

Research Article

TBL1XR1 Is Highly Expressed in Gastric Cancer and Predicts Poor Prognosis

Fang Liu,¹ Yuan He,² Qinghua Cao,³ Ni Liu,³ and Wenhui Zhang³

¹Department of Oncology, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

²State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine and Department of Molecular Diagnostics, Sun Yat-sen University Cancer Center, Guangzhou 510060, China

³Department of Pathology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China

Correspondence should be addressed to Fang Liu; liufang7250@163.com and Qinghua Cao; caoqhua@mail.sysu.edu.cn

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Objective. To investigate the expression of transducin- (β -) like 1 X-linked receptor 1 (TBL1XR1) in human gastric cancer (GC) and its correlation with prognostic and biologic significance. **Methods.** TBL1XR1 mRNA expression was analyzed in gastric cancer using a microarray dataset (GSE2701) from the Gene Expression Omnibus (GEO). Immunohistochemistry (IHC) analysis of TBL1XR1 was performed on GC tissue microarray (TMA) to assess its prognostic and biological significance in 334 patients of GC. **Results.** Analysis of GSE2701 showed that the mRNA levels of TBL1XR1 were significantly elevated in primary gastric tumor and lymph node tissues than normal gastric tissues ($P < 0.05$). The same results of TBL1XR1 protein level were observed by IHC staining in 334 GC tissues. 204 of 334 (60.1%) primary gastric cancer tissues showed high expression of TBL1XR1 protein. TBL1XR1 overexpression was significantly correlated with lymph node metastasis ($P = 0.000$) and advanced TNM stage ($P = 0.001$). Moreover, high levels of TBL1XR1 predicted worse overall survival ($P = 0.015$). Multivariate Cox regression analysis indicated that high expression of TBL1XR1 was an independent prognostic factor for poor overall survival (HR, 0.525; 95% confidence interval, 0.367–0.752; $P = 0.005$). **Conclusion.** This present study demonstrates that TBL1XR1 is overexpressed in gastric cancer and may be a potential predictor and therapeutic target for GC patients.

1. Introduction

Gastric cancer (GC) is the leading cause of cancer-related mortality worldwide, and in general, incidence rates are highest in Eastern Asia particularly in China [1]. Despite advances in efficient surgical techniques and novel chemotherapeutic interventions, the long-term survival rate of GC patients remains poor [2]. The major reason of poor prognosis in GC patients is mostly attributed to local invasion and distal metastasis by complex molecular mechanisms [3]. In addition, although prognostic biomarkers like HER2 [4], VEGFR-2 [5], and EGFR [6] are useful in some specific population of GC patients, it is not enough to fully predict individual GC patients outcomes. Therefore, it is urgent to exploit novel molecular markers.

Transducin- (β -) like 1 X-linked receptor 1 (TBL1XR1), a core component of nuclear receptor corepressor (NCoR)

complex, shows both corepressor and coactivator on nuclear receptor [7, 8]. It is thought to play a vital role in key cellular functions, including growth, antiapoptosis, and inflammation through mediating the exchange of corepressors [8, 9]. Recently, TBL1XR1 is reported to be overexpressed in multiple malignancies and contributes to carcinogenesis and tumor progression, including esophageal squamous cell cancer, cervical cancer, breast cancer, nasopharyngeal cancer, and hepatocellular carcinoma [10–14]. However, little is known about its role in gastric cancer. More interestingly, Liu et al. [10] reported that silencing TBL1XR1 in GC cells resulted in a significant decrease in VEGF-C expression, which is closely related with GC metastasis and poor prognosis [15, 16]. All of this information aroused us to address the clinical significance and potential role of TBL1XR1 in human GC patients.

In this study, we detected TBLIXR1 expression and characterized its clinicopathological function in a large cohort of GC tissues. We found that TBLIXR1 was overexpressed in GC tissues in both mRNA and protein level and correlated with present lymph node metastasis and advanced TNM stage. Importantly, TBLIXR1 overexpression predicted an inferior overall survival and could be a potential independent prognostic biomarker for GC.

2. Materials and Methods

2.1. Gene Expression Profile Data of GSE2701. Gene expression profile data GSE2701 was downloaded from the open Gene Expression Omnibus database (<http://www.ncbi.nlm.nih.gov/geo/>) and analyzed by the Qlucore Omics Explorer (QOE 3.1) bioinformatics software (<http://www.qlucore.com/>). The QOE offers state-of-the-art mathematical and statistical methods, and its main features are the ease of use and speed with which datasets can be analyzed and explored [17]. The mRNA levels of TBLIXR1 from 2 cohorts of GSE2701 were explored, respectively, in primary gastric tumor, lymph node metastases, and normal tissues.

2.2. Patients and Tissue Specimens. For immunohistochemistry study, paraffin-embedded pathological specimens from 334 patients with gastric cancer were obtained from the archives of the First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China, between 2001 and 2006. The cases were selected based on three criteria: (i) a distinctive pathological diagnosis of gastric adenocarcinoma, (ii) primary and curative resection of the tumor without preoperative anticancer treatment, and (iii) the availability of resection tissue and follow-up data. Postsurgical chemotherapies were performed depending on the severity of the disease and according to the National Comprehensive Cancer Network (NCCN) guidelines. Clinicopathological characteristics for these patients, including gender, age at surgery, tumor size, histological type, TNM stage, and lymph node metastasis status, are detailed in Table 1. All the samples were collected with patient's informed consent after approval from the Institute Research Medical Ethics Committee of the First Affiliated Hospital, Sun Yat-sen University.

2.3. Tissue Microarray Construction. Tissue microarrays (TMAs) were constructed according to the method described previously [18]. Briefly, a hollow needle was utilized to punch and remove bipartite cylinders tissue core (1.0 mm in diameter) from selected donor tissue regions. Further, the punched tissue cores were inserted into a recipient paraffin block with a precisely spaced array pattern, using an automatic tissue arraying instrument (Beecher Instruments, Silver Spring, Maryland, USA). For each sample, two cores from the selected tumor area and one core from adjacent nontumor mucosa were used to construct the TMA.

2.4. Immunohistochemical Staining. Immunohistochemical staining was performed on formalin fixed paraffin-embedded tissues using a standard streptavidin-biotin-peroxidase complex method as previously described [18]. TMA slides were

TABLE 1: Correlation of TBLIXR1 protein expression with clinicopathological parameters.

Variable	All cases	TBLIXR1 protein expression		P value ^a
		High	Low	
Gender				
Male	233	134	99	0.051
Female	101	70	31	
Age at surgery				
<57 ^b	172	109	63	0.432
≥57	162	95	67	
Tumor size				
≥5 cm	149	102	47	0.013
<5 cm	185	102	83	
Histological type				
Intestinal	265	162	103	0.537
Diffuse	69	42	27	
TNM				
I + II	117	5	112	0.001
III + IV	217	204	13	
Lymph node metastases				
Present	234	174	60	0.000
Absent	100	30	70	

^aChi-square test; ^bmedian age.

incubated at 4°C in a moist chamber overnight with rabbit polyclonal antibody against human TBLIXR1 (1:100, Abcam, ab190796). Staining with PBS instead of primary antibody against TBLIXR1 was used as negative control.

Nuclear immunoreactivity for TBLIXR1 protein was classified as positive signal. The scores were determined by combining the proportion of positively stained tumor cells and the intensity of staining as previously described [10]. The proportion of positively stained tumor cells was scored as follows: no positive tumor cells (score 0); <10% positive tumor cells (score 1); 10–35% positive tumor cells (score 2); 35–75% positive tumor cells (score 3); >75% positive tumor cells (score 4). Staining intensity was graded according to the following standard: no staining (score 1); weak staining (score 2); moderate staining (score 3); strong staining (score 4). The staining index was calculated as the staining intensity score multiplied by the proportion of positively stained tumor cells (values from 0 to 16). The staining was assessed by two independent pathologists (Qinghua Cao and Ni Liu) without knowing the identity of the samples. If there was a discrepancy in individual evaluations, then the two pathologists reevaluated the slides together to reach a consensus.

2.5. Statistical Analysis. Statistical analysis was performed with the SPSS package (version 20.0). The associations

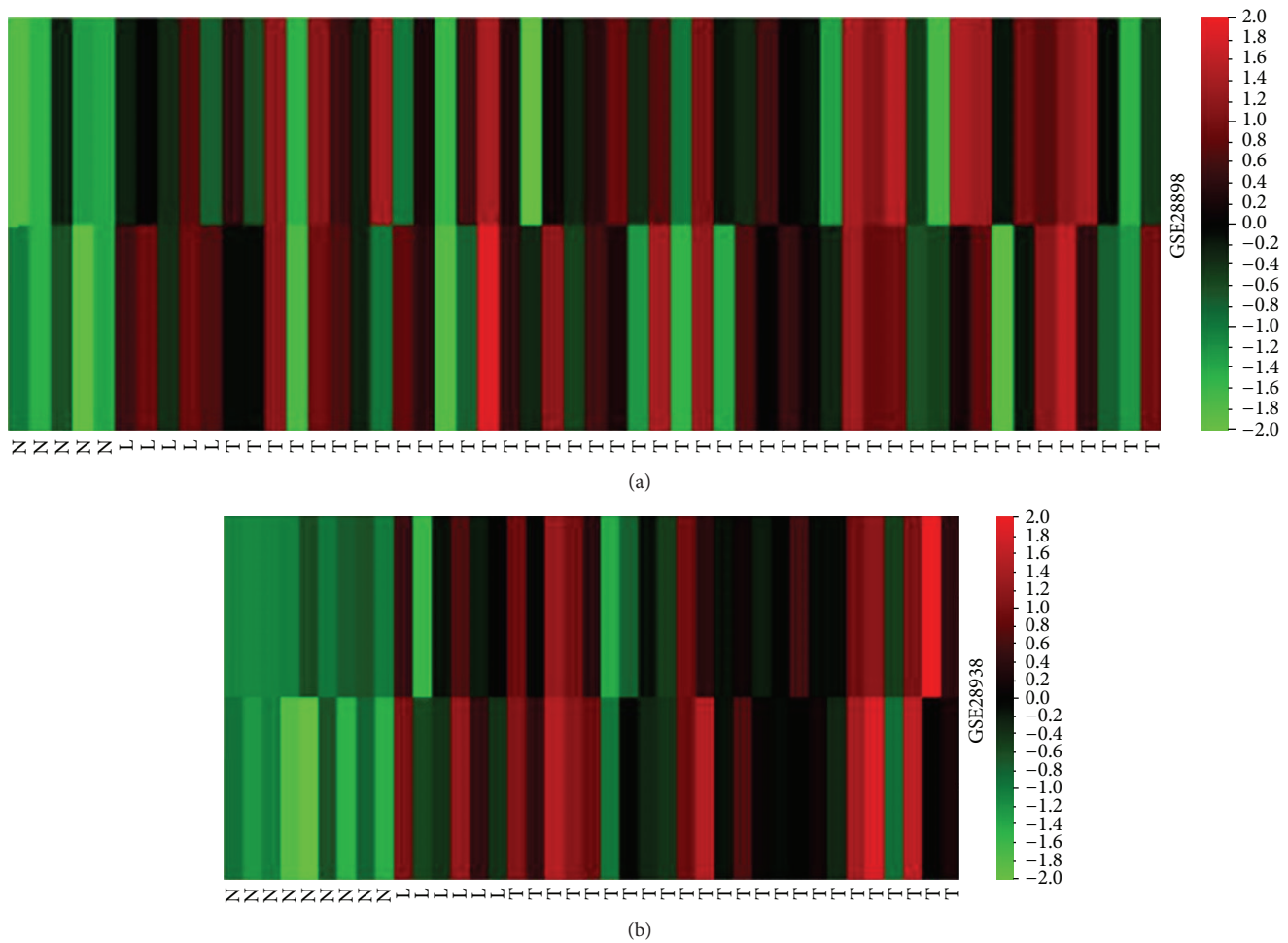


FIGURE 1: Analysis of the mRNA level of TBLIXR1 from GSE2701 dataset showed that TBLIXR1 was significantly higher in primary gastric cancer (GC) tumor (T) and lymph node metastasis lesions (L) than in normal gastric tissues (N) ($P < 0.05$). (a) Cohort 1: T + L versus N: $P < 0.05$; T versus L: $P > 0.05$. (b) Cohort 2: T + L versus N: $P < 0.05$; T versus L: $P > 0.05$.

between TBLIXR1 expression and clinicopathological features were analyzed by chi-square (χ^2) test. Kaplan-Meier analysis was used for univariate survival analysis and log-rank test was applied to compare different survival curves. The multivariate Cox regression model was used to assess the potential independent prognostic factors and 95% confidence intervals (CI) of hazard ratio (HR). Statistical significance was initially set at $P < 0.05$.

3. Results

3.1. Analysis of the mRNA Level of TBLIXR1 from GEO Dataset. GSE2701 consisted of 126 gastric tissues including 90 primary gastric cancers, 14 lymph node metastasis lesions, and 22 normal gastric mucosae. To compare the expression of TBLIXR1 mRNA in human gastric cancer tissues and nontumor mucosa, heat maps were made by QOE 3.1 showing the detail of TBLIXR1 mRNA expression. As shown in Figure 1, TBLIXR1 was significantly higher in primary GC and lymph node metastasis lesions than normal gastric tissues, respectively ($P < 0.05$). In addition, there was no

significant expression difference between primary gastric tumor and lymph node samples ($P > 0.05$).

3.2. The Expression of TBLIXR1 Protein in Gastric Cancer and Adjacent Nontumor Mucosa. In order to examine whether TBLIXR1 protein was overexpressed in gastric cancer, immunohistochemistry staining was performed in 334 GC tissues, 30 corresponding lymph node metastasis lesions, and 20 adjacent nontumor mucosa tissues. Samples with staining index ≥ 8 (median score of TBLIXR1 expression in the gastric cancers) were determined as high expression and samples with staining index < 8 were determined as low expression. High expression of TBLIXR1 protein was detected in 204 of 334 (60.1%) primary gastric cancer tissues (Figures 2(a) and 2(b)) and 19 of 30 (63.3%) lymph node metastasis lesions (Figure 2(d)) while 18 of 20 (90.0%) adjacent nontumor mucosae showed only low expression (Figure 2(e)) ($P < 0.001$, $P < 0.001$, resp.).

3.3. Association of TBLIXR1 Protein Expression with Clinicopathological Parameters. The high or low expression rates of

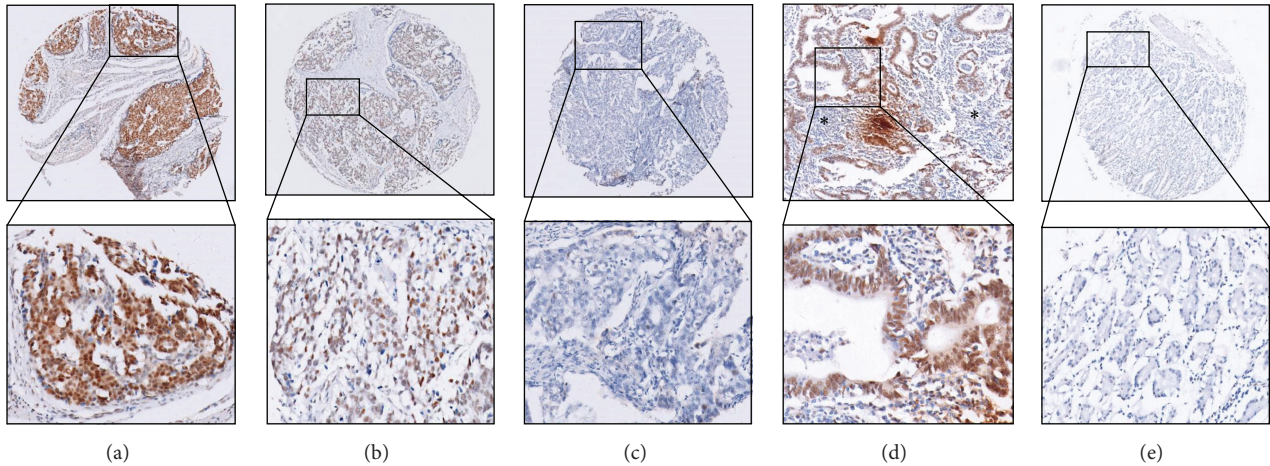


FIGURE 2: Expression of TBLIXR1 protein in GC tissue, lymph node metastasis lesions, and adjacent nontumor mucosal tissues. Immunohistochemistry staining revealed TBLIXR1 high expression (a, b) and low expression (c) in GC tissues, high expression in lymph node metastasis lesion (d) (*: lymphoid tissue around metastatic cancer), and low expression in adjacent nontumor mucosal tissues (e) ((a) scoring index = 16; (b) scoring index = 12; (c) scoring index = 4; (d) scoring index = 16; (e) scoring index = 0).

TBLIXR1 protein in gastric cancer with respect to several standard clinicopathological features are presented in Table 1. It was showed that TBLIXR1 protein overexpression was significantly related with advanced TNM stage ($P = 0.001$) and present lymph node metastasis ($P = 0.000$). There was no significant correlation between TBLIXR1 protein expression and the other clinicopathological parameters, such as gender, age at surgery, tumor size, and histological type ($P > 0.05$) (Table 1).

3.4. The Relationship between TBLIXR1 Protein Expression, Clinicopathological Features, and Overall Survival: Univariate Survival Analysis. To confirm the representativeness of the gastric cancers in our study, we analyzed established prognostic factors of patient survival. The Kaplan-Meier analysis demonstrated that there was a significant impact of the well-known clinicopathological prognostic parameters, such as histological type ($P = 0.006$), TNM stage ($P = 0.000$), and lymph node metastasis status ($P = 0.003$) on patients' overall survival (Table 2). Moreover, overall survival was significantly impaired in patients with high expression of TBLIXR1 protein compared to patients with low expression of TBLIXR1 protein in tumors ($P = 0.000$) (Table 2, Figure 3). In this regard, the mean value of overall survival time was 41.53 months in patients with low expression of TBLIXR1 compared to 28.99 months in patients with high levels of TBLIXR1 (Table 2).

3.5. Independent Prognostic Factors of Gastric Cancer Patients: Multivariate Cox Regression Analysis. A multivariate regression analysis based on the Cox proportional hazard model was used to test the independent value of each parameter in predicting overall survival. The expression of TBLIXR1 protein and other clinicopathological features that were significant by univariate analysis (histological type, TNM stage, and lymph node metastasis status) were included in the

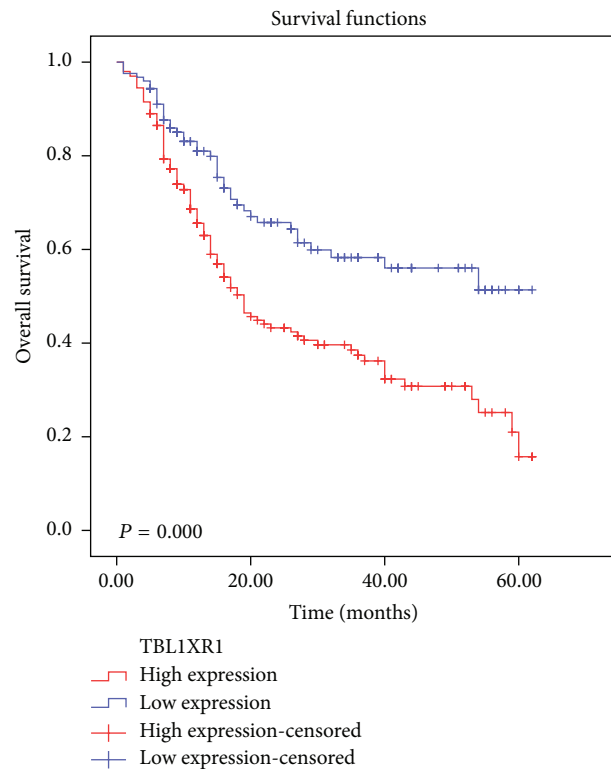


FIGURE 3: Survival curve for 334 gastric cancer patients according to TBLIXR1 protein expression status (log-rank test). High expression of TBLIXR1 protein was closely correlated with inferior overall survival (OS) ($P = 0.000$).

multivariate analysis. The results showed that high expression of TBLIXR1 was an independent prognostic factor for poor overall survival (hazard ratio, 0.525; 95% confidence interval, 0.367–0.752; $P = 0.005$), as well as histological type, TNM

TABLE 2: Univariate and multivariate analysis of different prognostic factors for overall survival of patients with gastric cancer.

Variable	All cases	Univariate analysis		Multivariate analysis		
		Mean \pm SE ^a	<i>P</i> value ^b	HR ^c	95% CI ^d	<i>P</i> value
Gender						
Male	233	35.66 \pm 1.87	0.053			
Female	101	28.83 \pm 2.59				
Age at surgery						
<57 ^e	172	32.34 \pm 2.14	0.312			
\geq 57	162	35.16 \pm 2.20				
Tumor size						
\geq 5 cm	149	31.42 \pm 2.21	0.289			
<5 cm	185	35.35 \pm 2.11				
Histological type						
Intestinal	265	35.04 \pm 1.68	0.006	1.507	1.004–2.262	0.048
Diffuse	69	24.81 \pm 3.22				
TNM						
I + II	117	52.14 \pm 2.15	0.000	1.862	1.348–2.573	0.000
III + IV	217	24.73 \pm 1.64				
Lymph node metastases						
Present	234	25.73 \pm 1.61	0.003	0.286	0.139–0.590	0.001
Absent	100	54.34 \pm 1.53				
TBLIXR1 protein expression						
High	204	28.99 \pm 1.86	0.000	0.525	0.367–0.752	0.005
Low	130	41.53 \pm 2.48				

^aSE, standard error; ^bChi-square test; ^cHR, hazard ratio; ^dCI, confidence interval; ^emedian age.

stage, and lymph node metastasis status ($P = 0.048$, $P = 0.000$, and $P = 0.001$, resp.) (Table 2).

4. Discussion

Although TBLIXR1 is thought to be involved in carcinogenesis and tumor progression in multiple studies, the relationship between TBLIXR1 and GC is unclear. In the present study, we demonstrated the oncological significance of TBLIXR1 in GC patients: (a) the expression of TBLIXR1 was significantly elevated in primary gastric tumor and lymph node tissues; (b) high levels of TBLIXR1 were associated with lymph node metastasis and advanced TNM stage; (c) TBLIXR1 overexpression is a negative predictor of prognosis in GC patients.

TBLIXR1, a transcriptional cofactor, plays an important role in controlling precise switch between gene repression and activation in transcriptional regulation [10, 19]. Consistent with our study, it was reported that TBLIXR1 was elevated in lung squamous cell cancer, esophageal squamous cell cancer, cervical cancer, breast cancer, nasopharyngeal cancer, and hepatocellular carcinoma [10–14, 20], suggesting that TBLIXR1 upregulation might be a common event in the progression of different cancers. In addition, we demonstrated that TBLIXR1 protein expression was significantly related with lymph node metastasis, advanced tumor stage, and poor prognosis but was not with gender, age at surgery, tumor size, and histological type. These findings were almost in line with previous studies. However, the study from Kuang

et al. [14] indicated that TBLIXR1 expression was associated with clinical stage, prognosis, tumor size, and histological grade. Li et al. [12] showed that TBLIXR1 expression was markedly related with pathological differentiation and *cerbB2* expression besides tumor stage and prognosis. These results indicated that, even sharing the similar prognosis prediction, the biological behavior and anatomical characteristics of TBLIXR1 might be distinguished among the tumor subtypes.

Moreover, accumulated studies suggest that TBLIXR1 may play an important role in tumorigenesis, invasion, metastasis, and developing resistance to therapies and has potential to be a negative prognosis biomarker in various cancers. Li et al. [12] reported that TBLIXR1 overexpression promoted whereas TBLIXR1 silencing inhibited proliferation and tumorigenicity in breast cancer cells *in vitro* and *in vivo*. Liu et al. [10] found that TBLIXR1 overexpression provoked lymphangiogenesis and lymphatic metastasis in ESCC and may represent a novel prognostic biomarker and therapeutic target. In nasopharyngeal cancer, Chen et al. [13] showed that increased TBLIXR1 expression suppressed cisplatin-induced apoptosis and may serve as an effective biomarker for selective therapeutic regimen for NPC patients. However, in contrast to these studies, Daniels et al. [19] demonstrated that TBLIXR1 was downregulated in prostate cancer and inhibited prostate cancer growth as a coactivator of androgen receptor. Also, TBLIXR1 downregulation was found in acute lymphoblastic leukemia with positive ETV6-RUNX1 fusion [21]. This discrepancy of TBLIXR1 expression may relate with cancer type, TBLIXR1 gene amplification, or focal deletions

[22], suggesting the complex role of TBLIXR1 in cancer progression.

Considerable researches have been carried out to determine the role and mechanism of TBLIXR1 in cancers. For instance, TBLIXR1 was involved in lung carcinogenesis by immortalizing a bronchial epithelial cell line that was considered “precancerous” [23]. It was reported that TBLIXR1 promoted cervical cancer cell metastasis by NF- κ B and Wnt/ β -catenin pathways to induce epithelial-to-mesenchymal transition (EMT) [11]. Furthermore, TBLIXR1 activated NF- κ B as to suppress cisplatin-induced apoptosis of nasopharyngeal cancer cells [13]. In ESCC cells, TBLIXR1 was demonstrated as an upstream target gene for VEGF-C and induced VEGF-C expression [10] and promoted lymphangiogenesis and lymph node metastasis. Interestingly, in GC, colorectal cancer, and breast cancer besides ESCC, analysis of datasets from GEO showed that TBLIXR1 levels were significantly correlated with VEGF-C expression, and silencing TBLIXR1 resulted in decrease in VEGF-C expression. These findings implied that TBLIXR1 contributed to lymphangiogenesis and lymph node metastasis through activating VEGF-C which may be a common mechanism for tumor metastasis in multiple cancer types, including GC. However, further studies should be performed to verify the role of TBLIXR1 in GC metastasis and related mechanisms.

In conclusion, our study showed that TBLIXR1 is overexpressed in gastric cancer in mRNA and protein level. Elevated TBLIXR1 expression is correlated with lymph node metastasis and advanced tumor stage and may serve as an independent factor for poor prognosis in GC patients.

Competing Interests

The authors declare no conflict of interests.

Authors' Contributions

Fang Liu, Yuan He, and Qinghua Cao contributed equally to this work.

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