



## Expression changes in the fibulin family in gastric cancer: A Systematic Review

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### Abstract

**Background:** Gastric cancer (GC) is one of the most widespread gastrointestinal tumors worldwide, with mortality rates among the highest. Globally, we face more than one million newly diagnosed stomach cancer patients every year. Various factors are closely associated with the formation of GC. One of these factors is the change in the level of components of the extracellular matrix in the microenvironment of the stomach tumor. Fibulins are one of the secreted glycoproteins of the extracellular matrix, known as matrix organizers. The purpose of this study was to investigate the changes in fibulins in gastric tumor tissue compared to control samples.

**Methods:** In this systematic review, a search was conducted on June 21, 2024, in alignment with the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Scopus, PubMed, and Web of Science databases were searched for articles that examined FBLN gene family and protein expression in patients with GC and GC cell lines.

**Results:** A total of 853 GC tumor samples, ranging from 8 to 197 per study, were analyzed across eight studies published between 2008 and 2023, all conducted in China. Several GC cell lines were also included, such as AGS, Kato III, MKN28, MKN45, SNU1, SNU16, NCI-N87, MGC-803, BGC-823, SGC-7901, and HGC27. Tumor size was reported in four studies, while histopathological grade and lymph node metastasis were each evaluated in four studies.

**Conclusion:** The downregulation of Fibulin-1 and Fibulin-2 supports their potential tumor-suppressive roles in GC, while the upregulation of Fibulin-5 is associated with tumor progression and worse prognosis, making it a candidate biomarker for aggressive disease.

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Fibulin

Extracellular matrix

Tumor suppressive



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## Introduction

Gastric cancer (GC) represents one of the most prevalent forms of malignancy and poses a considerable public health challenge globally (1,2). It is the fourth leading cause of cancer-related mortality and ranks fifth in terms of incidence (1,3). Early-stage GC often lacks prominent clinical symptoms, resulting in a diagnosis that typically occurs at more advanced stages (3). Surgery, as a standard treatment for GC, has substantial effectiveness in its treatment. However, the recurrence rate in GC patients after surgery is high, and the survival rate of patients has not improved significantly (1,4). The formation and development of GC is a multi-stage process, and various biological factors are involved in it (5,6).

The external environment and factors significantly influence the growth and development of GC cells (7). The extracellular matrix (ECM), which constitutes the non-cellular component of all tissues, undergoes regeneration in the context of GC, leading to alterations in the levels of its constituent components (8). Among these components, the fibulin family of proteins is notable, typically existing as homodimers. Fibulins are essential for the formation and stabilization of elastic fibers, basement membranes, and connective tissue (7).

The fibulin protein family constitutes a significant element of the ECM and is typically found as a homodimer. These proteins are essential for the development and maintenance of elastic fibers, basement membranes, and connective tissue (9,10).

The fibulin family, which includes Fibulin-1 (FBLN1) through Fibulin-8, consists of secreted glycoproteins that are key components of the ECM. The first member identified, FBLN1, is encoded by a gene situated on chromosome 22p13 in humans and produces a protein weighing between 90 and 100 kilodaltons (7,11,12). FBLN1 is a versatile protein within the ECM, playing a significant role in the structure and function of the basement membrane (13,14). It contributes

to ECM regeneration in tissues and binds to a variety of ECM constituents, including fibronectin, laminin-1, angiogenin, tropoelastin, versican, fibrinogen, proteoglycans, and nidogen. Furthermore, FBLN1 has been identified in plasma (14-17). The numerous interactions of FBLN1 with ECM elements allow it to regulate cell growth, adhesion, signaling, proliferation, and motility (8,15). Notably, variations in FBLN1 levels have been linked to several pathological conditions, including different types of cancer, where it has been proposed to act as both an oncogene and a tumor suppressor (7).

Fibulin-2 (FBLN2) is a prominent member of the fibulin family (18). This glycoprotein, which is secreted into the ECM, is situated between elastin nuclei and microfibrils, contributing to the stabilization of the ECM (18,19). Furthermore, FBLN2 plays a crucial role in regulating extracellular-intracellular signaling mediated by the ECM through integrin interactions (18).

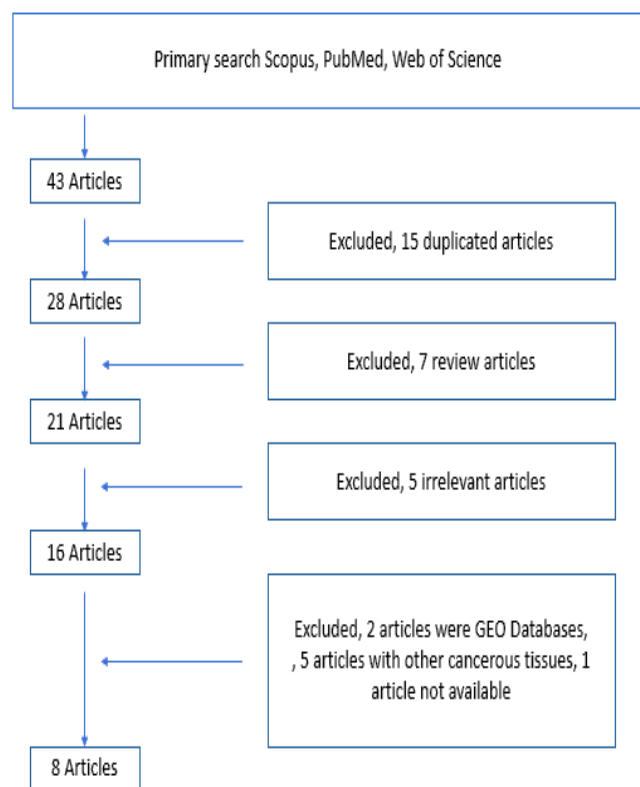
Fibulin-5 (FBLN5) is a significant member of the fibulin family, involved in cell adhesion, motility, and the association of cells with the ECM (9). Studies have shown that FBLN5 can exhibit contradictory functions, acting as either an inhibitor or a promoter of tumor cell growth, depending on the tumor type and the specific characteristics of the cancerous tissue (20). Moreover, FBLN5 is essential for the regulation of cell growth, metastasis, and tumorigenesis, and it possesses prognostic potential as a tumor suppressor (9,21).

Given the complex roles of fibulins in cancer biology, this study aimed to elucidate the specific contributions of FBLN1, FBLN2, and FBLN5 in GC progression. By focusing on these proteins, we sought to uncover new insights into their regulatory mechanisms and assess their potential as prognosis and therapeutic targets. This research not only enhances our understanding of fibulin's role in GC but also highlights the importance of ECM components in cancer development and treatment strategies.

## Methods

### Information sources

To ensure the integrity of our systematic review, we implemented a thorough process for eliminating duplicates. Initially, we gathered a total of 43 studies from three databases: PubMed (n = 11), Scopus (n = 11), and Web of Science (n = 21). After compiling the studies, we used EndNote as the reference management software to identify and remove duplicate articles. Each study was then cross-verified manually to ensure that all duplicates were eliminated. Following this process, a total of 28 unique articles remained for further screening (Figure 1).



**Figure 1.** Flowchart of the article selection process for the systematic review

### Search strategy

A comprehensive search was conducted on June 21, 2024, in alignment with the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The search yielded results based on the following keywords: (stomach cancer (Title/Abstract) OR gastric cancer (Title/Abstract) OR gastric carcinoma (Title/Abstract) OR stomach neoplasms (Title/Abstract) OR gastric neoplasms (Title/Abstract) OR stomach carcinoma (Title/Abstract)) AND (Fibulin (Title/Abstract) OR FBLN (Title/Abstract)).

### Selection process

The initial assessment was carried out by two reviewers, Jafari and Mahdizadeh, who independently evaluated the titles and abstracts of the articles until February 2024. Following this, the full texts were reviewed according to the specified inclusion and exclusion criteria. Each reviewer then examined all articles separately and later exchanged their selected studies. In situations where differing opinions emerged, particularly with articles featuring microarray analysis, the reviewers collaboratively reassessed the articles to reach an agreement.

### Eligibility criteria

- Studies investigating the effects of gene or protein expression of the fibulin family in GC cell lines
- Studies including human and mouse cancer samples related to GC
- Articles published in peer-reviewed journals
- Studies reporting original research data, including experimental findings, rather than relying solely on reviews or meta-analyses
- Studies utilizing data from Gene Expression Omnibus datasets
- Review articles, meta-analyses, and case reports
- Studies not focused on the fibulin family or GC

These criteria ensure that only relevant and high-quality studies contribute to our review.

### Data collection process

One reviewer independently evaluated the quality of the studies and the risk of bias as recommended by the Cochrane Prognosis Methods Group (Table 1) (22). After the final eight studies were selected, one reviewer thoroughly reviewed half of them, while another reviewer independently analyzed the other half. The reviewers conducted their evaluations separately. A meticulous review of all published reports, including tables and figures, was carried out to extract the pertinent information. This process involved seven criteria for assessing the risk of bias, which include: random sequence generation, blinding of both participants and staff, blinding of evaluators, allocation concealment, selective reporting, incomplete outcome data, and other potential biases.

**Table 1.** Assessing the quality of studies

Author and year of publication	Study type	Assessment tool	Risk of bias/Final quality
FKL Chan et al. (2008)	Observational studies	ROBINS-I	Moderate
Chen Li et al. (2014)	Observational studies	ROBINS-I	High
Xiaoxiao Wang et al. (2016)	Observational studies	ROBINS-I	High
Liang Feng et al. (2016)	Observational studies	ROBINS-I	High
Xiaohua Leng et al. (2016)	Observational studies	ROBINS-I	Moderate
Hongping Ma et al. (2019)	Observational studies	ROBINS-I	High
Kanger Shen et al. (2023)	Observational studies	ROBINS-I	Moderate
Tao Chen et al. (2023)	Observational studies	ROBINS-I	Moderate
Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies - of Interventions			

## Results

The reviewed articles were published between 2008 and 2023, with all studies performed in China. The studies reported a diverse range of gastric tumors, with the number of specimens ranging from 8 to 197 per study. In this systematic review, a cumulative total of 853 tumor samples were included. The GC cell lines utilized in these investigations included AGS, Kato III, MKN28, MKN45, SNU1, SNU16, NCI-N87, MGC-803, BGC-83, SGC-7901, SGC-790, and HGC27. In addition to human tumor samples, one study examined gastric tumors from mice.

The studies reviewed used various techniques and methods to conduct their analyses, including Western blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), quantitative real-time RT-PCR, methylation-specific PCR, flow cytometric analysis, immunohistochemistry, cell culture, plasmid construction, plasmid transfection, immunofluorescence staining, siRNA transfection, and tissue microarray.

Four studies provided data on tumor size measured in centimeters. Histopathological grading was assessed in two of the articles. The T stage was detailed in four studies, with the TNM stage also reported in four studies, and the N stage in three studies. Lymph node metastasis was noted in tumor samples from four studies. Follow-up of patients was limited to two studies, with a maximum duration of 75 months. Tumor differentiation was documented in four studies, while only one study examined the presence of *Helicobacter pylori* in patients. Kaplan–Meier survival curves were reported to assess patient survival in two studies. The principal features of the seven selected studies are outlined in Table 2. All primers for fibulin genes identified in these publications are summarized in Table 3.

Liang Feng et al. observed decreased expression of FBLN1 in 24 out of 36 GC samples. The FBLN1 mRNA level in non-cancerous stomach tissues ( $3.82 \pm 0.31$ ) was higher than in cancerous tissues ( $2.05 \pm 0.28$ ) ( $P < 0.001$ ). FBLN1 gene expression in non-cancerous tissues was one and a half times that of cancerous tissues. Median overall survival was decreased in cases with low FBLN1 expression compared to patients with high FBLN1 expression (OS: 33.25 vs. 53.41 months, respectively;  $P < 0.001$ ). Methylation-specific PCR was used to investigate the relationship between gene promoter methylation and FBLN1 expression level. FBLN1 gene promoter methylation was observed in 61.11% of cancer patients and 27.78% of non-cancer samples. Of the 24 GC samples with decreased FBLN1 expression, gene promoter methylation was observed in 20. They investigated the effect of FBLN1 on the growth of GC cells using a CCK8 assay. Two cell lines with high expression of FBLN1 proliferated less than control cells. Moreover, the two cell lines with high expression of FBLN1 formed fewer colonies compared to the control cells. FBLN1 was injected subcutaneously into mice with GC. Tumor growth in mice with high levels of FBLN1 was slowed compared to the control. After four weeks, the mean volume and weight of the tumor in the groups that received FBLN1 decreased in comparison with the control group. The high expression of FBLN1 did not affect the progression of the cell cycle in any of its phases. The repressive effects on tumor growth with increased FBLN1 were related to the impact of fibulin on apoptosis. High expression of FBLN1 increased cleaved caspase-3 and cleaved PARP protein. To assess whether DNA methylation or histone deacetylase inhibitors play a role in FBLN1 downregulation, all six GC cell lines were treated with 5-aza-dC or NaBT, respectively. Treatment with dimethyl sulfoxide was used as a control. Moreover, 5-aza-dC and NaBT treatments significantly increased FBLN1 transcript expression in all six GC cell lines (23). The reduction of FBLN1 expression in this study and the effect of FBLN1 injection in gastric tumors show that FBLN1 can be a new therapeutic approach in GC.

Cheng et al. stated that FBLN1 gene expression was downregulated in all five cell lines (AGS, Kato III, MKN28, MKN45, and NCI-N87). After treatment with Aza, FBLN1 expression increased across all lines. FBLN1 methylation was also observed in the CpG islands around exon 1 of the FBLN1 gene in each of the five cell lines. The expression of FBLN1 was decreased in most tumor samples compared to normal tissue. FBLN1 gene promoter methylation was also observed in most of the tumor samples, but not in tumor peripheral samples. They did not observe a significant relationship between FBLN1 methylation and clinical features. Since the expression of FBLN1 was decreased in GC tissues and samples, it can be concluded that FBLN1 has a tumor

suppressor role, which is lost in GC (24).

According to the results of Ma et al. in 2019, FBLN2 gene expression was significantly lower in GC tissue than in tumor margin tissue. In addition,  $\beta$ -catenin gene expression was significantly higher in GC tissue than in tumor margin tissue. FBLN2 protein was observed in the cytoplasm of cells in 73.47% of GC patients ( $P < 0.001$ ). The presence of  $\beta$ -catenin was observed in the cytoplasm of 77.55% of patients ( $P < 0.001$ ). There was a significant negative correlation between FBLN2 and  $\beta$ -catenin ( $r = -0.361$ ,  $P = 0.003$ ). The results showed that the expression of FBLN2 was decreased in AGS and SGC-790 cell lines. With the help of plasmids, they increased the expression of FBLN2 in AGS and SGC-790 cell lines. After increasing the expression of FBLN2, the expression of  $\beta$ -catenin and cyclin D decreased (25). The role of FBLN2 in controlling the cell cycle is reducing the level of cyclin D, which is lost in GC samples. Western blot analysis in Shen et al.'s study revealed that there was an inverse association between the expression of ITGBL1 and FBLN2 in WT and AR-GC cells. Furthermore, they observed that the FBLN2 protein level was considerably decreased in ITGBL1-overexpressing AR-AGS cells, whereas FBLN2 expression was significantly increased in ITGBL1-overexpressing AR-MKN45 cells. FBLN2 expression is substantially lower in the M1 stage of disease than in the M0 stage. There was a negative association between FBLN2 and ITGBL1 expression in GC tissues. They divided the patients into four groups based on the expression levels of ITGBL1 and FBLN2: ITGBL1 high/FBLN2 high, ITGBL1 high/FBLN2 low, ITGBL1 low/FBLN2 high, and ITGBL1 low/FBLN2 low. The Kaplan–Meier survival analysis indicated that patients in the ITGBL1 high/FBLN2 low group had a worse prognosis than the other three groups. Both univariate and multivariate regression models showed that high T stage, high N stage, high AJCC stage, high expression level of ITGBL1, and low expression level of FBLN2 were risk factors for overall survival in GC patients. These findings firmly suggest that ITGBL1 may inversely regulate FBLN2 in GC. In AR-AGS cells, where the expression of ITGBL1 increased, the expression of ITGBL1 decreased with the increase of FBLN2 level. Overexpression of FBLN2 increased the levels of CL-PARP1 and CL-Caspase9 and the rate of apoptosis (Opposite to the effects of increasing ITGBL1). By overexpressing FBLN2, some effects of ITGBL1, including migration and invasion ability, were suppressed in AR-AGS cells (26). The results of the study by Wang et al. showed that FBLN5 expression in GC samples was higher in stage III–IV than in stage I–II ( $P < 0.05$ ) (27).

According to the results of Lang et al.'s study, FBLN5 is expressed in gastric tumor tissue and para-carcinoma tissues. This protein was observed in the cytoplasm and nucleus of cells. FBLN5 expression was significantly higher in tumor tissue than in para-carcinoma tissue in both compartments ( $P = 0.029$  and  $P = 0.000$ , respectively). FBLN5 expression in the cancer cytoplasm had a positive and significant correlation with the age of patients ( $P = 0.044$ ,  $r = 0.213$ ). Older patients expressed higher levels of FBLN5 protein in the cytoplasm. Kaplan–Meier analysis with a log-rank statistical test was performed to analyze the relationship between patient survival and FBLN5 expression in the cytoplasm and nucleus. The results determined that FBLN5 expression in the cytoplasm of cancer cells had a negative correlation with the survival time of patients. The survival time of the high cytoplasmic FBLN5 group was significantly shorter than the low expression group (25.0% vs. 55.6%,  $P = 0.027$ ). Survival of patients with high nuclear FBLN5 expression was also associated with poor prognosis, but this difference was not significant (27.8% vs. 54.5%,  $P = 0.141$ ). FBLN5 expression in the cytoplasm is an independent prognostic factor in patients with GC ( $P = 0.037$ ) (28).

Shi et al. observed increased levels of FBLN5 mRNA in GC tissue compared to matched normal tumor-adjacent tissues. In addition, the increase in FBLN5 mRNA level was higher in cancerous tissue compared to normal non-cancerous tissue. Increased levels of FBLN5 are associated with malignant pathological parameters, including poor differentiation, lymph node metastasis, and advanced TNM tumor stage. In the MGC-803 cell line transfected with FBLN5 shRNA, a decrease in FBLN5 protein was observed. The reduction of FBLN5 in this cell line decreased cell invasion compared to control cells (29). Unlike other fibulins, the level of FBLN5 was increased in GC tissue. It can be concluded that FBLN5 is involved in the formation of GC through pathways distinct from those of other fibulin family members.



**Table 3.** Oligonucleotide primers of FBLNs

Author	Gene	Forward	Reverse
Cheng YY (24)	FBLN1	5'-TGCGAATGCAAGACGG-3'	5'-CGTAGACGTTGGCACA-3'
Xiao-Yu Shi (29)	FBLN5	5'-TCGCTATGGTTACTGCCAGCA-3'	5'-TTGGCAAGACCTTCCATCGTC-3'
Liang Feng (23)	FBLN1	5'-TGCGAATGCAAGACGG-3'	5'-CGTAGACGTTGGCACA-3'
Hongping Ma (25)	FBLN2	5'-GAGATCCCTGAGAGTGGCACTGAGG-3'	3'-GAGAAGGCACTCATCCTGGTCATCG-5'

## Discussion

This systematic review aimed to evaluate the alterations in the expression of fibulin family members in GC and their potential clinical implications. The findings of the included observational studies demonstrate a consistent dysregulation of fibulin proteins, particularly FBLN1, FBLN2, and FBLN5, in GC tissues compared to non-cancerous tissues.

FBLN1 was shown to have decreased expression in most tumor samples, with promoter methylation playing a role in this downregulation. Reduced FBLN1 expression correlated with worse overall survival, suggesting a tumor-suppressor role. Experimental data from animal and cell models reinforced this notion, as increased FBLN1 expression led to reduced tumor growth, increased apoptosis, and diminished colony formation. These results show that FBLN1 is a potential prognostic biomarker and a possible therapeutic target in GC.

Similar to FBLN1, FBLN2 expression was also downregulated in GC tissue and cell lines. FBLN2 showed an inverse correlation with  $\beta$ -catenin and cyclin D expression, indicating its role in regulating cell cycle and Wnt signaling pathways. Furthermore, FBLN2 overexpression promoted apoptosis and inhibited the invasive function of GC cells. These findings support the tumor-suppressive role of FBLN2 and suggest that its decreased expression may contribute to gastric tumorigenesis through deregulated signaling cascades and decreased apoptotic capacity.

FBLN5 expression was upregulated in GC tissues and correlated with adverse clinicopathological parameters, including higher TNM stage, poor differentiation, lymph node metastasis, and reduced survival. High levels of FBLN5 were significantly associated with poor prognosis, making it an independent prognostic factor. Moreover, functional experiments revealed that knockdown of FBLN5 led to decreased invasion of cancer cells, further supporting its pro-tumorigenic role. Interestingly, FBLN5 expression appears to be regulated by HIF1 $\alpha$ , linking it to hypoxia-related molecular pathways in GC.

The results suggest that fibulin family members exhibit divergent roles in GC. FBLN1 and FBLN2 act as tumor suppressors, while FBLN5 may function as an oncogene. These differences underline the complex biological behavior of FBLNs in GC and highlight their potential as biomarkers for diagnosis and prognosis, as well as therapeutic targets. The epigenetic silencing of FBLN1 and FBLN2 via promoter methylation, and the hypoxia-driven upregulation of FBLN5, depict regulatory mechanisms contributing to GC progression.

## Conclusion

Together, these findings underscore the complex regulatory mechanisms and varying impacts of fibulin family members in GC, offering insights into potential therapeutic targets and prognostic markers.

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## Ethical statement

Not applicable.

## Conflicts of interest

The authors declare that they have no competing interests.

## Author contributions

Jafari designed the research and edited the manuscript. The database search was conducted by Jafari and Mahdizadeh. The manuscript was written by Jafari and Mahdizadeh. All authors read and approved the final manuscript.

## Data availability statement

All research data generated in this work are openly available via PubMed and Scopus.

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