4*+Low *GBP5*
2	1	Low *GBP1*+High *GBP2*+Low *GBP3*+Low *GBP4*+Low *GBP5*
2	1	Low *GBP1*+Low *GBP2*+High *GBP3*+Low *GBP4*+Low *GBP5*
2	1	Low *GBP1*+Low *GBP2*+Low *GBP3*+High *GBP4*+Low *GBP5*
2	1	Low *GBP1*+Low *GBP2*+Low *GBP3*+Low *GBP4*+High *GBP5*
3	2	High *GBP1*+High *GBP2*+Low *GBP3*+Low *GBP4*+Low *GBP5*
3	2	High *GBP1*+Low *GBP2*+High *GBP3*+Low *GBP4*+Low *GBP5*
3	2	High *GBP1*+Low *GBP2*+Low *GBP3*+High *GBP4*+Low *GBP5*
3	2	High *GBP1*+Low *GBP2*+Low *GBP3*+Low *GBP4*+High *GBP5*
3	2	Low *GBP1*+High *GBP2*+High *GBP3*+Low *GBP4*+Low *GBP5*
3	2	Low *GBP1*+High *GBP2*+Low *GBP3*+High *GBP4*+Low *GBP5*
3	2	Low *GBP1*+High *GBP3*+Low *GBP3*+Low *GBP4* +High *GBP5*
3	2	Low *GBP1*+Low *GBP2*+High *GBP3*+High *GBP4*+Low *GBP5*
3	2	Low *GBP1*+Low *GBP2*+High *GBP3*+Low *GBP4*+High *GBP5*
3	2	Low *GBP1*+Low *GBP2*+Low *GBP3*+High *GBP4*+High *GBP5*
4	3	High *GBP1*+High *GBP2*+High *GBP3*+Low *GBP4*+Low *GBP5*
4	3	High *GBP1*+High *GBP2*+Low *GBP3*+High *GBP4*+Low *GBP5*
4	3	High *GBP1*+High *GBP2*+Low *GBP3*+Low *GBP4*+High *GBP5*
4	3	High *GBP1*+Low *GBP2*+High *GBP3*+High *GBP4*+Low *GBP5*
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4	3	Low *GBP1*+High *GBP2*+High *GBP3*+High *GBP4*+Low *GBP5*
4	3	Low *GBP1*+High *GBP2*+High *GBP3*+Low *GBP4*+High *GBP5*
4	3	Low *GBP1*+High *GBP2*+Low *GBP3*+High *GBP4*+High *GBP5*
4	3	Low *GBP1*+Low *GBP2*+High *GBP3*+High *GBP4*+High *GBP5*
5	4	High *GBP1*+High *GBP2*+High *GBP3*+High *GBP4*+Low *GBP5*
5	4	High *GBP1*+High *GBP2*+High *GBP3*+Low *GBP4*+High *GBP5*
5	4	High *GBP1*+High *GBP2*+Low *GBP3*+High *GBP4*+High *GBP5*
5	4	High *GBP1*+Low *GBP2*+High *GBP3*+High *GBP4*+High *GBP5*
5	4	Low *GBP1*+High *GBP2*+High *GBP3*+High *GBP4*+High *GBP5*
6	5	High *GBP1*+High *GBP2*+High *GBP3*+High *GBP4*+High *GBP5*

With the median value of the gene expression as cutoff, the patients were designated as high expression or low expression for every member of GBP family, and grouped based on the combination of the gene expression levels. Group 1 (all low expression genes, 0 points group, n=136), group 2 (1 high expression gene, 1 point group, n=60), group 3 (2 high expression genes, 2 points group, n=32), group 4 (3 high expression genes, 3 points group, n=39), group 5 (4 high expression genes, 4 points group, n=47), group 6 (all high expression genes, 5 points group, n=141). GBP, guanylate-binding protein.

expressions to be more highly correlated with favorable OS. The induced high co-expression of *GBP1-5* in cells by IFN-γ (10,34) suggests that it may be possible to increase patients' favorable OS through the induction of a higher co-expression of GBP genes with IFN-γ. This hypothesis needs to be further investigated and experimentally proved. The combination of *GBP1-5* may improve the sensitivity of predicting OS in SKCM patients.

There were limitations to the present study that should be recognized. First, since the data from the TCGA database and OncoLnc was not comprehensive, the present study evaluated the association between gene expression level and OS based on a log-rank test in Kaplan-Meier analysis. Second, the patients in the present study were exclusively from a single source, which meant that a multivariate analysis could not be used to validate the results. It is necessary to validate the prognostic value of these genes in patients with SKCM using independent external validation datasets containing complete clinical information. Despite these limitations, our current study was the first to report that the upregulation of the *GBP*

genes (*GBP1*, *GBP2*, *GBP3*, *GBP4* and *GBP5*) in SKCM was associated with a favorable prognosis. *GBP1-5* may be used as prognostic biomarkers for SKCM patients.

In conclusion, a high expression of 5 *GBP* genes (*GBP1*, *GBP2*, *GBP3*, *GBP4* and *GBP5*) was individually and coincidentally related to a favorable prognosis for SKCM. *GBP1-5* may be used as potential prognostic biomarkers for SKCM patients. These results need to be confirmed in further studies.

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