

# Exploring the Potential Biological Relationship Between Hypothyroidism and Gastric Cancer: Focus on SH2B3

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**Abstract:** *Background:* Gastric cancer (GC) is a common malignancy worldwide, and its development is influenced by genetic, metabolic, and immune microenvironmental factors. Hypothyroidism (HT), characterized by decreased thyroid hormone levels, has been suggested to influence tumor biology, but the molecular mechanisms linking HT to GC remain unclear. *Methods:* Based on Mendelian randomization (MR) studies identifying HT-related single-nucleotide polymorphisms (SNPs), the study annotated candidate genes using the Ensembl database and analyzed their differential expression in GC and normal tissues using GEPIA2. Functional enrichment analysis was performed using Metascape, and survival analysis was conducted with Kaplan–Meier Plotter. The study further evaluated the immune infiltration and clinicopathological associations of prioritized genes to investigate their potential roles in GC progression and therapeutic implications. *Results:* Among 121 candidate genes, 24 were differentially expressed in GC. Functional enrichment analysis revealed that these genes participate in cytokine response, angiogenesis, hemostasis, immune cell regulation, and autoimmune disease pathways. Survival analysis highlighted SH2B3 as a pivotal gene whose high expression correlated with poorer overall survival. Immune infiltration analysis revealed that SH2B3 expression positively correlated with CD8<sup>+</sup> T cells, neutrophils, and cancer-associated fibroblasts, but negatively with myeloid-derived suppressor cells, suggesting a complex role in shaping the tumor immune microenvironment. Clinicopathological analysis demonstrated an increasing SH2B3 expression with tumor stage, grade, T/N/M classification, and copy number alterations. *Conclusion:* SH2B3 may serve as a key regulator bridging HT and GC by influencing tumor progression and immune microenvironment dynamics. These findings provide novel molecular and immunological insights into the potential protective role of HT in GC and underscore SH2B3 as a promising prognostic biomarker and therapeutic target.

**Keywords:** Gastric cancer; Hypothyroidism; SH2B3; Tumor immune microenvironment

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# 1. Introduction

Gastric cancer (GC) is a prevalent malignancy worldwide, with incidence and mortality rates consistently ranking among the highest of digestive system malignancies<sup>[1]</sup>. The initiation and progression of GC are regulated by multiple factors, including genetic predisposition, metabolic abnormalities, and alterations in the immune microenvironment<sup>[2]</sup>. Hypothyroidism (HT) is a common endocrine disorder characterized by elevated serum thyroid-stimulating hormone (TSH) levels accompanied by reduced synthesis of triiodothyronine (T3) and/or thyroxine (T4); in iodine-sufficient regions, autoimmune diseases such as Hashimoto's thyroiditis represent the primary causes of HT<sup>[3]</sup>.

Thyroid hormones play key roles in metabolic regulation, the regulation of cell proliferation, and the mediation of immune responses, functions that may directly or indirectly influence tumor initiation and progression<sup>[4]</sup>. Previous studies have demonstrated that T3 and T4 can influence the biological behavior of tumor cells through various pathways, such as increasing cellular metabolic rate, inducing angiogenesis, and regulating cyclin expression, thus enhancing the proliferation and invasiveness of certain tumor cells<sup>[5]</sup>. In the field of GC research, multiple clinical and experimental studies have reported associations between abnormal thyroid hormone levels and GC patient outcomes, such as prognosis, survival duration, tumor stage, and lymph node metastasis; for example, higher free T4 (fT4) levels and lower T3 levels have been significantly associated with shorter survival in gastroesophageal cancer patients<sup>[6]</sup>. However, some studies have not observed significant associations between HT and GC, and the underlying mechanisms—particularly regarding immune regulation, inflammatory signaling pathways, and tumor microenvironmental interactions—remain unclear.

In traditional observational studies investigating the association between HT and GC, confounding factors such as age, *Helicobacter pylori* infection, dietary habits, and comorbid metabolic or autoimmune diseases pose challenges to accurate causal inference. In recent years, large-scale cohort studies have suggested a potential association between HT and GC risk; however, marked heterogeneity persists among study results<sup>[7]</sup>.

This study aims to systematically investigate the potential biological mechanisms linking HT and GC. The study analyzed the differential expression of genes mapped by HT-related single-nucleotide polymorphisms (SNPs) in GC tissues and evaluated their functional pathways and immune infiltration characteristics; the study further incorporated survival analyses and clinicopathological parameters to identify potential key genes and explore their mechanistic roles in the protective effects of HT on GC. This study seeks to provide molecular and immunological evidence elucidating the intrinsic relationship between HT and GC and to offer novel candidate targets for prognostic evaluation and immunotherapeutic strategies in gastric cancer.

## 2. Methods and materials

### 2.1. Experimental Design

Based on previously published Mendelian randomization (MR) studies suggesting a potential protective effect of HT on GC<sup>[8]</sup>, the study used the Ensembl database to annotate SNPs identified from MR analysis and determine their mapped genes. Subsequently, the study used GEPIA2 to analyze the differential expression of these genes between GC and normal tissues, and conducted functional and pathway enrichment analyses using Metascape to elucidate potential biological processes. The study further assessed the prognostic relevance of candidate genes using the Kaplan–Meier Plotter platform, selecting genes with  $P < 0.05$ , hazard ratio (HR)  $> 1$ , and expression trends consistent with adverse prognostic outcomes. Finally, the study performed a literature search for the selected genes, giving priority to genes that had not been extensively investigated as potential targets, and analyzed their

immune infiltration characteristics and clinicopathological associations in GC to explore their potential value as therapeutic targets (**Figure 1**).



**Figure 1.** Experimental flow chart.

## 2.2. Data source

Based on previously published Mendelian randomization (MR) analysis results <sup>[8]</sup>, the study further extracted single-nucleotide polymorphisms (SNPs) significantly associated with hypothyroidism (HT) and gastric cancer (GC) identified in the MR analysis and used them as candidate genetic variants for downstream analyses.

## 2.3. SNP functional annotation

Functional annotation and gene mapping of the candidate SNPs were performed using the Ensembl Genome Browser (<https://www.ensembl.org/>) <sup>[9]</sup>. The study retrieved each variant's chromosomal location and functional category (e.g., missense, synonymous, promoter region, intronic, or regulatory region) and obtained the corresponding target gene information.

## 2.4. Differential expression analysis

Differential expression analysis of the candidate genes between hepatocellular carcinoma samples (from the

TCGA database) and normal liver tissues (from the GTEx database) was performed using the GEPIA2 platform (<http://gepia2.cancer-pku.cn/>)<sup>[10]</sup>. Expression levels were normalized as  $\log_2(\text{TPM}+1)$ , and a univariate differential test was applied.

## **2.5. Metascape functional enrichment analysis**

Metascape (<http://metascape.org/gp/index.html#/main/step1>) is an integrative bioinformatics tool that integrates more than 40 distinct biological databases and offers interactive analyses, gene annotation, and other functions<sup>[11]</sup>. The study used Metascape to perform rapid functional enrichment analyses of the identified differentially expressed genes.

## **2.6. Survival analysis**

The study used the Kaplan–Meier Plotter online database (<https://kmplot.com/analysis>) to conduct survival analyses<sup>[12]</sup>. Patients were stratified into high- and low-expression groups based on the median gene expression level. Kaplan–Meier survival curves were generated, and differences between groups were compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Two-sided *P* values < 0.05 were considered statistically significant.

## **2.7. Immune infiltration analysis**

To explore the potential role of candidate genes in the tumor immune microenvironment, the study further used the TIMER3.0 database (<http://timer.cistrome.org/>) to analyze correlations between candidate genes and infiltration levels of various immune cell types<sup>[13]</sup>. The immune cell types analyzed included CD8<sup>+</sup> T cells, regulatory T cells (Tregs), macrophage subtypes (M0, M1, and M2), cancer-associated fibroblasts (CAFs), neutrophils, natural killer (NK) cells, and myeloid-derived suppressor cells (MDSCs). Correlations between gene expression and immune cell infiltration levels were evaluated using Spearman's correlation test, with significance set at  $p < 0.05$ .

## **2.8. Analysis of clinical pathological staging**

cBioPortal for Cancer Genomics (<http://cbioportal.org>) is an open-access cancer genomics resource that provides an integrated view of cancer genomic datasets and associated clinical information<sup>[14]</sup>. The study queried our target genes in cBioPortal to evaluate their mRNA expression levels and their relationships with clinical features in the TCGA-HNSC dataset. Gene expression distributions were extracted following cBioPortal's default workflow and compared across different pathological stages.

# **3. Results**

## **3.1. SNP Functional Annotation**

To further explore the potential functions and biological significance of SNPs identified in the MR analysis of hypothyroidism (HT) and gastric cancer (GC), the study used the Variant Effect Predictor (VEP) tool provided by the Ensembl database to perform functional annotation, identifying each SNP's genomic location, potential functional effects, and associations with diseases or phenotypes. After removing duplicates, 121 target genes were ultimately selected for further analysis.



### 3.2. Differential gene expression

The study analyzed the differential expression of the 121 selected genes between stomach adenocarcinoma (STAD) and normal tissues using the GEPIA2 platform. From this analysis, 24 differentially expressed genes were identified as candidate genes: AGO2, APOBR, ARID5B, C1QTNF6, CD44, CORO2A, DLEU1, GLIS3, HIVEP2, HLA-DPB1, IFIH1, IL2RA, ITGB4, ITPK1, LPP, NEK6, PHF20L1, RAPGEF3, SH2B3, SKAP2, SYN2, TLR3, TMEM86B, and TMOD1.

### 3.3. Enrichment analysis

To further investigate the potential biological roles of candidate genes in hypothyroidism (HT) and gastric cancer (GC), the study conducted multi-level enrichment analyses, including Pathway & Process, Cell Type Signatures, and disease enrichment using DisGeNET.

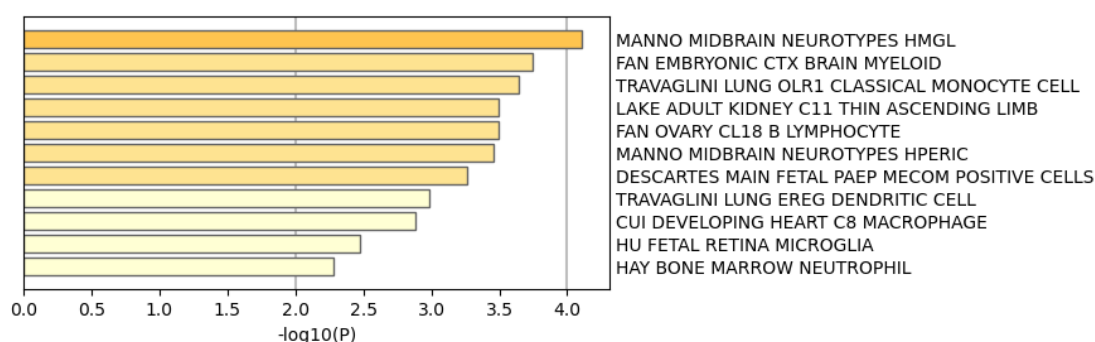
In the Pathway & Process enrichment analysis (**Table 1**), the differentially expressed genes were significantly enriched in cellular response to cytokine stimulus (6 genes, 25%), response to wounding (4 genes, 16.7%), positive regulation of angiogenesis (3 genes, 12.5%), hemostasis (4 genes, 16.7%), cell-cell communication (3 genes, 12.5%), and membraneless organelle assembly (3 genes, 12.5%). Additionally, these genes were enriched in the Influenza A pathway (3 genes, 12.5%).

In the Cell Type Signatures analysis (**Figure 2**), the differentially expressed genes were primarily enriched in immune cells and certain tissue-specific cell types. The most significantly enriched cell types included classical monocytes (TRAVAGLINI LUNG OLR1 CLASSICAL MONOCYTE, 5 genes, 21%), B lymphocytes (FAN OVARY CL18 B LYMPHOCYTE, 4 genes, 17%), dendritic cells (TRAVAGLINI LUNG EREG DENDRITIC CELL, 4 genes, 17%), and neutrophils (HAY BONE MARROW NEUTROPHIL, 3 genes, 12%). Additionally, some genes were enriched in midbrain neuronal subtypes (MANNO MIDBRAIN NEUROTYPES HMGL/HPERIC, 5 genes, 21%), embryonic brain myeloid cells (FAN EMBRYONIC CTX BRAIN MYELOID, 3 genes, 12%), and kidney thin ascending limb cells (LAKE ADULT KIDNEY C11 THIN ASCENDING LIMB, 3 genes, 12%). These results suggest that hypothyroidism-associated genes play a key role in immune surveillance and inflammation regulation, potentially enhancing anti-tumor immune responses by modulating the activity of monocytes, B lymphocytes, and dendritic cells. Moreover, the expression of some genes in neuronal and epithelial cells indicates that they may further influence gastric cancer risk through neuro-immune interactions and tissue homeostasis maintenance.

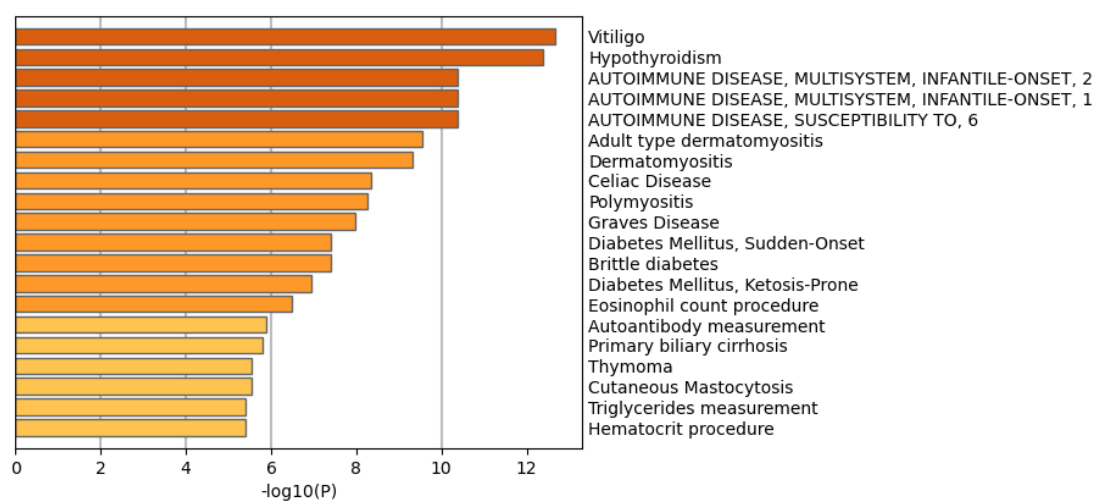
In the DisGeNET disease enrichment analysis (**Figure 3**), the differentially expressed genes were highly enriched in autoimmune diseases and disorders related to thyroid dysfunction. Significantly enriched diseases included hypothyroidism (11 genes, 46%), vitiligo (10 genes, 42%), celiac disease (8 genes, 33%), Graves' disease (8 genes, 33%), dermatomyositis/polymyositis (6–7 genes, 25%–29%), and multi-system autoimmune diseases (6 genes, 25%). Additionally, enrichment was observed for diabetes-related conditions (brittle diabetes, sudden-onset diabetes, ketosis-prone diabetes, 4 genes each, 17%), hematological parameters (eosinophil count, hematocrit), and lipid parameters (triglyceride levels). These findings indicate that hypothyroidism-associated genes are involved not only in autoimmune and endocrine regulation but may also indirectly influence gastric cancer development by modulating metabolic homeostasis.

**Table 1.** Top 7 clusters with representative enriched terms (one per cluster)

| GO            | Category                | Description                            | Count | %     | Log10(P) | Log10(q) |
|---------------|-------------------------|----------------------------------------|-------|-------|----------|----------|
| GO:0071345    | GO Biological Processes | Cellular response to cytokine stimulus | 6     | 25    | -4.56    | -0.22    |
| hsa05164      | KEGG Pathway            | Influenza A                            | 3     | 12.5  | -3.47    | 0        |
| GO:0009611    | GO Biological Processes | Response to wounding                   | 4     | 16.67 | -3.35    | 0        |
| GO:0045766    | GO Biological Processes | Positive regulation of angiogenesis    | 3     | 12.5  | -3.34    | 0        |
| R-HSA-109582  | Reactome Gene Sets      | Hemostasis                             | 4     | 16.67 | -2.87    | 0        |
| R-HSA-1500931 | Reactome Gene Sets      | Cell-cell communication                | 3     | 12.5  | -2.64    | 0        |
| GO:0140694    | GO Biological Processes | Membraneless organelle assembly        | 3     | 12.5  | -2.51    | 0        |



**Figure 2.** Enrichment of differentially expressed genes in various cell type signatures.

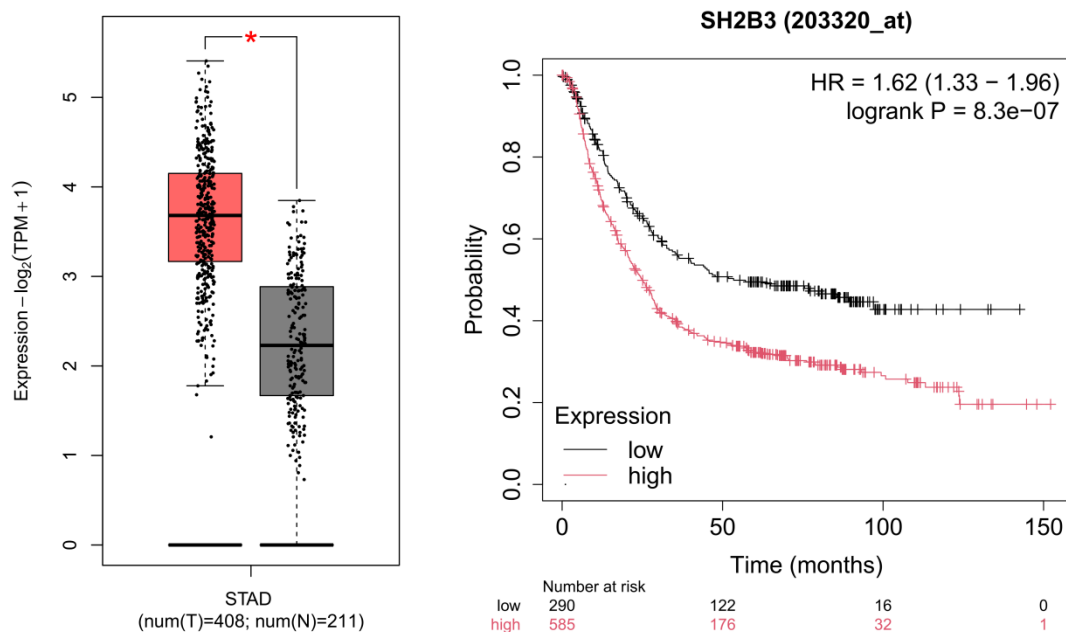


**Figure 3.** Disease enrichment analysis of differentially expressed genes based on DisGeNET.

### 3.4. Survival analysis of candidate genes and selection of target gene SH2B3

The 24 differentially expressed candidate genes in gastric cancer tissues were subjected to survival analysis using the Kaplan–Meier Plotter platform to evaluate their association with overall survival (OS). Genes with  $P < 0.05$ , hazard ratio (HR)  $> 1$ , and expression trends consistent with prognostic outcomes were selected. Ultimately, six genes—AGO2 ( $HR = 1.8$ ), C1QTNF6 ( $HR = 2.25$ ), GLIS3 ( $HR = 1.28$ ), ITGB4 ( $HR = 1.62$ ), LPP ( $HR =$

1.73), and SH2B3 ( $HR = 1.62$ )—were identified. All were highly expressed in gastric cancer tissues, and higher expression was associated with poorer OS. Subsequently, literature searches were performed for these six genes, revealing that SH2B3 has been relatively understudied in gastric cancer, although studies in other cancer types suggest it may have tumor-suppressive roles. Therefore, SH2B3 was selected as the target gene in this study for further analysis of its potential functions and clinical significance in gastric cancer (**Figure 4**).

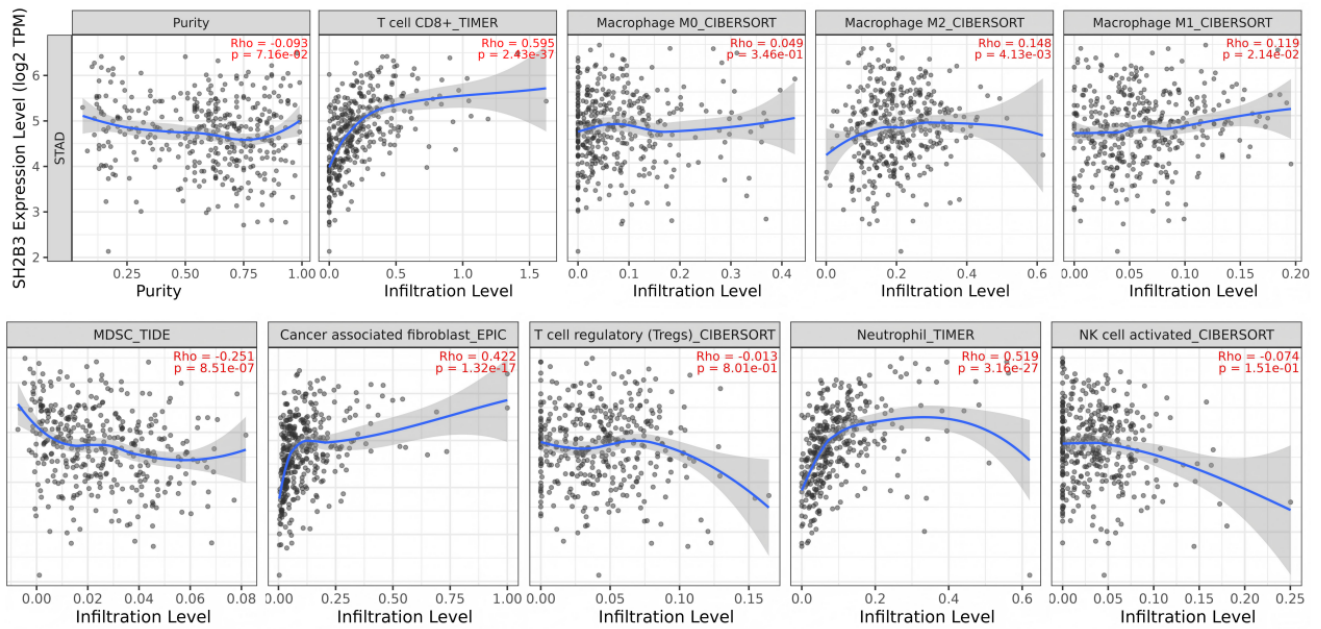


**Figure 4.** Expression difference and survival analysis of SH2B3 in STAD.

### 3.5. Immune infiltration analysis of SH2B3

To further investigate the role of SH2B3 in the tumor immune microenvironment, the study conducted a comprehensive analysis of its correlation with the infiltration levels of various immune cells (**Figure 5**). The results indicated that SH2B3 expression was significantly positively correlated with CD8<sup>+</sup> T cells ( $Rho = 0.595$ ,  $p = 2.43 \times 10^{-37}$ ), as well as with neutrophils and cancer-associated fibroblasts ( $Rho = 0.519$ ,  $p = 3.16 \times 10^{-27}$ ;  $Rho = 0.422$ ,  $p = 1.32 \times 10^{-17}$ ), suggesting that high SH2B3 expression may be associated with increased recruitment of antitumor effector T cells and may influence the inflammatory status and stromal remodeling within the tumor microenvironment.

Additionally, SH2B3 showed mild positive correlations with M2 macrophages ( $Rho = 0.148$ ,  $p = 4.13 \times 10^{-3}$ ) and M1 macrophages ( $Rho = 0.119$ ,  $p = 2.14 \times 10^{-2}$ ), indicating that SH2B3 may contribute to a complex balance between inflammation and immune suppression within the tumor microenvironment. Notably, SH2B3 was significantly negatively correlated with myeloid-derived suppressor cells (MDSCs) ( $Rho = -0.251$ ,  $p = 8.51 \times 10^{-7}$ ), whereas its correlations with regulatory T cells (Tregs), activated natural killer (NK) cells, and M0 macrophages were not significant, suggesting that SH2B3 has limited or potentially negative regulatory effects on certain immunosuppressive cell subsets.



**Figure 5.** Correlation analysis between SH2B3 expression and tumor purity as well as immune cell infiltration levels in STAD.

### 3.6. Clinicopathological association analysis of SH2B3

To further investigate the association between SH2B3 and clinicopathological features in gastric cancer, the study systematically analyzed multiple dimensions, including tumor stage, histologic grade, T stage, lymph node stage, metastasis stage, and gene alteration types (**Figure 6**). The results indicated that SH2B3 expression in gastric cancer tissues displayed a progressively increasing trend with tumor progression.

In tumor stage analysis (based on Neoplasm Disease Stage American Joint Committee on Cancer Code), SH2B3 expression was generally low in STAGE I samples and gradually increased from STAGE IA. During mid-to-late STAGE II and STAGE III, expression levels were more dispersed, with some samples showing high expression; high-expression samples were still present in STAGE IV. Significant differences were observed among the tumor stage groups, indicating that SH2B3 expression may be closely associated with tumor progression.

In histologic grade analysis (based on Neoplasm Histologic Grade), G<sub>1</sub> tissues exhibited dispersed SH2B3 expression with a predominance of low-to-moderate levels; in G<sub>2</sub> tissues, the number of high-expression samples increased; in G<sub>3</sub> tissues, high-expression samples were more concentrated with overall elevated expression; GX tissues showed intermediate expression levels. Significant differences were also observed among histologic grade groups, suggesting that SH2B3 expression may reflect the differentiation status of gastric cancer tissues.

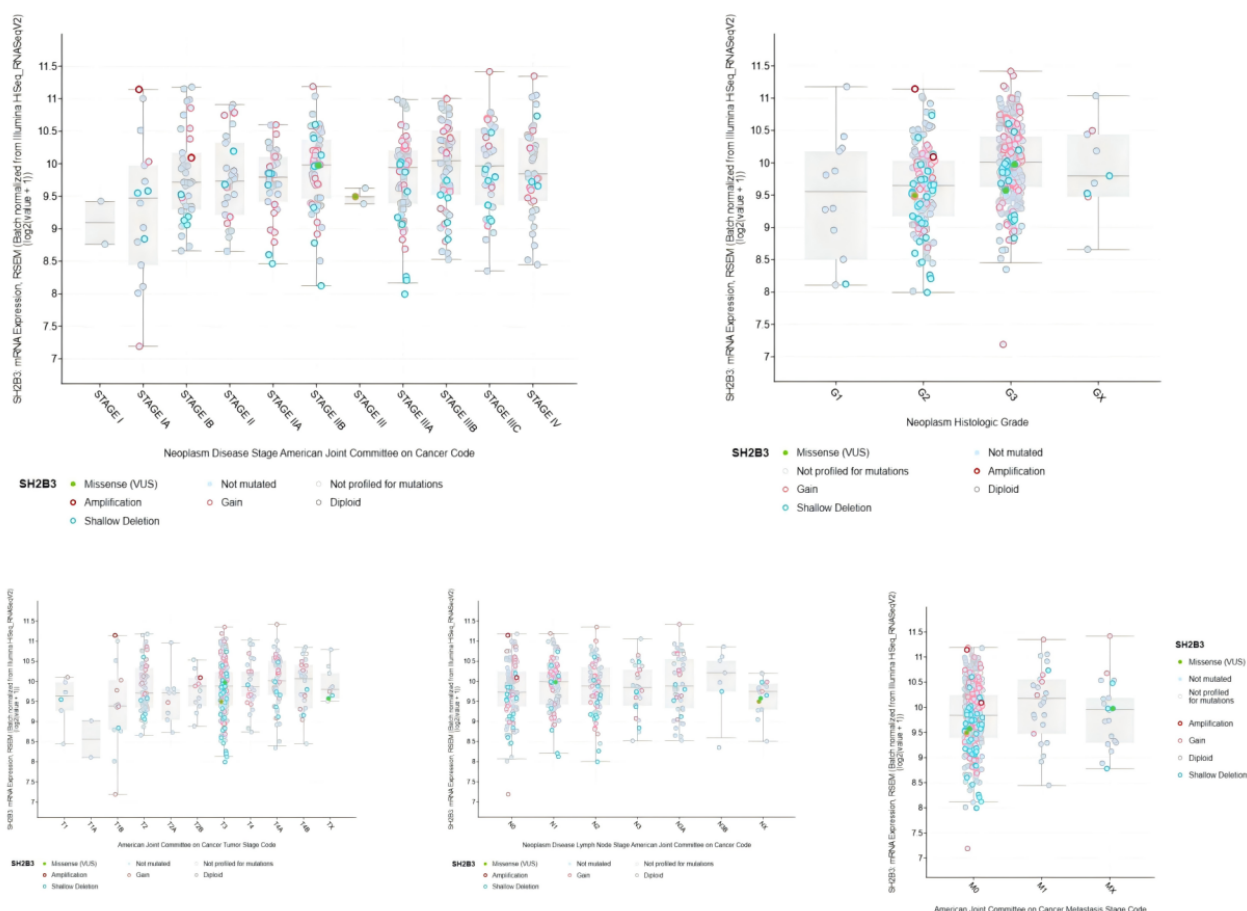
Regarding T stage (based on American Joint Committee on Cancer Tumor Stage Code), T<sub>1</sub> samples predominantly displayed low-to-moderate SH2B3 expression; expression gradually increased with T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> stages, with higher expression samples becoming more concentrated in T<sub>3</sub> and T<sub>4</sub>. Notable differences were observed among T-stage groups, indicating that SH2B3 may be closely related to tumor invasion depth.

In lymph node stage analysis (based on Neoplasm Disease Lymph Node Stage American Joint Committee on Cancer Code), N<sub>0</sub> samples showed relatively low SH2B3 expression with few high-expression samples; expression increased progressively with lymph node involvement (N<sub>1</sub>–N<sub>3</sub>B), with high-expression samples significantly enriched in N<sub>3</sub>A and N<sub>3</sub>B; NX samples displayed a wide distribution. Significant differences were

observed among lymph node stage groups, suggesting that SH2B3 expression may be associated with lymph node metastasis.

In metastasis stage analysis (based on American Joint Committee on Cancer Metastasis Stage Code), M<sub>0</sub> samples mostly exhibited low-to-moderate expression; M<sub>1</sub> samples had a marked increase in high-expression proportion; MX samples showed a wide distribution, with some high-expression samples still present. Significant differences were observed among metastasis stage groups, indicating that SH2B3 expression may be related to distant metastasis.

Furthermore, SH2B3 expression was influenced by different gene alteration types. Missense (VUS) samples exhibited moderate and broadly distributed expression; amplification samples displayed overall higher expression, with several showing marked upregulation; shallow deletion samples had relatively low expression; gain-type samples exhibited moderate-to-high expression levels. Significant differences in expression were observed among different alteration types, suggesting that gene alterations may influence gastric cancer development and progression by modulating SH2B3 expression.



**Figure 6.** Correlation analysis between SH2B3 expression and clinicopathological features in STAD.

## 4. Discussion

This study utilized MR analysis as a starting point, combined with multidimensional bioinformatics tools, to explore the potential molecular mechanisms linking HT and GC. Based on candidate gene selection, differential



expression, functional pathway enrichment, and prognostic analyses, the study ultimately focused on SH2B3. This gene has not been extensively studied in the context of GC.

Functional enrichment analysis revealed that the candidate genes were primarily involved in cytokine response, hemostasis, angiogenesis, and immune cell-specific pathways, providing insights into potential mechanisms underlying the association between HT and GC. Cytokine-mediated responses are closely associated with gastric carcinogenesis; previous studies have shown that elevated levels of IL-6 and TNF- $\alpha$  in the gastric tumor microenvironment can activate the STAT3 and NF- $\kappa$ B signaling pathways, promoting tumor cell proliferation and therapy resistance<sup>[15,16]</sup>. HT, as an autoimmune disease, is characterized by chronic inflammation and cytokine imbalance<sup>[17]</sup>. For example, IL-2 levels are significantly increased in HT patients, which may enhance antigen presentation and immune surveillance, potentially exerting a protective effect against tumor development<sup>[18]</sup>. In our enrichment analysis, the “cellular response to cytokine stimulus” pathway was highly significant, suggesting that HT-related genes may reduce GC risk by maintaining or enhancing immune surveillance.

Additionally, the enrichment of angiogenesis and hemostasis pathways warrants attention. Angiogenesis is a critical factor in tumor growth and metastasis, particularly in GC, where VEGF signaling is closely associated with prognosis<sup>[19]</sup>. Some studies have reported that thyroid hormone deficiency can inhibit VEGF-mediated angiogenesis<sup>[20]</sup>, potentially slowing tumor progression. In our study, the enrichment of “positive regulation of angiogenesis” and “hemostasis” pathways suggests that HT-related genes may indirectly influence GC development by modulating angiogenic and coagulation processes. Immune cell-specific analysis revealed that the candidate genes were significantly enriched in monocytes, B lymphocytes, and dendritic cells, indicating that HT may exert protective effects by promoting antigen presentation and adaptive immune responses. Activated dendritic cells are critical for inducing anti-tumor T cell responses, yet their function is often impaired in GC patients<sup>[21]</sup>. Therefore, HT-related genes may partially restore or enhance this immune mechanism.

Disease enrichment analysis further indicated that the candidate genes are closely associated with multiple autoimmune disorders, including celiac disease, Graves’ disease, and vitiligo, consistent with the autoimmune nature of HT and suggesting a potential link to GC via a “shared immunogenetic background.” For instance, IL2RA is both a susceptibility gene for autoimmune diseases and a participant in immune evasion mechanisms in GC<sup>[22,23]</sup>.

SH2B3 (Src homology 2B adaptor protein 3, also known as LNK) is an intracellular signaling adaptor protein that plays critical roles in hematopoietic homeostasis, autoimmune responses, and inflammation regulation<sup>[24]</sup>. Previous studies have primarily focused on its role in hematopoietic proliferation and leukemia, where it is thought to exert tumor-suppressive effects through inhibition of the JAK-STAT pathway<sup>[24]</sup>. However, our results revealed that SH2B3 is highly expressed in GC, and its high expression is significantly associated with shorter overall survival, suggesting a potentially distinct function in solid tumors.

Analysis of immune infiltration showed that SH2B3 expression is significantly positively correlated with CD8<sup>+</sup> T cells, indicating its potential involvement in recruiting anti-tumor effector cells. Simultaneously, SH2B3 was positively correlated with neutrophils and CAFs, which are known to promote inflammation, extracellular matrix remodeling, and immunosuppression in the tumor microenvironment<sup>[25,26]</sup>. Moreover, the positive correlation with M2 macrophages suggests a role in promoting an immunosuppressive microenvironment. Interestingly, SH2B3 was negatively correlated with MDSCs, indicating limited or inhibitory effects on certain immunosuppressive subsets. These observations suggest that SH2B3 may act as a “double-edged sword” in



the GC immune microenvironment: promoting anti-tumor immune responses while simultaneously activating inflammatory and immunosuppressive networks, collectively facilitating tumor progression.

Clinicopathological analysis revealed that SH2B3 expression progressively increased with tumor stage, histologic grade, T stage, lymph node involvement, and distant metastasis, particularly in advanced-stage (Stage III–IV), high-grade (G<sub>2</sub>–G<sub>3</sub>), deeply invasive (T<sub>3</sub>–T<sub>4</sub>), extensively lymph node-positive (N<sub>3</sub>), and metastatic (M<sub>1</sub>) patients. Notably, copy number amplification was associated with significantly higher SH2B3 expression, whereas shallow deletion corresponded to lower levels, indicating that gene dosage effects may be an important driver of aberrant SH2B3 overexpression. Collectively, these results suggest that SH2B3 overexpression is not only closely related to GC occurrence and progression but may also serve as a molecular marker reflecting tumor invasiveness and metastatic potential.

Despite these findings, several limitations exist. First, the study relied primarily on publicly available databases, and the results may be influenced by sample size and inherent biases. Second, MR and bioinformatics analyses reveal associations rather than direct causal relationships. Third, the specific functions of SH2B3 in GC remain unvalidated *in vitro* and *in vivo*. Future studies should combine molecular biology experiments and clinical sample analyses to elucidate the mechanistic role of SH2B3 in GC and assess its potential as a therapeutic target.

In conclusion, this study identified a potential key role for SH2B3 in GC, suggesting that it may modulate the tumor immune microenvironment and disease progression. SH2B3 could serve as a prognostic marker and potential target for immunotherapy in GC. These findings provide new insights into the intrinsic link between autoimmune hypothyroidism and gastric cancer and offer a novel candidate gene for the development of precision therapeutic strategies in GC.

## 5. Conclusion

This study identified SH2B3 as a potential key gene linking HT and GC. SH2B3 is highly expressed in GC, correlates with poor prognosis, and is associated with tumor stage, histologic grade, metastasis, and immune cell infiltration. Functional analyses suggest that SH2B3 may regulate cytokine responses, angiogenesis, and the tumor immune microenvironment, potentially exerting dual roles in GC progression. These findings highlight SH2B3 as a potential biomarker and therapeutic target, providing new insights into the molecular and immunological connections between HT and GC.

## Disclosure statement

The authors declare no conflict of interest.

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