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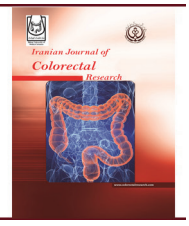

Finding New Biomarkers and Therapeutic Targets for Gastric Cancer Using a System Biology Approach

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Abstract

Background: Gastric cancer is one of the leading causes of cancer-related mortality worldwide, with approximately one million new cases diagnosed annually. Identifying key genes involved in this cancer is crucial for proposing suitable therapeutic targets and facilitating early diagnosis. This study aims to analyze the transcriptomic profile of gastric cancer cells to identify these critical genes.
Methods: Gene expression profiles from six gastric cancer datasets (GSE13911, GSE79973, GSE103236, GSE116312, GSE118916, and GSE161533) were analyzed. Differentially expressed genes were identified, and their protein-protein interaction networks were investigated using graph-based analysis.
Results: Transcriptome analysis of gastric cancer versus normal tissues identified 516 significantly differentially expressed genes. Among these, three genes, *ATP4A*, *SPP1*, and *GKN1*, were prioritized as potential biomarkers based on their significant expression changes ($\log^2$ fold change of 6.76, 3.5, and 6.88, respectively ; p-value=0.01) and central roles in the protein-protein interaction network, with node degrees of 17, 22, and 11.
Conclusion: The combination of SPP1, ATP4A, and GKN1 provides a powerful and minimally invasive tool for diagnosing gastric cancer. This multi-marker approach utilizes the gastric specificity of ATP4A and GKN1 for early detection, alongside the malignant indicator SPP1, to effectively distinguish gastric cancer from benign conditions, thereby reducing false positives.

Keywords: Gastric cancer; Gene expression profiling; Systems biology; Transcriptome

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Introduction

Gastric cancer is one of the leading causes of cancer-related death worldwide. It is estimated that approximately one million new cases of gastric cancer are diagnosed annually. In 2018, 784000 deaths were attributed to gastric cancer (1). Epidemiological studies have shown that its incidence in males is twice that in females. Gastric cancer is a multifactorial disease, with both genetic and environmental factors contributing to its onset and progression (2). The median survival time is estimated to be less than 12 months (3). Identified risk factors include Epstein-Barr virus and *Helicobacter pylori* infections, alcohol consumption, smoking, and poor diet (4). To identify suitable targets for treatment and enable early detection, numerous studies have been conducted to identify effective biomarkers for

this purpose (5){Matsuoka, 2018 #14}. Well-known biomarkers identified to date include regulators of apoptosis, factors controlling cell membrane configuration, cell cycle proteins, and microsatellite instability (6). Carbohydrate antigen 19-9 (CA 19-9) is the most prominent serum-based biomarker for the early detection of gastric cancer; however, its diagnostic utility remains controversial due to limitations in reliability (7). Other serum biomarkers currently in use include carcinoembryonic antigen, CA 125, CA 72-4, CA 50, and CA 24-2. Similar to CA 19-9, the diagnostic value of these markers is questionable due to their low sensitivity and specificity (8). Advances in molecular biology have significantly clarified the underlying mechanisms of gastric cancer. Leveraging these achievements, The Cancer Genome Atlas (TCGA) has classified gastric cancer into four molecular subtypes: tumors with microsatellite instability, Epstein-Barr virus-positive tumors, chromosomally unstable tumors, and genomically stable tumors (9).

Recently, several genes have been identified as being associated with the occurrence and progression of gastric cancer, including matrix metalloproteinase 9 (*MMP-9*) (10), transmembrane protein 1 (*IFTIM1*), and pituitary tumor transforming gene-1 (11). Despite significant efforts to elucidate the genes, pathways, and mechanisms involved in gastric carcinogenesis, the complex molecular networks underlying its development remain poorly understood. The aim of this study is to investigate the genes and pathways involved in the incidence and progression of gastric cancer and to identify suitable biomarkers and therapeutic targets for its diagnosis and treatment.

Materials and Methods

Data Acquisition and Validation

Gene expression data for gastric cancer were retrieved from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/gds). Datasets were selected based on sample size (more than five samples) and Principal component analysis (PCA) results. Studies involving patients with comorbidities other than gastric cancer were excluded to avoid confounding factors in our investigation. Six datasets were selected including GSE13911, GSE79973, GSE103236, GSE116312, GSE118916, and GSE161533. Additionally, data on mutated genes in gastric cancer were obtained from TCGA (https://portal.gdc.cancer.gov/).

Differential Gene Expression Analysis

To identify differentially expressed genes (DEGs), the datasets were normalized and analyzed using the GEO2R web server (https://www.ncbi.nlm.nih.gov/geo/geo2r). Log2 fold changes were calculated, and the false discovery rate (FDR) was controlled using the Benjamini-Hochberg method. Genes with an adjusted p-value less than 0.05 were considered statistically significant. A volcano plot visualizing the log2 fold changes between cancerous and normal tissues was generated using the Limma package in R.

Gene Annotation Analysis

DEGs were enriched for their related pathways using the Gene Ontology (GO) database (https://geneontology.org/). The PANTHER Overrepresentation Test was used for analyzing the data. Fisher's exact test was used to evaluate the correlations of expressed genes across different metabolic pathways. The Benjamini-Hochberg method was utilized to estimate the FDR of gene expressions. All analyses were performed using the clusterProfiler R package, with a significance threshold of an adjusted multiplied p-value<0.05.

Graph Network Analysis

Protein-protein interactions (PPIs) of the genes were mapped and analyzed using the STRING online web server (https://string-db.org/) developed by ELIXIR. The list of significant DEGs (both up- and down-regulated genes) was submitted to the STRING database. The PPI enrichment p-value was set at $<1.0e^{-16}$, the minimum required confidence score to map the network was set at 0.4, and the FDR stringency was adjusted to 0.05. The resulting network, which includes both physical and functional interactions, was downloaded from STRING in TSV (tab-separated values) format for further analysis.

Results

Summary of Key Findings

Transcriptome analysis of cancerous and normal tissues, combined with PPI network investigation, identified three genes, *ATP4A*, *SPP1*, and *Human gastrokine 1 (GKN1)*, that exhibited significant expression changes. These genes displayed log fold changes of 6.76, 3.50, and 6.88, respectively, each with a p-value of 0.01, and node degrees of 17, 22, and 11, respectively. Their overall calculated scores were 1.00, 0.67, and 1.66, further supporting their potential significance in gastric cancer.

Overall Study Design

The primary aim of this study is to identify the genes and gene networks associated with initiation and progression of the gastric cancer, as well as to identify genetic signatures and biomarkers for its diagnosis. The transcriptome of the gene sets was obtained from the GEO dataset. A list of DEGs was created and those exhibiting the most significant changes in expression were selected for further enrichment and analysis. The selected genes were then compared with the list of mutated genes from the TCGA database. the PPIs among the gene products were analyzed using graph network analysis. Finally, genes exhibiting both significant differential expression in cancerous tissues compared to normal tissues and a high degree

of centrality within the network were identified as potential biomarkers for gastric cancer.

Gene Expression Analysis

PCA and hierarchical clustering demonstrated clear separation between gastric cancer and non-tumor tissues across all six datasets. A small number of outlier samples, identified by inconsistent positioning in PCA space, were excluded. From the 3,000 DEGs, a total of 516 genes exhibiting a log2 fold change greater than 2 were selected for further analysis (Figure 1, Table 1).

Analysis of Enriched Metabolic Pathways

The 516 selected DEGs were enriched for important metabolic pathways in the Gene Ontology database. The most significantly altered pathway was the urokinase plasminogen activator signaling pathway (Table 2). Increased expression of core genes in this pathway has been observed in many malignancies. The next pathway exhibiting elevated expression, accounting for 16.12%, was gastric acid secretion.

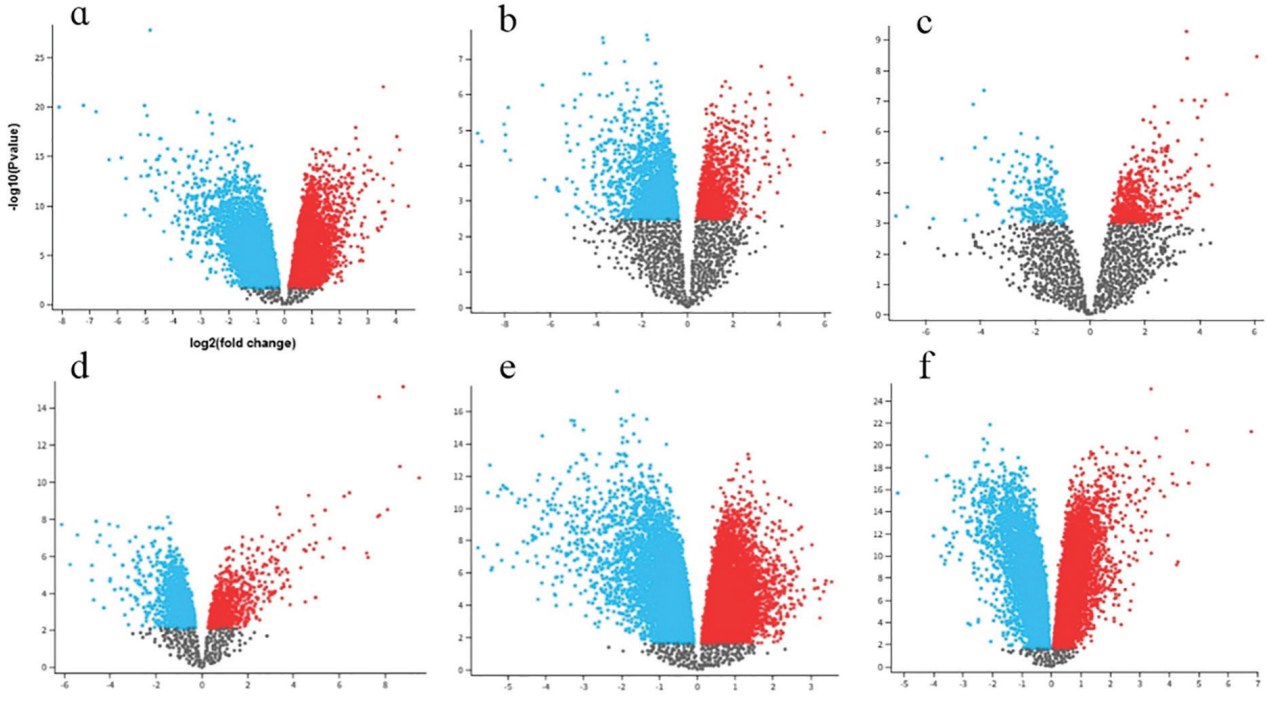

Figure 1: Volcano plots of gene expression in six gastric cancer datasets compared to normal tissues. Fold changes are presented as log2 values and the p-values are represented as –log10. Red and blue spots indicate upregulated and downregulated genes respectively. (a): GSE13911; (b): GSE79973; (c): GSE103236; (d): GSE116312; (e): GSE118916; and (f): GSE161533.

Table 1: Most prominent upregulated and downregulated genes

	Gene symbol	Protein function
Down-regulated	ATP4B	ATPase H+/K+ transporting beta subunit
	GIF	Gastric intrinsic factor
	ATP4A	ATPase H+/K+ transporting alpha subunit
	ESRRG	Estrogen related receptor gamma
	AQP4	Aquaporin 4
	PGA4	Pepsinogen 4
	GKN1	Gastrokine 1
	KCNE2	Potassium voltage-gated channel subfamily E regulatory subunit 2
	GKN2	Gastrokine 2
	LIPF	Lipase F, gastric type
Up-regulated	SPP1	secreted phosphoprotein 1
	INHBA	Inhibin beta A subunit
	COL10A1	Collagen type X alpha 1 chain
	FAP	Fibroblast activation protein alpha
	COL11A1	Collagen type XI alpha 1 chain
	KRT17	Keratin 17
	CST1	Cystatin SN
	FNDC1	Fibronectin type III domain containing 1
	SFRP4	Secreted frizzled related protein 4
	CEMIP	Cell migration inducing hyaluronan binding protein

Table 2: Enrichment analysis of genes and their related pathways

GO biological process complete	Number of genes	Fold change	P-value	FDR
Urokinase plasminogen activator signaling pathway	3	21.49	1.58E-03	4.47E-02
Gastric acid secretion	6	16.12	1.68E-05	1.19E-03
Monoterpenoid metabolic process	4	14.33	6.58E-04	2.31E-02
Lipid hydroxylation	4	12.28	9.97E-04	3.18E-02
Positive regulation of corticosteroid hormone secretion	4	10.75	1.44E-03	4.20E-02
Doxorubicin metabolic process	5	10.75	3.55E-04	1.42E-02
Polyketide metabolic process	5	10.75	3.55E-04	1.42E-02
Negative regulation of plasminogen activation	4	10.75	1.44E-03	4.19E-02
Regulation of plasminogen activation	9	10.75	1.49E-06	1.61E-04
Detoxification of copper ion	7	9.4	4.40E-05	2.65E-03
Stress response to copper ion	7	9.4	4.40E-05	2.64E-03
Negative regulation of homotypic cell-cell adhesion	6	9.21	1.72E-04	7.90E-03
Positive regulation of steroid hormone secretion	5	8.95	6.80E-04	2.37E-02
Negative regulation of platelet aggregation	5	8.95	6.80E-04	2.37E-02
Ganglion development	7	8.85	5.98E-05	3.38E-03
Positive regulation of heterotypic cell-cell adhesion	6	8.6	2.32E-04	1.01E-02
Primary alcohol catabolic process	6	8.6	2.32E-04	1.01E-02
Cellular response to mineralocorticoid stimulus	5	8.27	9.07E-04	3.00E-02
Carbon dioxide transport	5	8.27	9.07E-04	2.99E-02
Epoxygenase P450 pathway	7	7.92	1.05E-04	5.46E-03
Fibrinolysis	7	7.92	1.05E-04	5.44E-03
Detoxification of inorganic compound	7	7.92	1.05E-04	5.42E-03

*FDR: false discovery rate.

Table 3: Commonly altered genes from The Cancer Genome Atlas and Differentially Expressed Genes

TCGA	Function
CDH11	Cadherins are calcium-dependent cell adhesion proteins
MYH11	Provides instructions for making a protein called smooth muscle myosin heavy chain 11
FLT4	Provides instructions for making a protein called vascular endothelial growth factor receptor 3 (VEGFR-3)
SALL4	SALL proteins are transcription factors, which means they attach (bind) to specific regions of DNA and help control the activity of particular genes.

Infection with *Helicobacter pylori* is associated with increased gastric acid secretion. The third upregulated metabolic pathway was lipid hydroxylation, showing an increase of 12.8%. Comparison of the DEGs with the TCGA database for gastric cancer revealed four genes common to both gene sets (Figure 2, Table 3).

Graph Network Analysis

The PPI network for the products of the 516 selected genes was mapped and analyzed. The protein with the highest node degree centrality was COL1A1, with a score of 27 (Figure 3). This finding suggests that COL1A1 plays a central role in cancer development and may serve as a potential biomarker for gastric cancer. COL11A1 and COL2A1 also exhibited high connectivity, with 14 and 13 interactions, respectively. The second most connected protein was MMP9, with a degree of 25. Proteins in the MMP family function in the breakdown of the extracellular matrix. The third most interconnected protein was SPP1.

Discussion

The identification of biomarkers and key genes is critical for cancer diagnosis and drug development. In this study, DEGs between gastric cancer and normal tissues were identified, and their PPI networks were further analyzed using graph theory. Genes were ranked based on their log2 fold change and degree of centrality to evaluate their potential roles and significance in cancer incidence and progression.

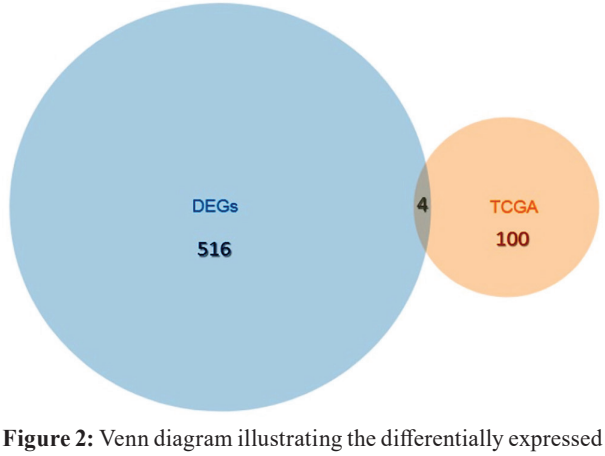

Figure 2: Venn diagram illustrating the differentially expressed genes and mutated genes in The Cancer Genome Atlas database. Four genes, *CDH11*, *MYH11*, *FLT4*, *SALL4*, are both differentially expressed between normal and cancerous tissues and mutated in more than 12% of gastric cancer patients.

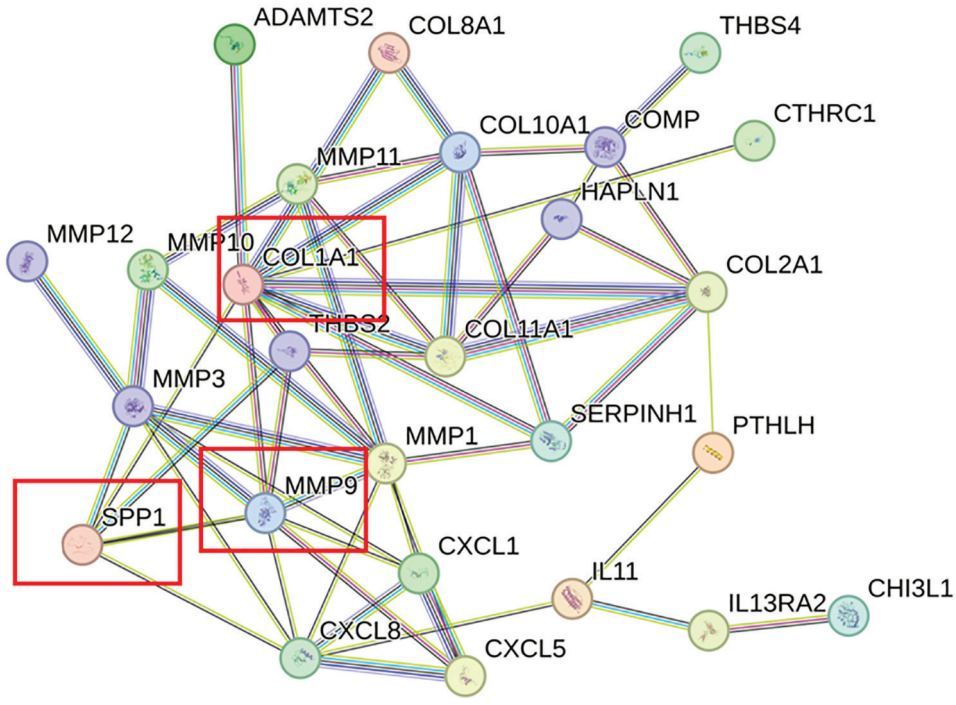

Figure 3: Protein-protein interactions of key gene products involved in the incidence and progression of gastric cancer. As shown in the figure, the core proteins in this network are MMP-9, COL1A1, and SPP1.

The top ten genes with the highest changes in expression indicate that their transcriptome levels are associated with gastric cancer (Table 1). The ESRRG gene encodes a protein belonging to the estrogen receptor-related receptor family. All members of this family exhibit identical DNA-binding properties, based on a C4-type zinc finger motif. Studies have shown that the products of this gene modulate proliferation in breast cancer cells and have a negative impact on bone formation. AQP4 encodes proteins that are intrinsic membrane channels responsible for transporting water molecules (12). The PGA4 gene encodes a precursor to pepsin, a protein-digesting enzyme secreted by gastric chief cells. This protein undergoes catalytic activation caused by the acidic conditions of the stomach, converting it into its active form to digest dietary proteins. GKN1 and GKN2 encode proteins with unknown functions, but they are thought to have mitogenic activity and a probable role in maintaining the gastric mucosal epithelium. KCNE2 encodes a component of a voltage-gated potassium channel and is commonly expressed in the heart and muscle. The LIPF gene product, gastric lipase, is responsible for digesting triglycerides in the stomach and accounts for approximately 30% of digestive fatty acid metabolism in the human body. In addition to its role in bone metabolism, the protein encoded by *SPP1* acts as a cytokine and upregulates the expression of interleukin-12 and interferon-gamma. The INHBA protein is a member of the TGF-beta superfamily. The increased expression level of this protein has been associated with human cancer cachexia. The *COL10A1* and *COL10A11* genes encode the alpha chain of type X collagen. Mutations in these genes are responsible for the occurrence of Schmid-type metaphyseal chondrodysplasia. Fibroblast Activation Protein Alpha encodes a homodimeric integral membrane gelatinase belonging to the serine protease family. This protein is believed to regulate fibroblast growth during tissue repair and carcinogenesis. *KRT17* encodes keratin 17, a type I intermediate filament protein that regulates protein synthesis and epithelial cell growth by stimulating the AKT/mTOR signaling pathway. The *CST1* gene encodes a member of the cystatin superfamily, which consists of cysteine proteinase inhibitors found in various body fluids. The protein encoded by *FNDC1* is involved in several processes, including the positive regulation of protein phosphorylation, enhancement of cardiac muscle cell apoptosis, and induction of cellular responses to hypoxia. This gene also plays a role in the development of prostate cancer (or, potentially, a specific sarcoma type). soluble frizzled-related protein 4 encodes a protein belonging to the SFRP family, which modulates Wnt signaling by directly binding to Wnt ligands. In the myocardium, expression of this protein is associated with the induction of apoptosis. The product of the CEMIP gene, cell migration-inducing hyaluronidase 1, is involved in several processes, including the positive regulation of protein transport, protein phosphorylation, and the regulation of hyaluronan catabolism.

The highest-scoring gene, considering both expression level and node degree, was assigned a value of 1, with all other genes ranked proportionally relative to this value (Table 4). The highest score was attributed to the gene *ATP4A*, which received a value of 1. The fold change in expression of this gene was considerable and also has 17 PPIs with other gene products. The K^+, H^+ -ATPase enzyme secretes H^+ ions in exchange for K^+, consuming ATP within parietal cells.

Table 4: Gene scoring based on expression changes and interactions

	Gene	Node degree	Avg. fold change	Score
1	*ATP4A*	17	6.76	1
2	*SPP1*	22	3.5	0.67
3	*GKN1*	11	6.88	0.66
4	*GIF*	10	6.62	0.57
5	*MMP3*	18	3.42	0.53
6	*COL1A1*	27	2.19	0.51
7	*AQP4*	9	6.3	0.49
8	*ATP4B*	8	7.04	0.49
9	*COL11A1*	14	3.74	0.45
10	*CXCL8*	21	2.356	0.43

*GIF: Gastric intrinsic factor; GKN1: Gastrokine 1; MMP: matrix metalloproteinase; COL1A1: Collagen type X alpha 1 chain; AQP: Aquaporin.

This enzyme consists of two subunits: a catalytic α subunit (encoded by ATP4A) and a β subunit (encoded by ATP4B). The ATP4A gene encodes the 114-kDa catalytic unit of this membrane protein (13). These proteins belong to the P-type cation-transporting ATPase family and are responsible for gastric acid secretion. The GIF gene, also known as gastric intrinsic factor, encodes a member of the cobalamin transport protein family. This gene encodes a glycoprotein essential for vitamin B12 absorption and is secreted by parietal cells of the gastric mucosa. The fold changes of ATP4A and ATP4B were nearly identical, suggesting co-regulated expression of these subunits. However, the PPIs involving the ATP4A gene product and other DEGs were significantly more complex and frequent, indicating a fundamental role for ATP4A in the development of gastric cancer. The H+/K+-ATPase complex is essential for maintaining parietal cell membrane integrity and mediates gastric acid secretion (14). Additionally, the gastric acid secretion pathway exhibited a significant change (16.12%), involving six of the DEGs. Circulating ATP4A mRNA or methylated ATP4A DNA can be detected in plasma, representing a minimally invasive early-detection approach for gastric cancer. Combining ATP4A with other gastric-specific methylated genes as a panel can reduce false-positive results. SPP1, also known as osteopontin, belongs to a group of factors involved in bone matrix association. SPP1 interacts with and binds to type I collagens such as COL1A1 and COL1A2. Junnila *et al.* investigated the expression of *SPP1*, *COL1A1,* and *COL1A2* in gastric cancer, and their results showed that these three genes are overexpressed in tumor cells. This finding indicates that the interaction of these genes is important for tumor cells to interact with the surrounding tissue matrix (15). In another study, the upregulation of ADIPOR1 and SPP1 in cancerous tissues was shown to correlate with poor survival in colorectal cancer patients. The authors speculated that there is a link between obesity and colorectal cancer (16). Alterations in *SPP1* expression have also been associated with many types of cancers, including ovarian (17), breast (18), lung (19), and prostate cancer (20). The combination of SPP1, ATP4A, and GKN1 provides a powerful diagnostic panel for gastric cancer. While ATP4A and GKN1 reflect gastric-specific differentiation and early tumorigenic changes, elevated SPP1 expression indicates malignant behavior, enabling clear distinction between gastric cancer and benign gastric conditions. GKN1 consists of 185 amino acids and is produced by gastric mucus-secreting cells. It is stored in specialized granules within the cytoplasm and secreted as an extracellular protein. This protein plays an essential role in maintaining mucosal integrity and homeostasis of gastric cells. It also acts as a tumor suppressor by regulating cell proliferation and differentiation. Recently, Yoon et al. evaluated the diagnostic value of this biomarker and showed that serum GKN1 protein provides 91.2% sensitivity and 96% specificity for gastric cancer diagnosis (21). Xing et al. investigated the physiological role of GKN1 in gastric cancer using a cell invasion assay to study its effect on cell invasion. GKN1 has been shown to inhibit cell invasion by downregulating MMP2 expression in the NF-κB signaling pathway. They concluded that GKN1 inhibits metastasis in gastric cancer cells (22). Yan et al. conducted a comprehensive study to assess the proteomic interactions of GKN1 in gastric cancer cells. They reported that GKN1 could inhibit cancer cell growth and induce cell cycle arrest in tumor tissue. It has also been claimed that GKN1 inhibits PKCδ/θ protein kinases while increasing the activity of JNK1/2 and ERK1/2, suggesting that GKN1 synergistically regulates these protein kinases to induce cell growth inhibition (23). Similar to ATP4A, GKN1 can also be detected in circulating plasma in the form of mRNA and methylated DNA. However, due to its high specificity to gastric tissue, measuring GKN1 alone also holds significant diagnostic value.

Conclusion

This study demonstrates that ATP4A, SPP1, and GKN1 are significantly altered in gastric cancer. The detection of circulating ATP4A and GKN1 in plasma provides a minimally invasive method

for early diagnosis. When combined with SPP1, a marker of malignant progression, these biomarkers form a powerful diagnostic panel. The SPP1/ATP4A/GKN1 panel enhances specificity, reduces false positives, and represents a robust, clinically viable tool for improving gastric cancer diagnosis. Future studies validating this panel in larger, prospective cohorts are warranted to confirm its clinical utility for population screening and disease monitoring.

Ethics Approval

Not applicable.

Competing Interest

The author declares that there is no potential conflict of interest related to this research and publication.

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