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METABOLIC PATHWAY AND MOLECULAR SIGNATURE ANALYSIS OF GASTRIC CARCINOMA FROM PERIPHERAL BLOOD MONONUCLEAR CELLS FROM HOSPITALIZED PATIENTS

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Abstract
Gastric carcinoma (GC) is one of the most aggressive cancers globally, characterized by high death rates resulting from late-stage diagnosis and poor therapeutic effectiveness. This research examines the metabolic pathways and molecular signature changes in peripheral blood mononuclear cells (PBMCs) from hospitalized gastric cancer patients, with the objective of identifying novel biomarkers for early detection and prognosis. Gene expression data from the Gene Expression Omnibus (GEO) collection (GSE118916 and GSE54129) were examined to find differentially expressed genes (DEGs) between gastric cancer (GC) and normal samples. The research used bioinformatics tools such as GEO2R, STRING, Cytoscape, and DAVID to identify differentially expressed genes (DEGs), create protein-protein interaction (PPI) networks, and conduct gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment studies. A total of 764 differentially expressed genes (DEGs) were discovered in GSE54129 and 356 in GSE118916, with 189 genes exhibiting overlap. Significant upregulation of key hub genes, such as FN1, MMP9, COL1A1, SPP1, CXCL8, COL1A2, THBS2, and THBS1, was observed, indicating their involvement in extracellular matrix remodelling, immunological modulation, and oxidative stress responses. The KEGG pathway study indicated the participation of focal adhesion, ECM-receptor interaction, xenobiotic metabolism, and protein digestion and absorption, underscoring their significance in tumour growth. Survival research indicated that THBS1, FN1, and THBS2 have considerable predictive significance. The results indicate that PBMC profiling provides a less intrusive method for elucidating GC etiology and discovering possible indicators for patient classification and targeted treatments. Future investigations, including multi-omics methodologies, are advised to corroborate these results and examine their therapeutic relevance in personalized treatment for gastric cancer.

Keywords: Gastric carcinoma, peripheral blood mononuclear cells, differentially expressed genes, bioinformatics analysis, gene expression profiling, extracellular matrix remodelling, protein-protein interaction, KEGG pathway, biomarker discovery, prognosis, personalized medicine.

INTRODUCTION

Gastric carcinoma (GC) stands out as one of the most aggressive and lethal malignancies globally, positioning itself among the top causes of cancer-related fatalities. The elevated mortality rate is mainly due to late-stage diagnosis, swift disease progression, and the restricted effectiveness of existing treatment methods. The development of gastric cancer is shaped by a multifaceted interaction of genetic, epigenetic, and environmental elements, such as Helicobacter pylori infection, dietary practices, persistent inflammation, and genetic predisposition [1–3]. Metabolic reprogramming has become a notable characteristic of cancer, including gastric cancer. In this process, tumour cells experience significant changes in their metabolic pathways, enabling them to support their unchecked growth, adjust to low oxygen levels, avoid detection by the immune system, and withstand programmed cell death. The metabolic alterations observed are not limited to the tumour itself; they also have systemic implications, influencing immune

cells and various circulating elements within the bloodstream [4–6]. Peripheral blood mononuclear cells (PBMCs), primarily consisting of lymphocytes and monocytes, are essential in modulating immune responses and serve as indicators of systemic changes in cancer patients. Recent studies indicate that metabolic and molecular alterations in PBMCs may reflect the tumour microenvironment, providing important insights into disease progression, immune dysregulation, and metabolic adaptations in GC patients [7–9]. The examination of metabolic pathways and molecular signatures in PBMCs can aid in pinpointing essential biomarkers linked to tumour-induced metabolic changes, inflammation, and immune reactions. In contrast to tumour biopsies, which can be invasive and may not fully capture the complexity of disease heterogeneity, PBMC profiling presents a minimally invasive, dynamic, and comprehensive method for tracking cancer-related changes. Recent developments in high-throughput omics technologies, such as transcriptomics, metabolomics, and proteomics, have facilitated a thorough characterization of metabolic and molecular changes in PBMCs [10–12]. By integrating these approaches, it is possible to uncover key dysregulated pathways involved in glycolysis, lipid metabolism, oxidative stress, and immune signalling, which may contribute to GC pathogenesis. Recognizing these biomarkers can facilitate early detection, prognosis, and the creation of tailored therapeutic approaches. Furthermore, exploring the interactions between metabolic pathways and immune responses in PBMCs could unveil novel strategies for addressing metabolic weaknesses in gastric carcinoma [13–18]. This investigation seeks to examine the metabolic and molecular characteristics in PBMCs from hospitalized GC patients, providing insights into disease biology and identifying potential targets for enhancing diagnosis and treatment outcomes.

MATERIALS AND METHODS

Data collection

The raw data used in this investigation was obtained from the Gene Expression Omnibus (GEO) database. Specific keywords and selection criteria were used to get expression profiles from tissue or clinical samples. Expression data for Gastric Adenocarcinoma (GAC) was obtained using Accession IDs GSE118916 and GSE54129 from the Gene Expression Omnibus (GEO). This GAC research evaluated matched tumours and normal samples from 162 individuals to find differentially expressed genes. Each sample pair pertains to a specific patient, allowing direct comparisons between the gene expression patterns of malignancies and normal tissue [19,20].

Data pre-processing

The Series Matrix Files for GSE118916 and GSE54129 were acquired from the GEO database for comprehensive examination. Before analysis, probe data in each dataset were transformed to standard gene symbols to synchronize gene identification with globally accepted nomenclature. To maintain consistency and mitigate any technological biases, the datasets were normalized with the Robust Multi-Array Average (RMA) approach, executed in the R software environment (version 26.0). RMA standardizes gene expression data, guaranteeing consistency in magnitude and distribution across the datasets [21].

Identification of Differentially Expressed Genes (DEGs)

This work used GEO2R to assess differentially expressed genes (DEGs) in gastric adenocarcinoma (GAC) and normal tissue samples. This tool produced a volcano plot illustrating the fold change in gene expression along the x-axis and the statistical significance (p-value) along the y-axis. To identify differentially expressed genes (DEGs), a rigorous criterion was employed: a p-value threshold of <0.05 and an absolute log fold change above 2. Furthermore, we used FunRich V3.13 software to illustrate the overlap and variance in differentially expressed genes (DEGs) across these datasets. The Venn diagram generated by FunRich illustrates the shared molecular targets or pathways across datasets.

Protein-protein interaction and hub gene identification

A protein-protein interactions (PPI) study using STRING entails submitting a list of proteins into a database to illustrate a network of anticipated connections, including both physical and functional relationships. Interactions with a cumulative score over 0.08 are deemed important, signifying the dependability of the recognized protein connections. The resultant DEGs were used to create and display the PPI network using Cytoscape software (version 3.5.1; http://www.cytoscape.org). In the generated PPI network, protein interactions are shown as edges, with edge widths indicating interaction intensity according to the combined score. Hub genes within this network were found using the CytoHubba plugin in Cytoscape software. The detected hub genes are defined by nodes exhibiting a degree greater than 10, indicating their significance within the network. The integrated approach provides a thorough tool for examining complex protein interactions and finding essential components of biological activities.

mRNA expression and survival analysis of hub genes

In silico techniques, including UALCAN and KM Plotter, were used to assess survival rates and gene expression relationships in patients with gastric adenocarcinoma. The Kaplan-Meier analysis, in conjunction with log-rank testing, substantiated the survival analysis. A statistically significant correlation between gene expression levels and patient survival was identified, with a significance threshold of $P < 0.05$. Patient data with gastric cancer, obtained from The Cancer Genome Atlas, were used for expression validation. The data, expressed as transcripts per million (TPM) values, facilitated the establishment of two different groups.

Gene ontology and pathway enrichment analysis

The Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses of differentially expressed genes (DEGs) were conducted using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, https://david.ncifcrf.gov/tools.jsp) with a significance threshold of $P < 0.05$. Furthermore, KEGG pathway analysis revealed pathways highly enriched in relation to the DEGs. Pathway crosstalk analysis was performed using particular criteria: a Benjamini-Hochberg adjusted p-value of less than 0.05 and both a Jaccard coefficient and an overlap coefficient more than 0.5, deemed statistically significant. This thorough analysis of the DEGs inside certain pathways underscores their possible role in critical biological processes and regulatory networks.

RESULT

Identification of DEGs in GAC

In the GAC cancer dataset GSE54129, a total of 764 differentially expressed genes (DEGs) were identified, while the GAC cancer dataset GSE118916 revealed 356 DEGs (Figure 1A). The identification was conducted using GEO2R analysis with the Limma package, applying strict selection criteria of an adjusted p-value of <0.05 and a log fold change of >1. Following this, the process enabled the creation of volcano plots for each dataset (Figures 1B and 1C). The most regulated genes are illustrated in Figures 2A and 2B, respectively.

Figure 1A

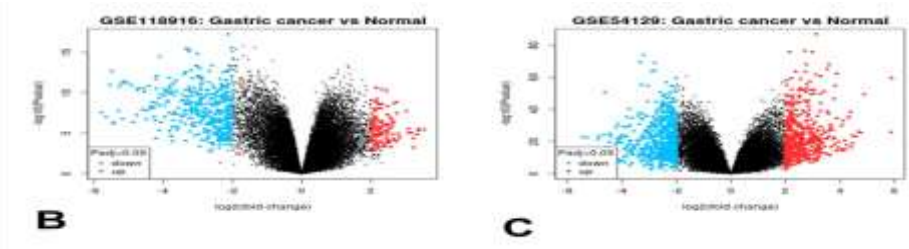


Figure 1B and 1C

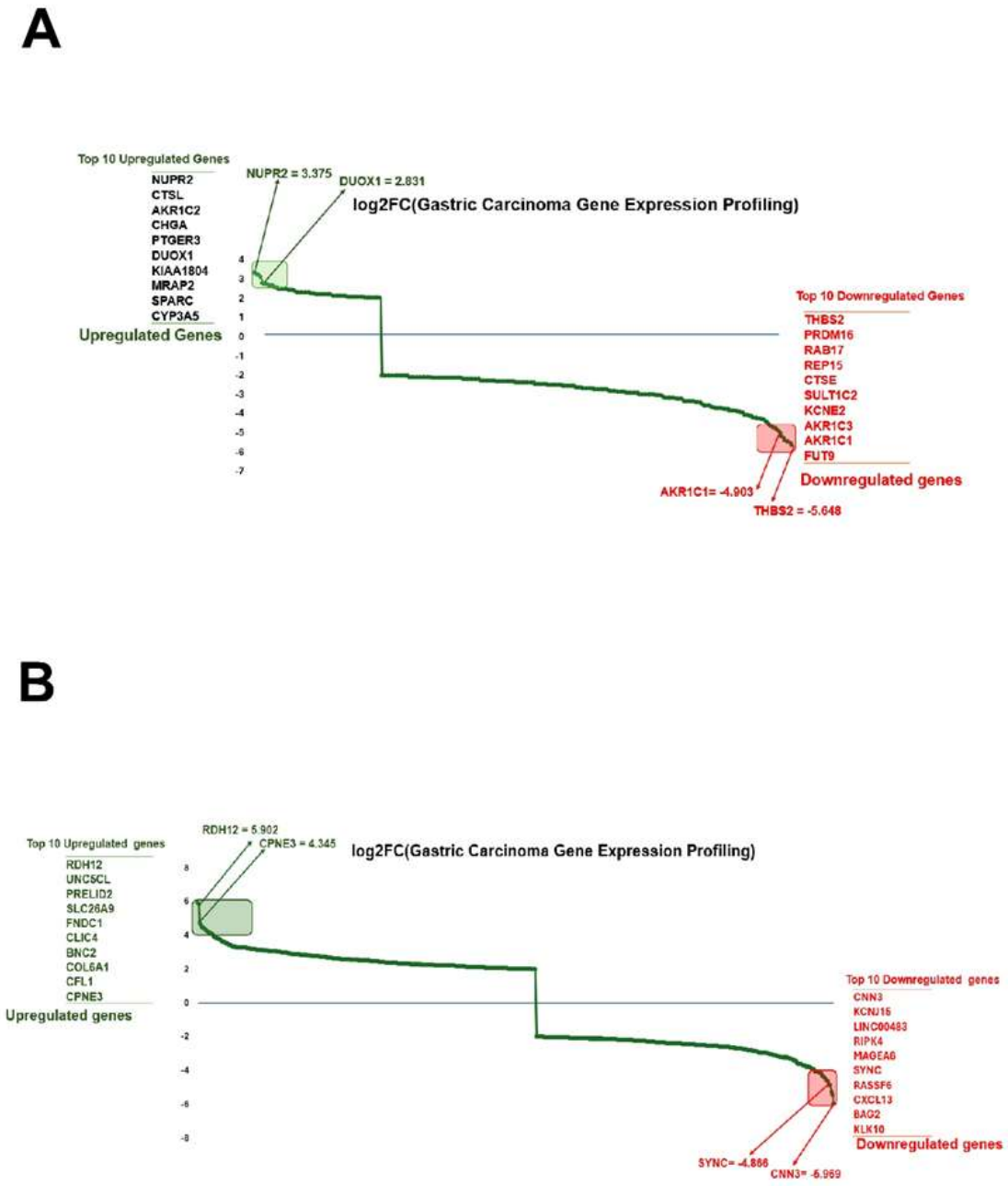


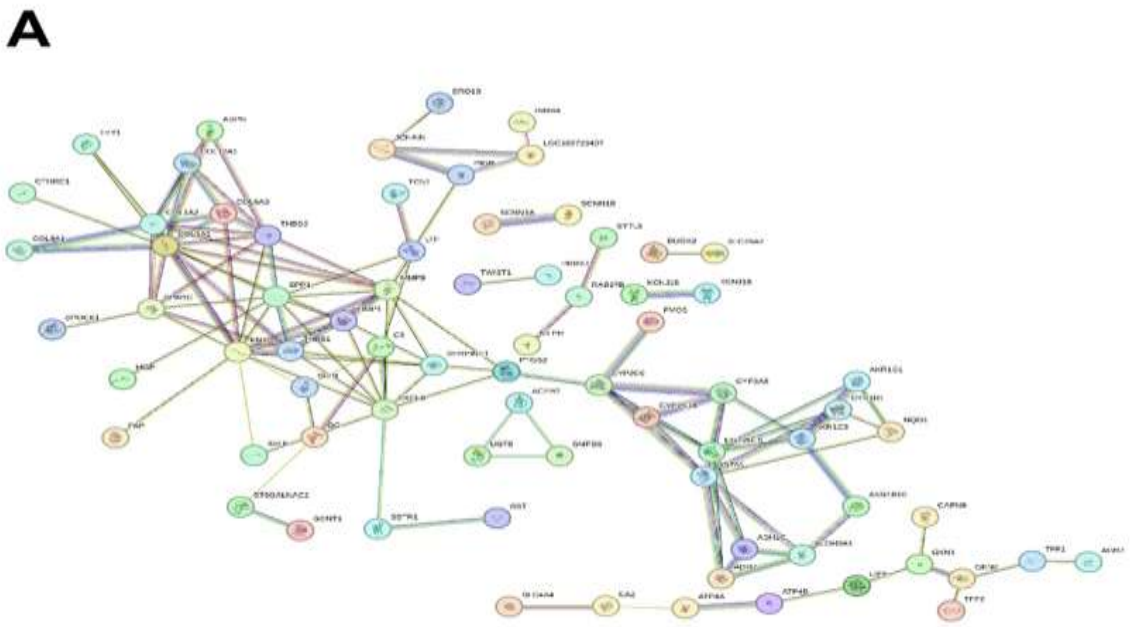
Figure 2A and 2B

PPI network construction and hub gene identification

A protein-protein interaction (PPI) network was constructed for proteins generated by 189 overlapping differentially expressed genes (DEGs) by STRING analysis (Figure 3A). All proteins were shown to be linked, as further

demonstrated by Cytoscape visualization. Furthermore, eight hub genes (FN1, MMP9, COL1A1, SPP1, CXCL8, COL1A2, THBS2, THBS1) were found by methodologies including MCC, proximity, and degree centrality (Figures 3B and 3C). Notably, all these hub genes exhibited up-regulation in the overlapping DEGs, indicating their potential significance in the progression of GAC.

Figure 3A



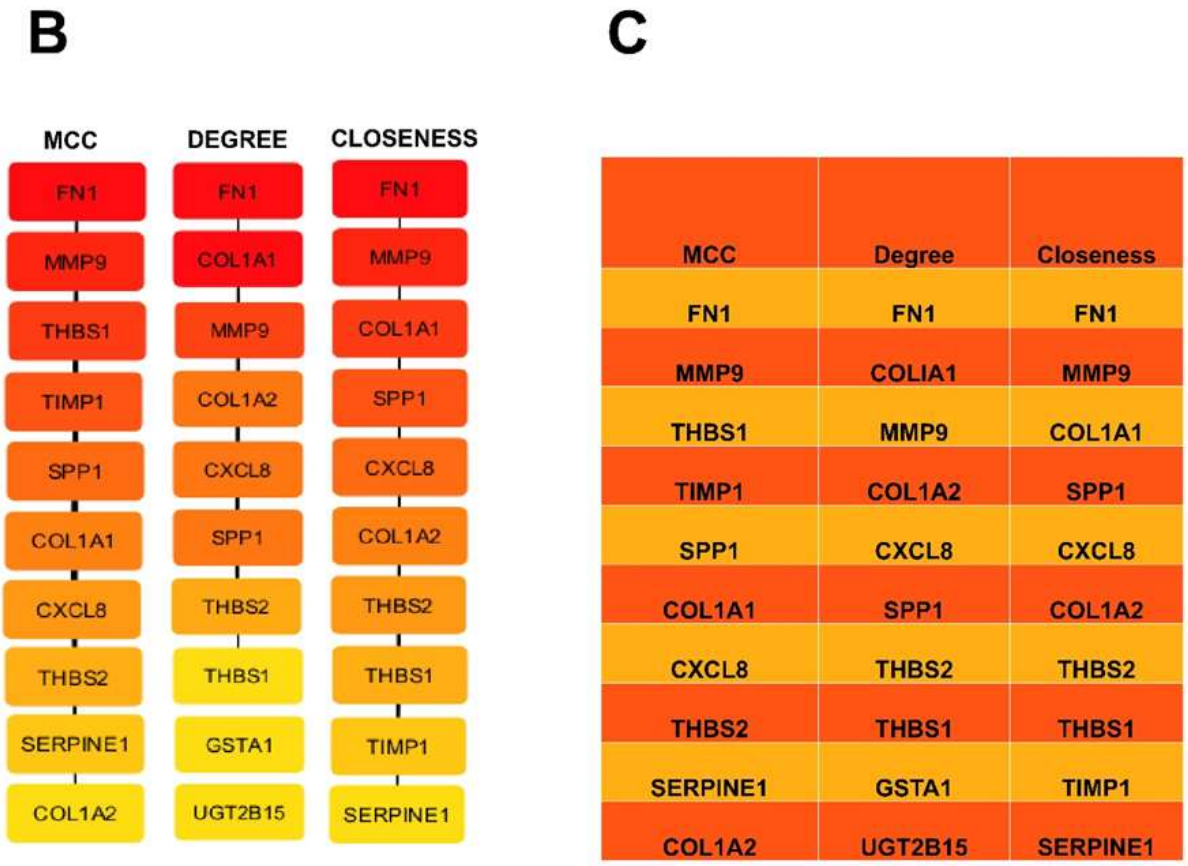


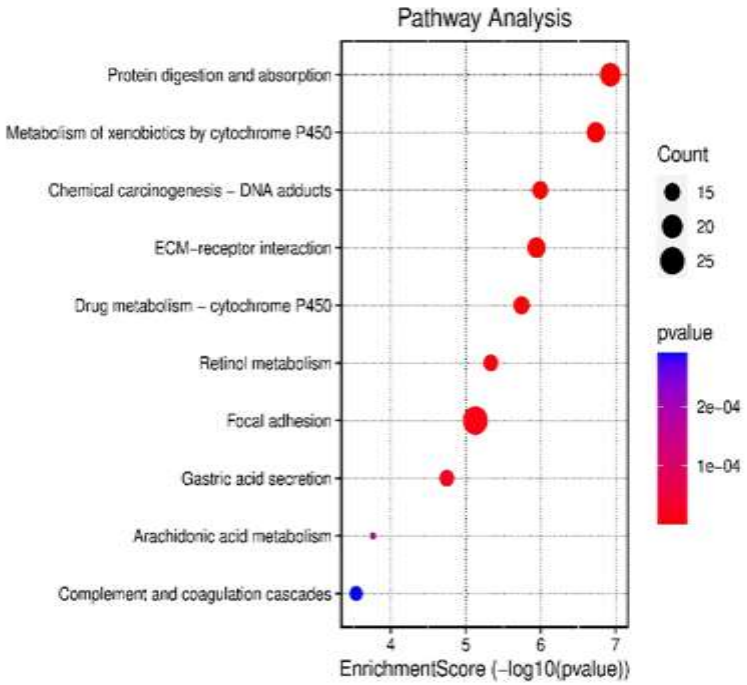
Figure 3B and 3C

Gene ontology and KEGG pathway analysis of DEGs

The examination of differentially expressed genes (DEGs) using Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways uncovers complex biological processes and pathways involved in the pathogenesis of GAC. The Gene Ontology analysis classifies differentially expressed genes into three primary categories: biological process, cellular component, and molecular function. In the realm of biological processes, significant activities such as extracellular matrix organization, extracellular structure organization, hormone metabolism, digestion, xenobiotic metabolism, and cellular responses to xenobiotic stimuli have been emphasized (Figure 4A). These mechanisms highlight the intricate relationship between cellular metabolism and the reaction to exogenous substances, which are vital in the development of stomach cancer. The study highlights the importance of the collagen-rich extracellular matrix, endoplasmic reticulum lumen, apical plasma membrane, platelet alpha granule, and collagen trimer (Figure 4B). These components signify the essential structural and functional modifications in the cellular architecture of stomach cancer cells. Moreover, the molecular function domain identifies differentially expressed genes (DEGs) linked to essential tasks, including extracellular matrix structural components, glycosaminoglycan binding, heparin binding, oxidoreductase activity, and collagen binding (Figure 4C). These molecular capabilities are crucial in cell-matrix interactions, signalling cascades, and metabolic processes, possibly providing insights into therapeutic targets and diagnostic indicators. The GO and KEGG pathway analyses together provide an extensive picture of the genetic and molecular framework of gastric cancer, emphasizing possible avenues

for intervention and more study. The pathway analysis of differentially expressed genes (DEGs) reveals their participation in essential biological pathways, such as protein digestion and absorption, metabolism of xenobiotics by cytochrome P450, chemical carcinogenesis—DNA adducts, ECM-receptor interaction, drug metabolism—cytochrome P450, retinol metabolism, focal adhesion, and gastric acid secretion (Figures 5 and 6). These pathways emphasize the intricacy of gastric cancer, illustrating the functions of DEGs in processes including food metabolism, sensitivity to environmental contaminants, cell adhesion and migration, and the metabolism of therapeutic medications. This thorough analysis enhances our comprehension of gastric carcinogenesis while pinpointing possible treatment targets and biomarkers for early diagnosis and tailored medication. The GO and KEGG pathway analyses together provide a thorough picture of the genetic and molecular framework of gastric cancer, emphasizing possible intervention routes and avenues for future investigation.

Figure 4A, 4B and 4C



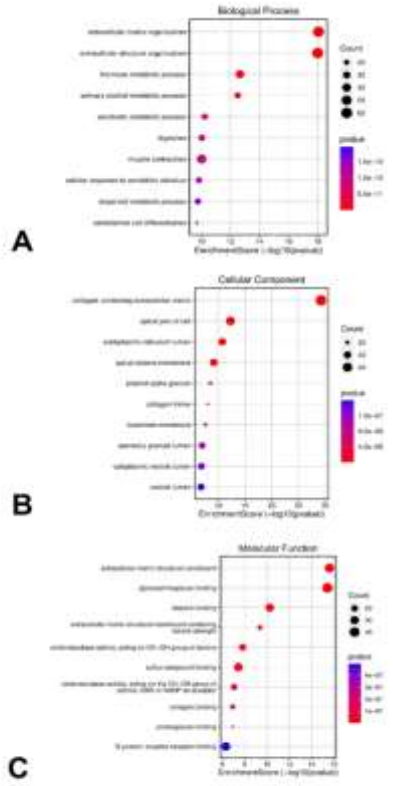


Figure 5

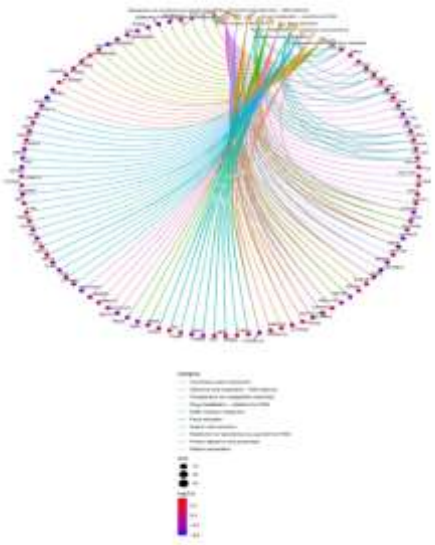


Figure 6

Verification and survival analysis of hub genes

The evaluation of expression levels and survival analysis of key genes is crucial for understanding the molecular dynamics of gastric cancer. Our work focused on eight essential hub genes using the UALCAN web server, a platform recognized for cancer data processing. All these genes exhibited significant overexpression in gastric carcinoma tissues relative to normal tissues, suggesting their possible involvement in cancer formation. The survival analysis, arranged by the significance of their p-values, demonstrated diverse prognostic effects seen in Figure 7. THBS1 was identified as the most important factor, with a p-value of 0.001, highlighting its crucial function as a prognostic marker. FN1, with a p-value of 0.0076, and THBS2, having a p-value of 0.0087, demonstrated significant relationships with survival outcomes, underscoring their relevance in patient prognostication. COL1A2, with a p-value of 0.029, demonstrated a statistically significant correlation with survival, underscoring its importance. Despite COL1A1 exhibiting a p-value of 0.089, it yet indicated potential prognostic significance. Conversely, MMP9, SPP1, and IL8 (CXCL8) with p-values of 0.93, 0.95, and 0.2, respectively, had no significant effect on survival, indicating their restricted prognostic usefulness in gastric cancer. This comprehensive analysis confirms the upregulation of these hub genes in gastric cancer and emphasizes their prognostic importance, providing essential insights into the molecular mechanisms underlying gastric carcinoma and identifying potential biomarkers for patient stratification and targeted therapy. The overexpression of eight hub genes is seen in Figure 8.

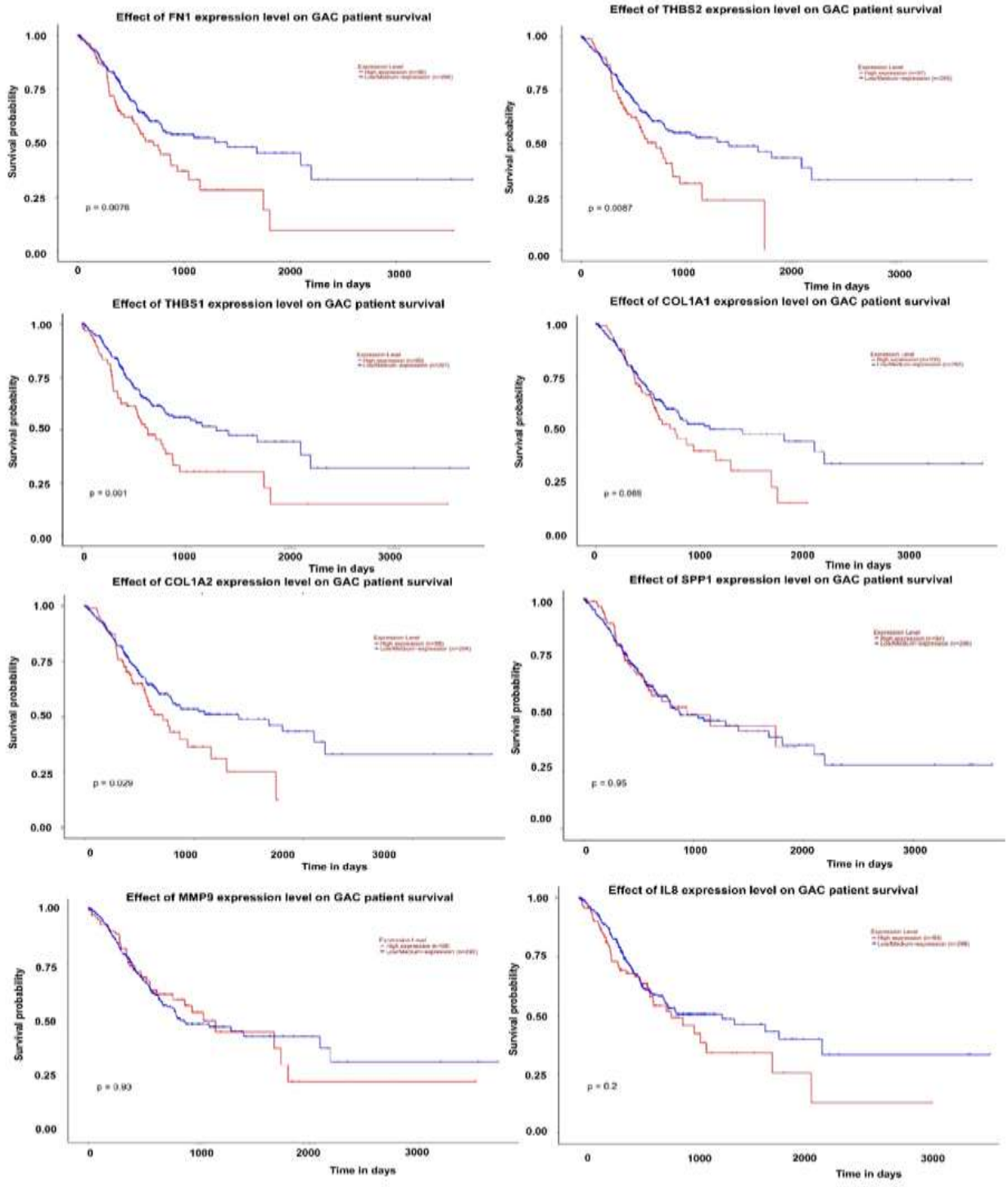
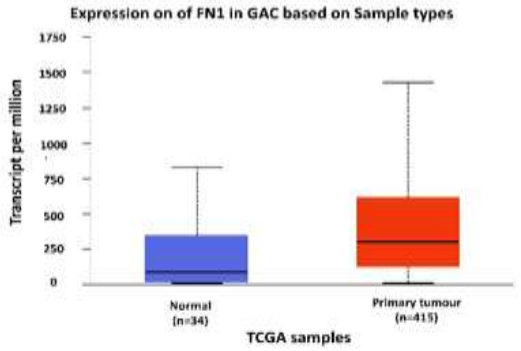
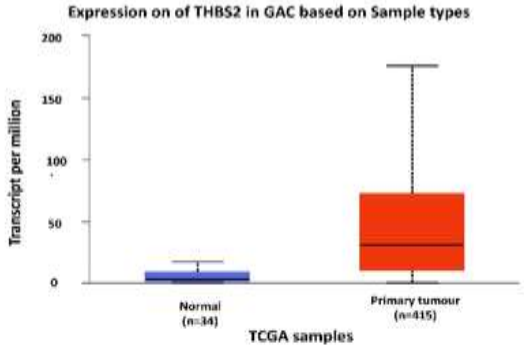
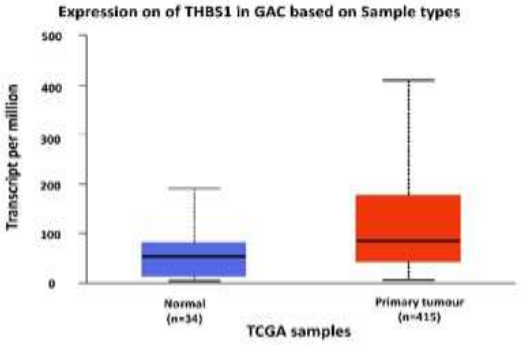

Effect of FN1 expression level on GAC patient survival
Survival probability
Time in days
p = 0.0076
Effect of THBS2 expression level on GAC patient survival
p = 0.0087
Effect of THBS1 expression level on GAC patient survival
p = 0.001
Effect of COL1A1 expression level on GAC patient survival
p = 0.068
Effect of COL1A2 expression level on GAC patient survival
p = 0.029
Effect of SPP1 expression level on GAC patient survival
p = 0.95
Effect of MMP9 expression level on GAC patient survival
p = 0.93
Effect of IL8 expression level on GAC patient survival
p = 0.2

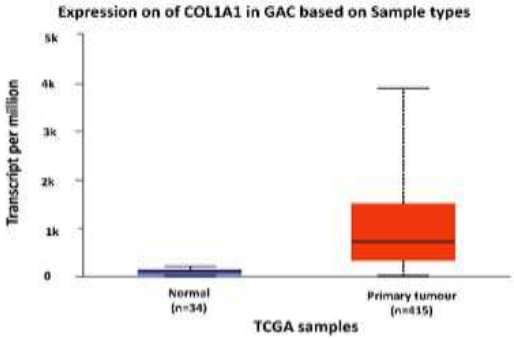
Figure 7

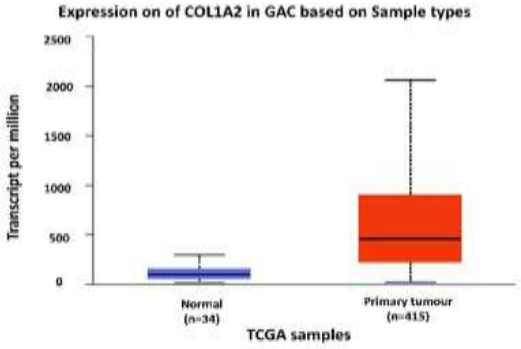
Figure 8

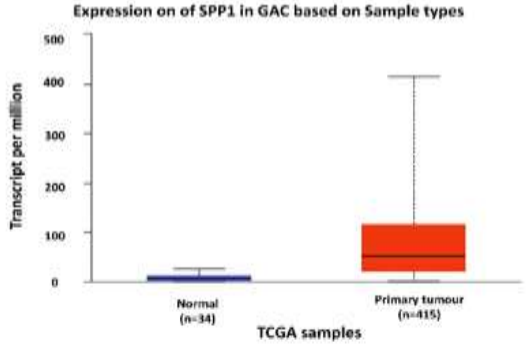

Expression on of FN1 in GAC based on Sample types
Transcript per million
1750
1500
1250
1000
750
500
250
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples

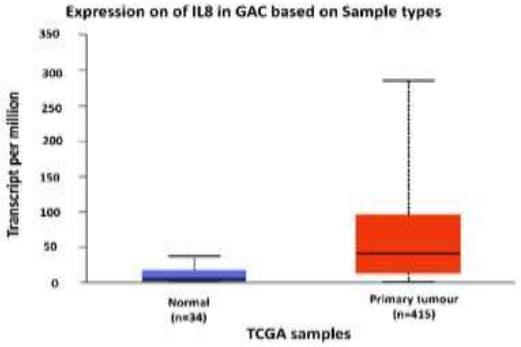

Expression on of THBS2 in GAC based on Sample types
Transcript per million
200
150
100
50
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples

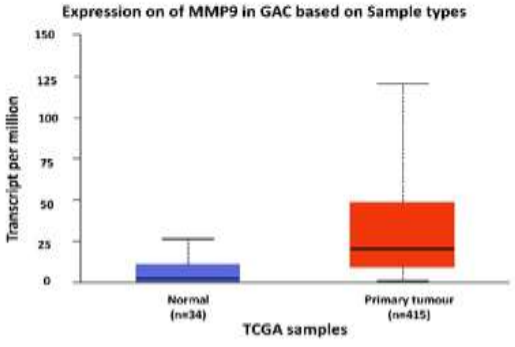

Expression on of THBS1 in GAC based on Sample types
Transcript per million
500
400
300
200
100
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples


Expression on of COL1A1 in GAC based on Sample types
Transcript per million
5k
4k
3k
2k
1k
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples


Expression on of COL1A2 in GAC based on Sample types
Transcript per million
2500
2000
1500
1000
500
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples


Expression on of SPP1 in GAC based on Sample types
Transcript per million
500
400
300
200
100
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples


Expression on of IL8 in GAC based on Sample types
Transcript per million
350
300
250
200
150
100
50
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples


Expression on of MMP9 in GAC based on Sample types
Transcript per million
150
125
100
75
50
25
0
Normal (n=34)
Primary tumour (n=415)
TCGA samples

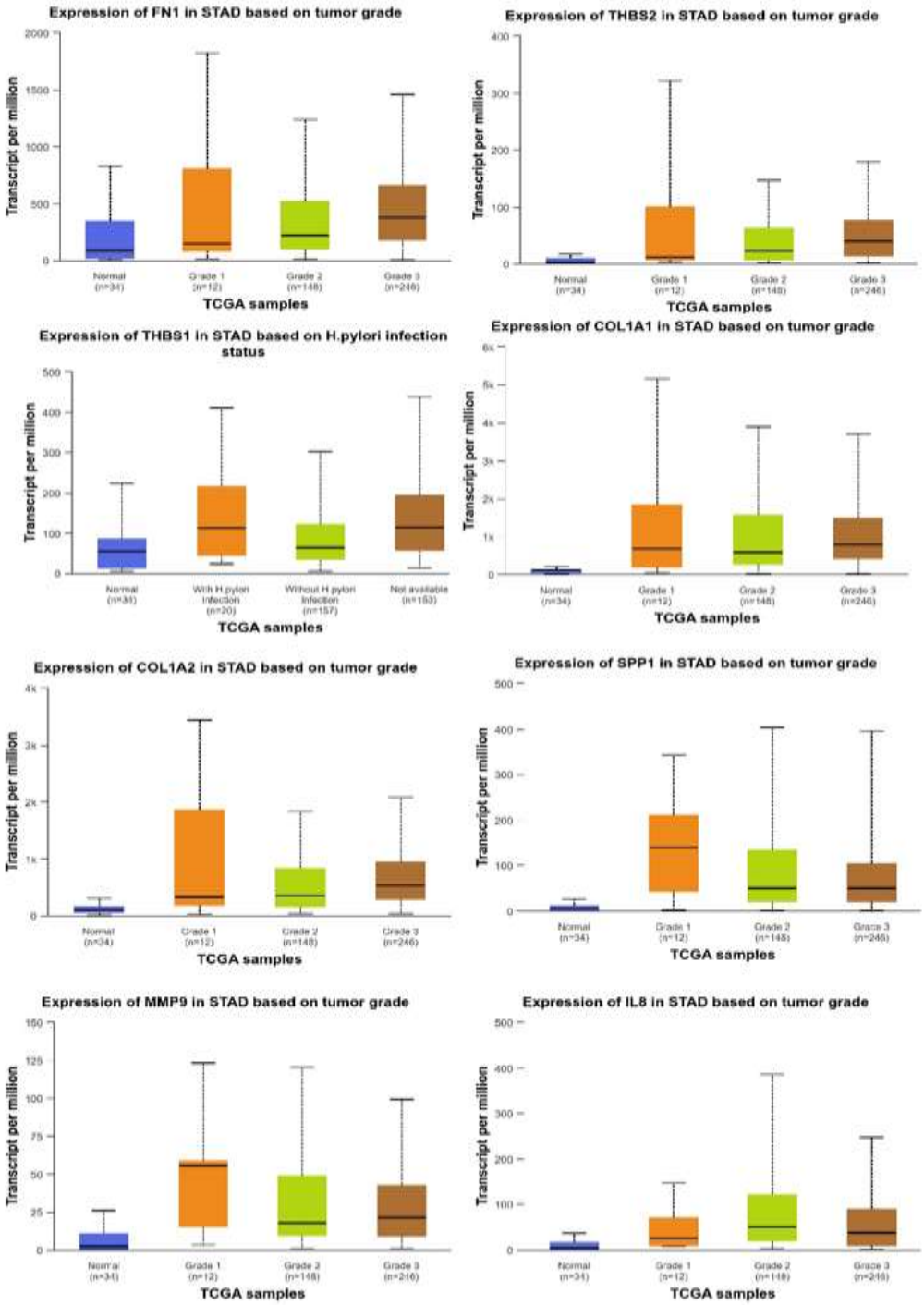


Figure 9 – Expression of 8 hub genes in Stomach Adenocarcinoma (STAD) based on tumour grade

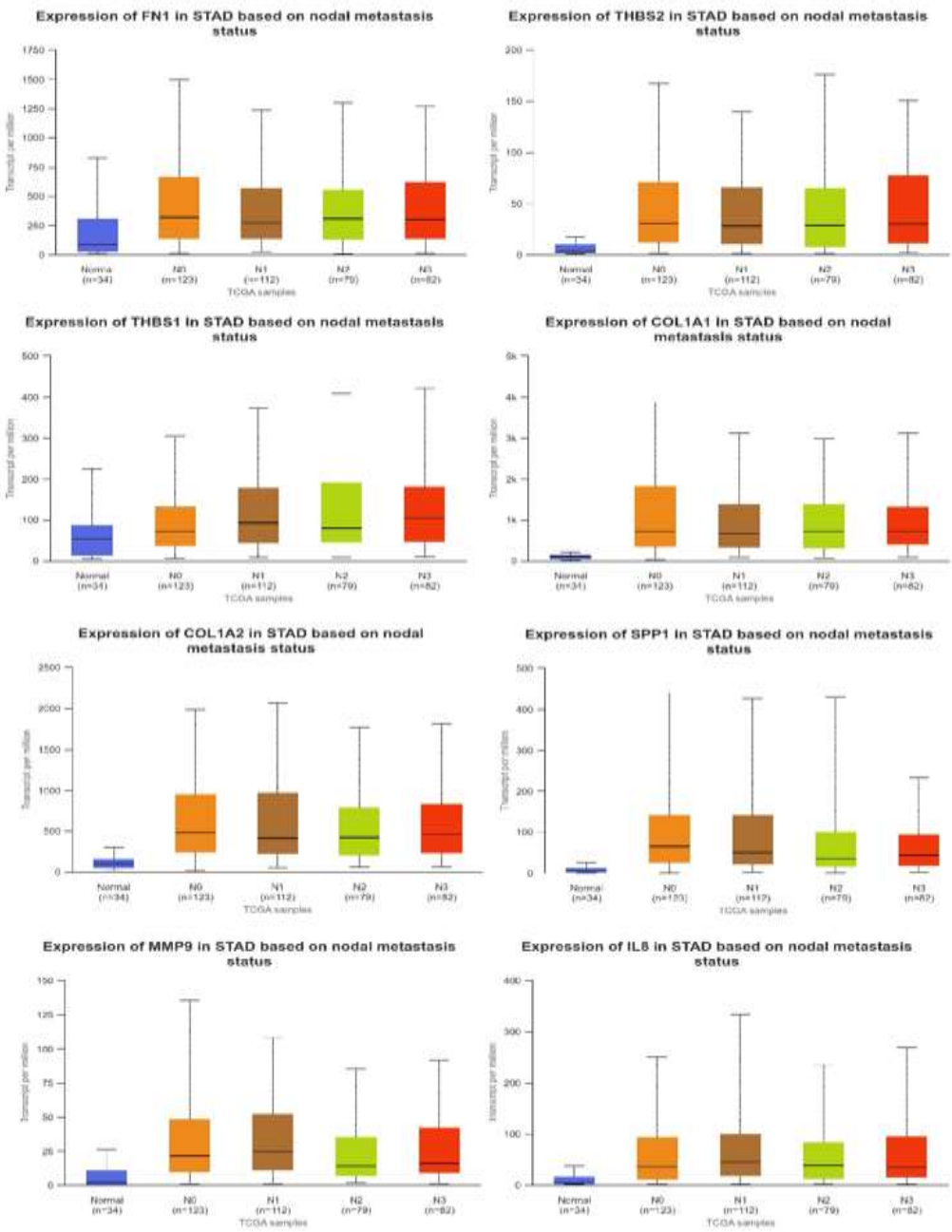


Figure 10- Expression of 8 hub genes in Stomach Adenocarcinoma (STAD) based on nodal metastasis status

DISCUSSION

This study offers an in-depth examination of metabolic pathways and molecular signatures in peripheral blood mononuclear cells (PBMCs) obtained from hospitalized gastric carcinoma (GC) patients. The results underscore notable metabolic alterations in PBMCs, potentially indicating systemic changes induced by tumors. The identification of differentially expressed genes (DEGs) in PBMCs highlights their potential as minimally invasive biomarkers for disease diagnosis, progression monitoring, and therapeutic targeting [8,22–24]. This study highlights a significant finding: the upregulation of genes that play crucial roles in the organization of the extracellular matrix, the response to oxidative stress, and the modulation of immune functions. The elevated levels of genes like FN1, MMP9, COL1A1, SPP1, and CXCL8 in PBMCs indicate a significant remodelling of the tumour microenvironment and systemic inflammatory responses in patients with gastric cancer. The results align with earlier research demonstrating that ECM components significantly contribute to tumour progression by aiding in the invasion, migration, and metastasis of cancer cells. Moreover, the deregulation of pathways associated with oxidative stress could lead to immune cell dysfunction and chronic inflammation, which may further intensify tumor progression. The KEGG pathway analysis indicated that significant dysregulated pathways in PBMCs encompass focal adhesion, ECM-receptor interaction, protein digestion and absorption, and xenobiotic metabolism. These pathways have been associated with multiple facets of cancer biology, such as cell adhesion, immune evasion, and reactions to environmental influences [25–27]. The enrichment of cytochrome P450-related pathways indicates a possible involvement of altered drug metabolism in GC patients, which could influence personalized therapeutic approaches. The survival analysis of hub genes revealed THBS1, FN1, and THBS2 as crucial prognostic markers, demonstrating significant correlations between their expression levels and patient outcomes. The prognostic significance of these genes corresponds with earlier studies highlighting their role in tumour progression, angiogenesis, and immune suppression [28,29]. Conversely, genes like MMP9, SPP1, and IL8 (CXCL8) showed no significant correlations with survival, indicating that their functions might be more influenced by the specific context of the tumour microenvironment. This study's findings expand on earlier investigations into the molecular features of PBMCs across different types of cancer. Previous investigations have shown that PBMC transcriptomic profiling can yield significant insights into systemic immune changes and metabolic adjustments in individuals with cancer [30,31]. A study conducted by [32,33]revealed notable metabolic changes in PBMCs from colorectal cancer patients, underscoring the potential of blood-based biomarkers for non-invasive cancer detection. In a similar vein, Wang et al. (2020) uncovered unique immune-related gene signatures in the PBMCs of lung cancer patients, highlighting the significance of immune-modulating pathways in the progression of tumours [34,35]. Furthermore, the involvement of metabolic reprogramming in gastric cancer has been thoroughly recorded, with cancer cells displaying increased glycolysis, changes in lipid metabolism, and responses to oxidative stress. Our findings support these observations by showing that metabolic changes in PBMCs reflect those happening within the tumour microenvironment. This systemic metabolic shift reinforces the idea that PBMCs may act as effective surrogates for tracking tumour-induced metabolic disturbances.

CONCLUSION

The present study provides a comprehensive look at the metabolic pathways and molecular fingerprints in peripheral blood mononuclear cells (PBMCs) from hospitalized gastric cancer (GC) patients. The results highlight substantial metabolic and molecular changes in PBMCs, indicating systemic modifications caused by the tumour microenvironment. The discovery of differentially expressed genes (DEGs) and hub genes, including FN1, MMP9, COL1A1, SPP1, CXCL8, COL1A2, THBS2, and THBS1, underscores their possible functions in extracellular matrix structure, oxidative stress response, and immunological regulation. These findings underscore the significance of PBMC profiling as a minimally intrusive method for detecting biomarkers linked to GC development. Gene ontology and KEGG pathway analysis identified dysregulated pathways, such as focal adhesion, ECM-receptor interaction, protein digestion and absorption, and xenobiotic metabolism, which are pivotal in tumour development, immune evasion, and drug metabolism. The survival study of hub genes further confirmed the predictive importance of THBS1, FN1, and THBS2, emphasizing their potential as biomarkers for patient classification and targeted treatment. This result corroborates other studies highlighting the significance of PBMCs in reflecting systemic immunological and metabolic alterations in cancer patients. The results bolster the accumulating data advocating for the use of blood-based biomarkers in non-invasive cancer diagnosis and prognosis. Subsequent research should investigate the functional roles of the discovered genes and pathways in gastric cancer development, focusing on confirming their

clinical applicability in broader patient populations. Furthermore, the use of multi-omics methodologies may enhance biomarker identification and therapeutic targeting, hence advancing early diagnosis and individualized therapy methods for gastric cancer.

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