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Identification of shared hub genes and pathways between gastric cancer and *Helicobacter pylori* infection through bioinformatics analysis

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ABSTRACT

Background: Gastric cancer (GC), the third leading cause of cancer-related deaths, has become a worldwide health issue. Gastric cancer is causally associated with *Helicobacter pylori* (*H. pylori*) infection. This study characterizes functional genes and critical biological pathways involved in GC and *H. pylori* infection simultaneously by using bioinformatics approaches.

Materials and methods: Microarray datasets of GC and *H. pylori* infection diseases were selected from the Gene Expression Omnibus (GEO) public database. So as to discover differentially expressed genes (DEGs), datasets from both diseases (GSE13911, GSE54129, and GSE60427) were examined separately using the GEO2R web tool. Shared DEGs among both conditions were utilized for downstream analyses. Afterward, protein-protein interaction (PPI) networks were generated through the STRING database and visualized via Cytoscape. The degree method was used to define the hub genes using Cytoscape's cytoHubba plug-in. Ultimately, interaction networks for the microRNA (miRNA)-hub genes and transcription factor (TF)-hub genes were evaluated, followed by an analysis of drug-hub gene interactions.

Results: In this current study, a total of 136 overlapped DEGs, including 101 up- and 35 downregulated genes, were screened between GC and *H. pylori* infection datasets. The PPI network obtained from the STRING database was subjected to analysis by the Cytoscape's cytoHubba plug-in, and 10 hub genes subsequently were determined using the degree method (which included TLR4, MMP9, ICAM1, CXCL10, CCL4, ITGB2, CXCL1, PTGS2, APOE, and CD80). Based on the obtained results, mir-146a-5p was found to have the highest association with the hub genes among the miRNAs, and RELA was recognized as a TF that regulates most of the hub genes among the TFs. Finally, 104 drugs were identified that might have therapeutic effects on both diseases.

Conclusions: This study provides a new perspective on the genetic association, and molecular pathways between GC and *H. pylori* infection could result in new treatment methods and diagnostic tests. Further experimental examinations are needed to validate critical genes and biological pathways discovered in this work.

1. Introduction

Gastric cancer (GC) is the fifth most prevalent cancer and the third most common cause of cancer-related death across the globe (Bray et al., 2018; Ferlay et al., 2019). Earlier studies have demonstrated strong and consistent associations between GC and obesity, alcohol consumption, processed food, and *Helicobacter pylori* (*H. pylori*) (Yusefi et al., 2018; Joshi and Badgwell, 2021). *H. pylori* is categorized as a group 1 carcinogen by the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC) (Møller et al., 1995). Correa et al. (1992) described that GC evolves in a cycle of histological occurrences. Normal mucosa turns into chronic gastritis, bringing about

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atrophic gastritis, intestinal metaplasia, dysplasia, and eventually gastric cancer (Correa, 1992; Fox and Wang, 2007; Polk and Peek, 2010).

Previous research explored the expression profile of GC and its adjacent tissue with the microarray technique, indicating modification in genes pertaining to the repair mechanisms, regulation of the cell cycle, DNA damage, inactivation of the tumor suppressor genes, and activation of oncogenes that are involved in carcinogenesis (*Cell Cycle, DNA Damage, Inactivation of the Tumor Suppressor Genes*, 2023). Moreover, another study depicted the link between Il-17, interleukin 10, Il-17, β-catenin, mucin 1, CDX1, SERPINE1, SMAD4, hypoxia-inducible factor 1 subunit alpha CDH17, RUNX3, GSK3β, matrix metalloproteinase 7, TFF1, HAI-2, RASSF1A and COX-2 genes with gastric carcinogenesis either that act as with inactivation of tumor suppressor genes or oncogenic activation (Rivas-Ortiz et al., 2017).

In a study conducted by Rivas-Ortiz et al. (2022), the gene expression in chronic atrophic gastritis and its relationship with progression to GC in people infected with *H. pylori* was evaluated using gene expression microarray analysis and validated by qPCR and immunohistochemistry. They found out that CLDN1 and MMP9 proteins could be applied as biomarkers in the early detection of this cancer (Rivas-Ortiz et al., 2022).

Recent advancements in sequencing technology have resulted in groundbreaking discoveries in computational biology. In addition, the bioinformatics approaches and microarray technologies have facilitated the identification of hub genes engaged in different diseases. (Yoo et al., 2009). Bioinformatics research has yielded convincing and reliable results in a multitude of studies. As a result, comprehensive bioinformatics analysis can help to comprehend the complicated molecular mechanisms that underlie the development of GC in people diagnosed with *H. pylori* infection.

A large number of published studies describe the link between GC and *H. pylori* infection; however, the genetic association between GC and *H. pylori* infection is not studied comprehensively.

The principal objective of this study was to investigate the correlation between GC and *H.pylori* infection using bioinformatics tools. To fulfill this aim, the vital genes engaged in the occurrence of both diseases, as well as miRNA and TF, were identified along with the drug targets.

2. Materials and methods

2.1. Data selection

In order to find datasets related to GC and *H. pylori* infection, the GEO database was searched. The NCBI-GEO database (https://www.ncbi.nlm.nih.gov/geo/) is a freely accessible collection of gene expression datasets (Barrett et al., 2012). GSE13911 and GSE54129 datasets containing individuals with GC and healthy controls, respectively, were selected from the GEO database. Also, the GSE60427 dataset, including individuals with *H. pylori* infection and healthy individuals, was chosen. Table 1 includes all of the information related to the microarray datasets.

Table 1
complete details of datasets.

Datasets	Platform	Disease	Affected	Control	sample
GSE13911	GLP570	Gastric cancer	38	31	Gastric tissue
GSE54129	GLP570	Gastric cancer	111	21	Gastric tissue
GSE60427	GPL17077	*Helicobacter pylori* infection	24	8	Gastric tissue

2.2. Screening of DEGs

GEO2R (https://www.ncbi.nlm.nih.gov/geo/geo2r/), a web-based online software, was utilized to screen DEGs for both illnesses, separately. DEGs are defined as genes that match the cutoff criteria (*P-value* lower than 0.05 and |log fold-change (logFC) higher than 1.0). Both diseases' screened DEGs (up and down-regulated genes) were subjected to Venn diagram analysis to determine shared genes between GC and *H. pylori* infection conditions. In the downstream analysis, common DEGs between both diseases were utilized.

2.3. Analysis of GO terms and pathways

The Enrichr online database (https://maayanlab.cloud/Enrichr/) was used to enrich the DEGs into the GO terms, including cellular components (CC), molecular functions (MF), and biological processes (BP) (Kuleshov et al., 2016). Moreover, the KEGG pathway enrichment analysis was performed using the Enrichr tool. This analysis allowed us to identify pathways that were significantly enriched among the DEGs. Additionally, the MSigDB pathway enrichment analysis was carried out to further complement our investigation into enriched biological pathways. This comprehensive approach helped us gain a more holistic understanding of the functional implications of the DEGs in the context of both KEGG and MSigDB pathways. A p-value <0.05 was regarded statistically significant for GO and KEGG enrichment analysis.

2.4. PPI network analysis and identification of hub genes

The STRING database (https://string-db.org), a repository of known and anticipated protein-protein interactions, was utilized to create the PPI network for DEGs with a confidence score ≥ 0.7 (Szklarczyk et al., 2021). Protein-protein interactions extracted from STRING were visualized through the Cytoscape software. Cytoscape is a powerful bioinformatics platform for visualizing biological networks and integrating data. Thereafter, hub genes were identified through the Cytohubba plug-in of Cytoscape. Based on the degree method, the top 10 hub genes were selected that have the highest degree of connectivity.

2.5. MiRNA-hub gene network construction

The miRNet online database (https://www.mirnet.ca/) was utilized to analyze the miRNAs of associated hub genes (Fan et al., 2016). Also, Cytoscape was used to visualize the miRNA-hub gene regulatory networks.

2.6. TF-hub gene network construction

The Networkanalyst software was used to examine the TFs of related hub genes (Zhou et al., 2019). Among the available databases in the Networkanalyst, the ChEA database was used to find the TFs related to the hub genes (Lachmann et al., 2010).

2.7. Investigation of drug-hub gene interaction

The Drug-Gene Interaction database (DGIdb) was used to predict drugs that target hub genes (Cotto et al., 2018). Medications with a DrugBank source that have been approved by the FDA were visualized via Cytoscape.

3. Results

3.1. DEGs identification

In this study, microarray datasets of GC and *H.pylori* infection were analyzed by using the GEO2R tool. In GC disease, GSE13911 and GSE54129 datasets were analyzed, yielding 2319 and 3042 DEGs,

respectively. On the other hand, in the case of the *H. pylori* infection dataset, GSE60427 was analyzed resulting in 1485 DEGs. Venn diagrams were used to identify overlapping genes across all microarray datasets. Overall, 136 overlapped DEGs, including 101 up- and 35 downregulated genes (Fig. 1), were found that are shared between both diseases. The list of shared genes among both diseases is inserted in supplementary file 1.

3.2. Analysis of GO terms and KEGG pathway

GO and KEGG pathway analysis of DEGs was evaluated by employing the Enrichr database. According to the results of GO analysis, in BP terms, inflammatory response (GO:0006954), neutrophil chemotaxis (GO:0030593), and granulocyte chemotaxis (GO:0071621) are the most enriched processes (Fig. 2). Based on CC terms, DEGs were mostly enriched in the tertiary granule (GO:0070820), collagen-containing extracellular matrix (GO:0062023), and the specific granule (GO:0042581) (Fig. 2). MF terms were primarily enriched in chemokine activity (GO:0008009), chemokine receptor binding (GO:0042379), and amyloid-beta binding (GO:0001540) (Fig. 2). Furthermore, the top 5 enriched KEGG pathways were associated with leishmaniasis, rheumatoid arthritis, *Staphylococcus aureus* infection, NF-κB signaling, and IL-17 signaling pathways (Fig. 3). In addition to the KEGG pathway analysis, the MSigDB pathway enrichment analysis was conducted, revealing the top five enriched MSigDB pathways as TNF-alpha Signaling via NF-kB, Inflammatory Response, KRAS Signaling Up, Interferon Gamma Response, and Complement (Fig. 3). The NF-κB signaling pathway serves as a shared pathway between both KEGG and MSigDB analyses.

3.3. PPI network analysis and identification of hub genes

In order to identify the hub genes, a PPI network of DEGs obtained from STRING (Fig. 4), containing nodes and edges, was imported into Cytohubba. The top 10 hub genes, including TLR4, MMP9, ICAM1, CXCL10, CCL4, ITGB2, CXCL1, PTGS2, APOE, and CD80, were identified.

3.4. MiRNA-hub gene network construction

The miRNet database was used to identify miRNAs targeting hub genes, and the interaction network between miRNA and the hub genes was visualized through the Cytoscape tool. Results revealed that hsa-mir-146a-5p interacted with 9 of the hub genes (Fig. 5), which could play an essential role in prognosis of GC and *H. pylori* infection.

3.5. TF-hub gene network construction

The TFs of target hub genes were identified using the ChEA database via Networkanalyst, and the TF-hub gene regulatory network was visualized by Cytoscape (Fig. 6). Results indicated that RELA regulates 9 of the hub genes and might have an essential role in developing GC and *H.pylori* infection.

3.6. Analysis of drug-hub gene interaction

Based on the obtained results, a total of 104 FDA-approved drugs were identified by DGIdb that could have therapeutic effects in both diseases (Fig. 7). Results revealed that the promising targets for the potential drugs include the PTGS2 (50.96%, 53/104), APOE (13.46%, 14/104), and ITGB2 (11.54%, 14/104) genes.

4. Discussion

In the past 50 years, one of the most significant advancements in our apperceiving of GC pathogenesis has been discovering that *H. pylori* is responsible for gastritis in most cases of GC (Moss, 2017). *H. pylori* induces epithelial cell degeneration and damage by causing an inflammatory response with plasma cells, lymphocytes, neutrophils, and macrophages within the mucosal layer. Infection is responsible for about 15% of all carcinogenesis. *H. pylori* is the most common cause of GC and the most common carcinogenic infectious agent (Crankshaw et al., 2020; Narayanan et al., 2018). GC is one of the most common types of cancer worldwide (Sistani Karampour et al., 2019). There are still some gaps in our understanding of the underlying mechanism, genetic association, and correlation between GC and *H. pylori* infection. So investigation of genes and pathways dysregulation involving gastric carcinogenesis is essential (Rawla and Barsouk, 2019; Marta et al., 2020).

In the present study, we identified 10 key genes using bioinformatics tools, including TLR4, MMP9, ICAM1, CXCL10, CCL4, ITGB2, CXCL1, PTGS2, APOE and CD80. Toll-like receptors (TLRs) are a family of pattern detection receptors that play a critical role in the innate immune response to pathogen-associated molecular patterns (PAMPs) as well as endogenous damage-associated molecular patterns (DAMPs) in afflicted host cells (Jin et al., 2021). TLR4's significance in lipopolysaccharide (LPS) detection, *H. pylori* infection, and gastric ulcer disease remain contentious, despite being researched more than other TLRs (Zargari et al., 2022; Nadatani et al., 2013). When LPS binds to the TLR4/CD14/MD2 complex, the TLR4 ectodomain becomes homodimerized. According to the animal model, a lack of TLR4 and receptor for advanced

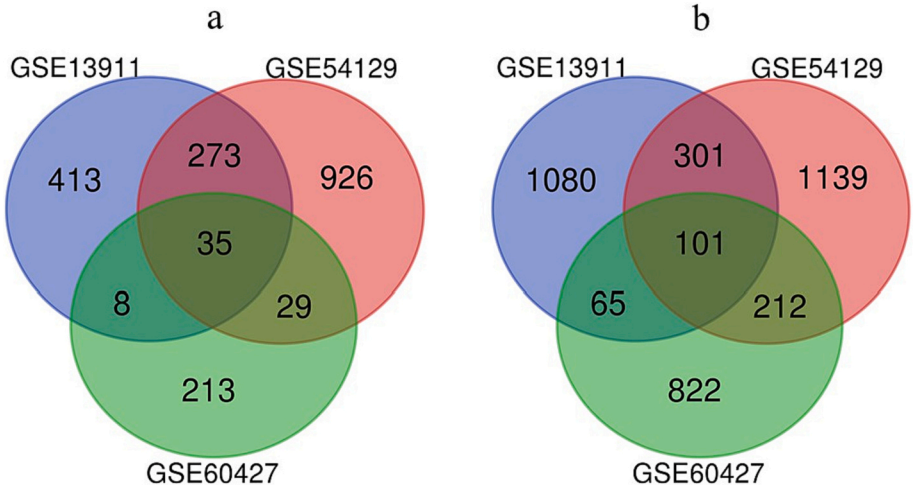

Fig. 1. Venn diagrams of DEGs from GSE13911 (GC-controls), GSE54129 (GC-controls), and GSE60427 (*H. pylori* infection-controls) microarray datasets. (a) The intersection of genes between down-regulated DEGs of datasets. (b) The intersection of genes between up-regulated DEGs of datasets.

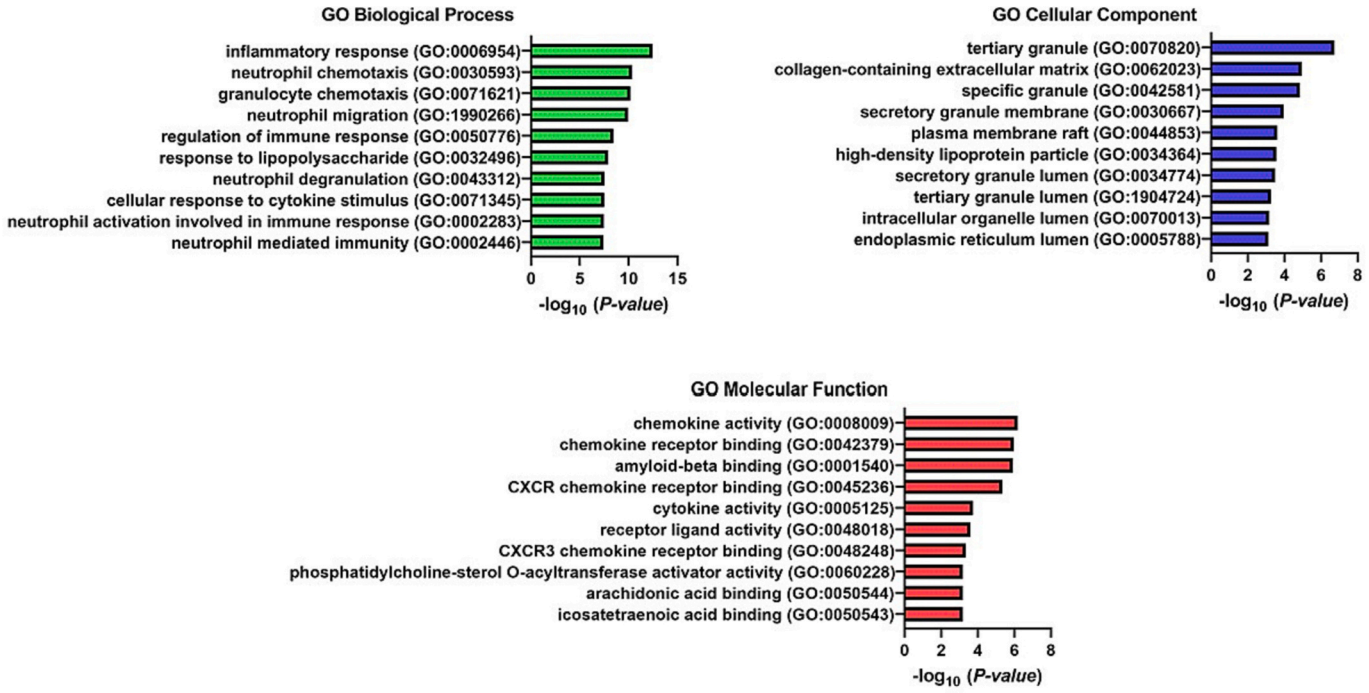

Fig. 2. The top 10 significant gene ontology terms of common DEGs.

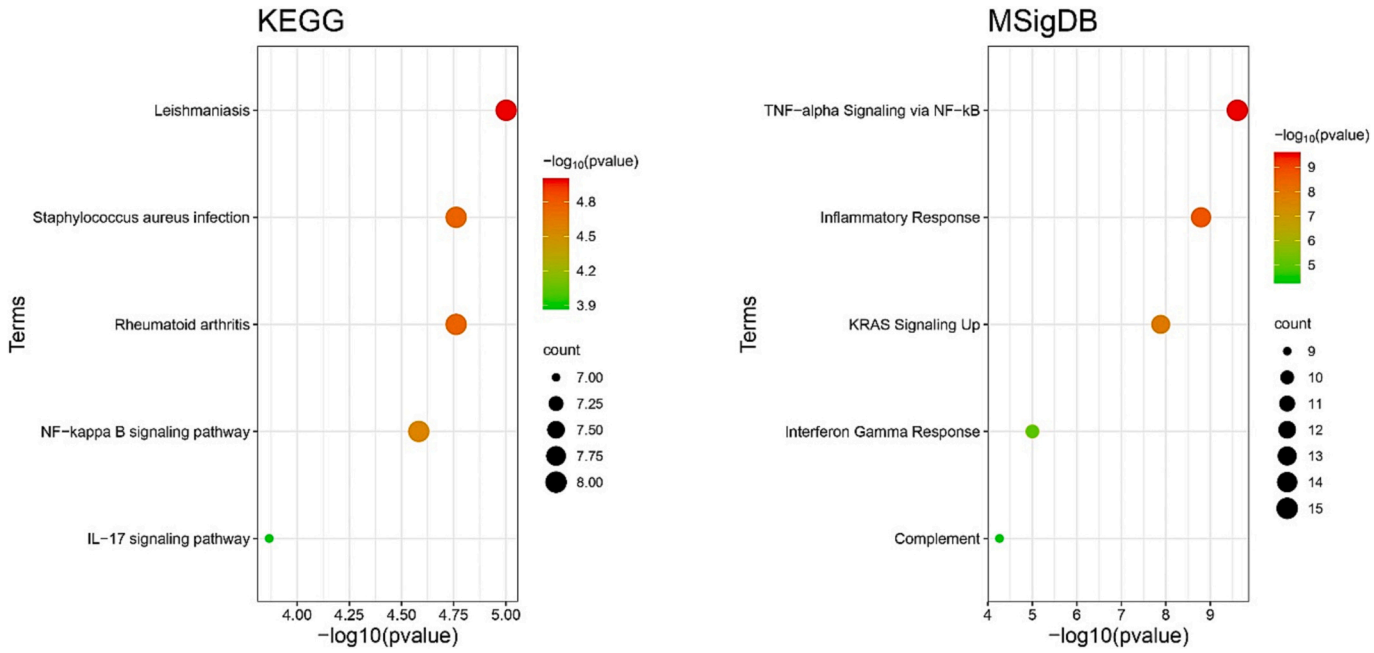

Fig. 3. The top five significant KEGG and MSigDB pathway **terms of common DEGs.**

glycation end-products (RAGE) may cause gastric ulcers while also controlling the rise in TNF-mRNA expression that occurs after ulceration. Studies have shown that TLR4 and its associated pro-inflammatory cytokines, as well as other inflammation-related molecules, could be implicated in the development and progression of GC (Zargari et al., 2022; Nadatani et al., 2013).

The family of matrix metalloproteinases (MMPs) is a group of zinc-dependent enzymes that degrade the extracellular matrix (ECM) and are involved in a variety of inflammatory disorders. As mentioned above, the zinc-dependent MMP-9 found in the extracellular milieu plays a major role in tumor microenvironment regulation (Prathipaa et al., 2021). The expression of MMP-9 is increased due to tumor-stromal interplay mediated by different cytokines and growth factors, leading to changes in proteolysis. One of the most important events in gastric carcinoma is the destruction of the epithelial cells' extracellular matrix-basement membrane, which serves as the first line of defense against tumor invasion, cancer advancement, and metastasis, resulting in cancer becoming more deadly (Li et al., 2013; Lempinen et al., 2000). There are 23 human MMPs, and two of them, MMP-2 and MMP-9, play a vital role in the invasion and angiogenesis of tumors. They do so by degrading type IV collagen of the basement membrane, which serves as the initial barrier in the invading process. MMP-9 is 25 times more effective than

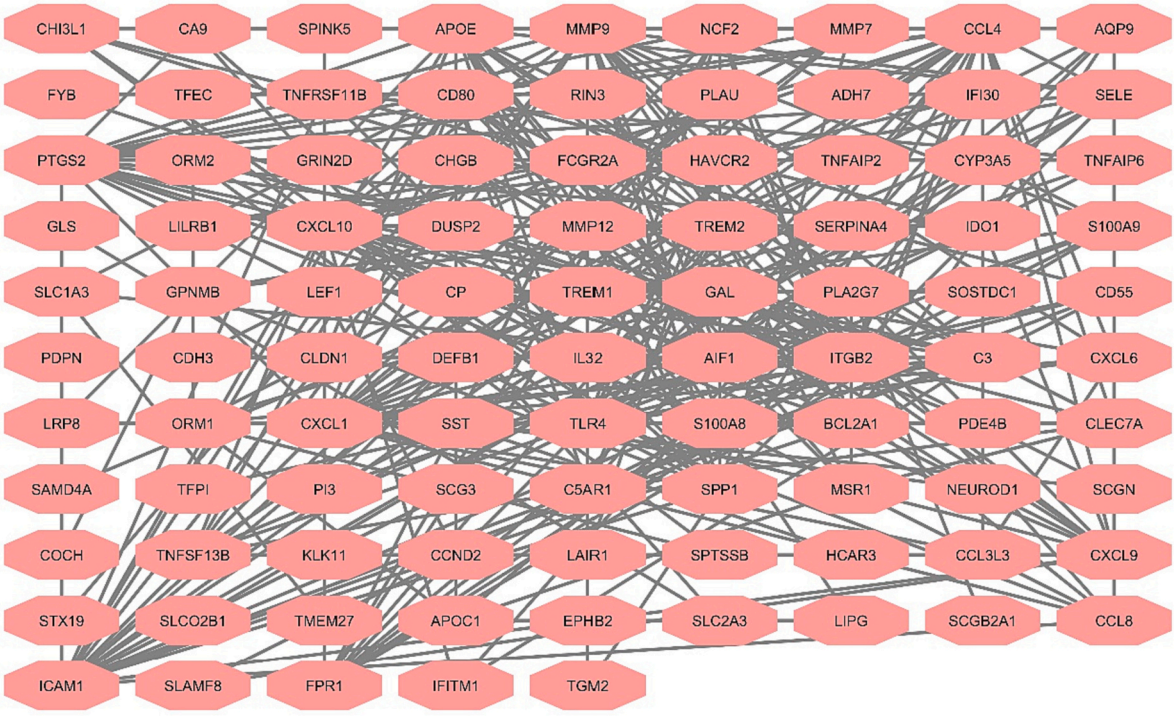

Fig. 4. The results of PPI network analysis of common DEGs.

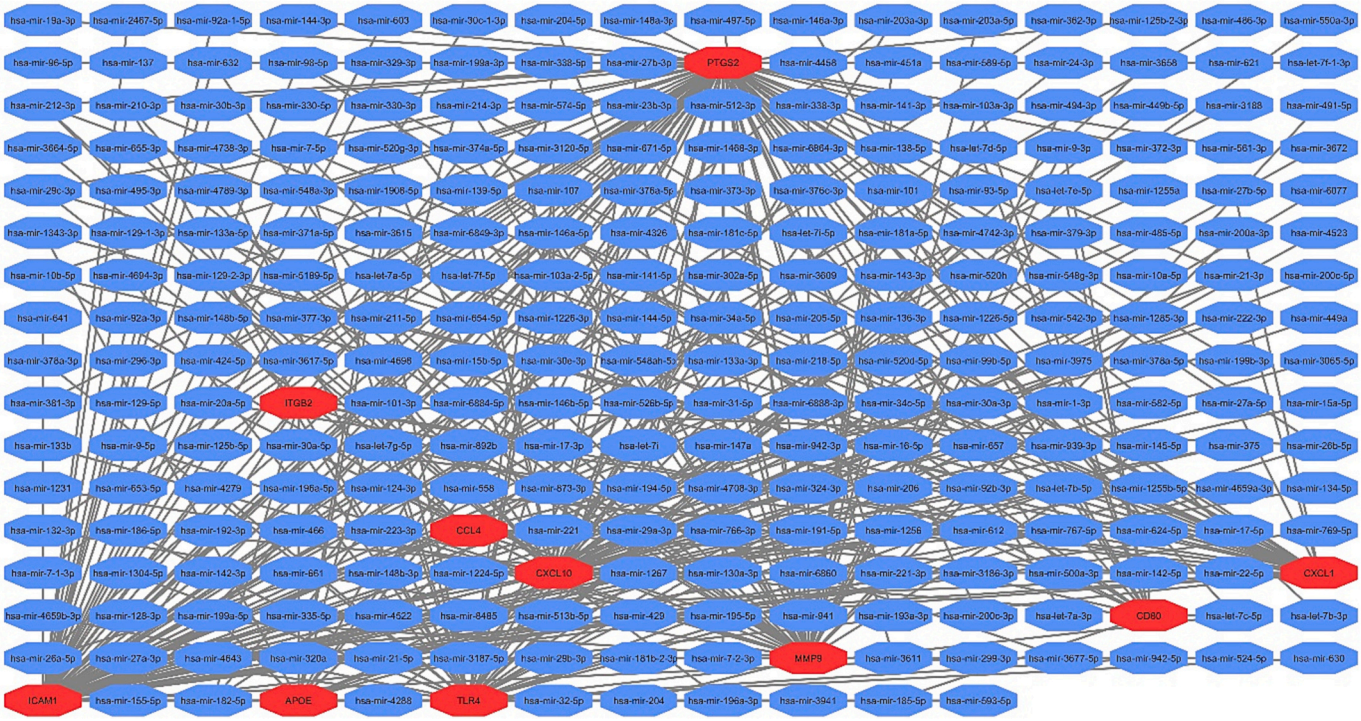

Fig. 5. The miRNA-hub genes regulatory network. The blue octagon represents miRNAs, and the red octagon represents hub genes.

MMP-2, and is involved in physiological situations, including embryogenesis, remodel of tissue, and healing of the wound, as well as pathological situations, including autoimmune disorders, inflammation, and diabetes. It also has a significant impact on the function of immunological cells (Ganguly and Swarnakar, 2012).

ICAM-1 is an immunoglobulin superfamily cell adhesion molecule that binds to the ligand of β2 integrin (LFA-1 and Mac-1). Expression of ICAM-I has been observed in leukocytes, epithelial and endothelial cells, fibroblasts, keratinocytes, and antigen-presenting cells, including Langerhans cells. ICAM-1 expression in gastric ulcers following *H. pylori* infection may be enhanced via incitement of local mucosal inflammation and inflammatory cytokines (Lian et al., 2020; Velikova et al., 1997). The finding demonstrated that all metastatic carcinoma cells expressed significant levels of ICAM-1 compared to the normal gastric

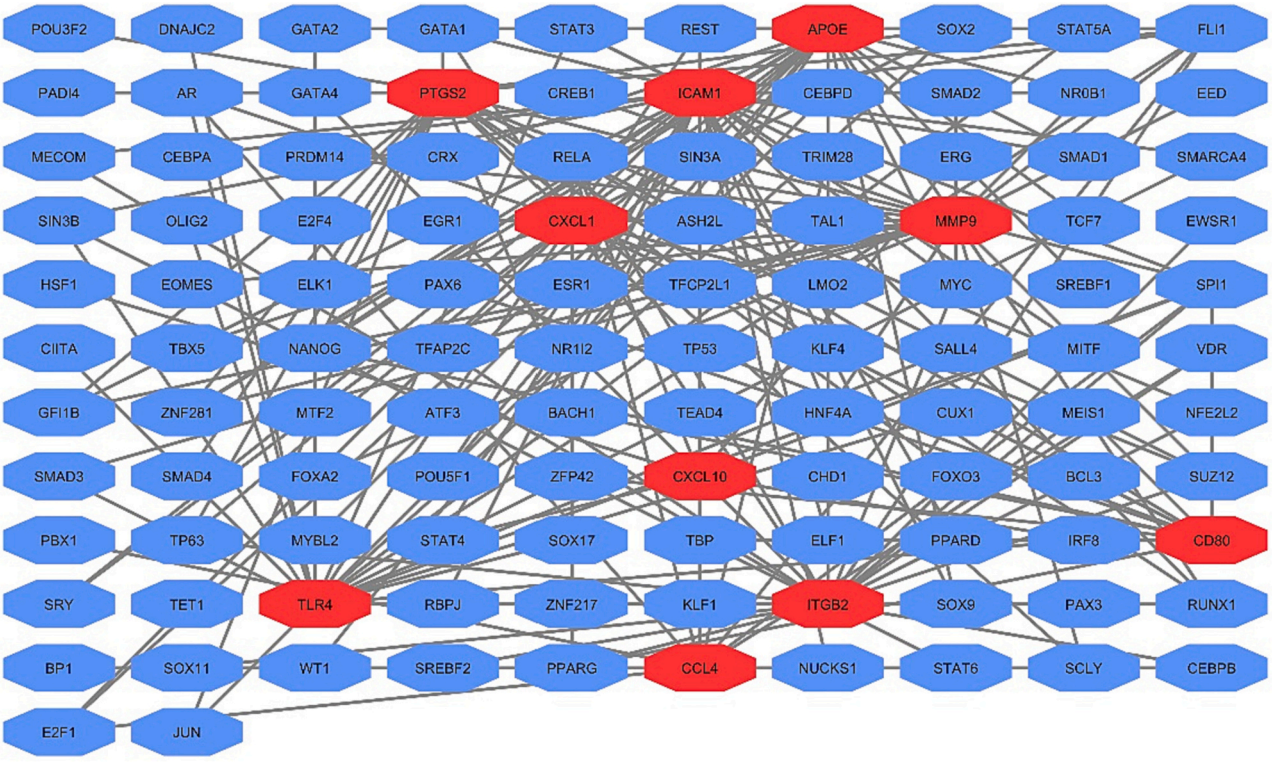

Fig. 6. The TF-hub genes regulatory network. The blue octagon represents T.F.s, and the red octagon represents hub genes.

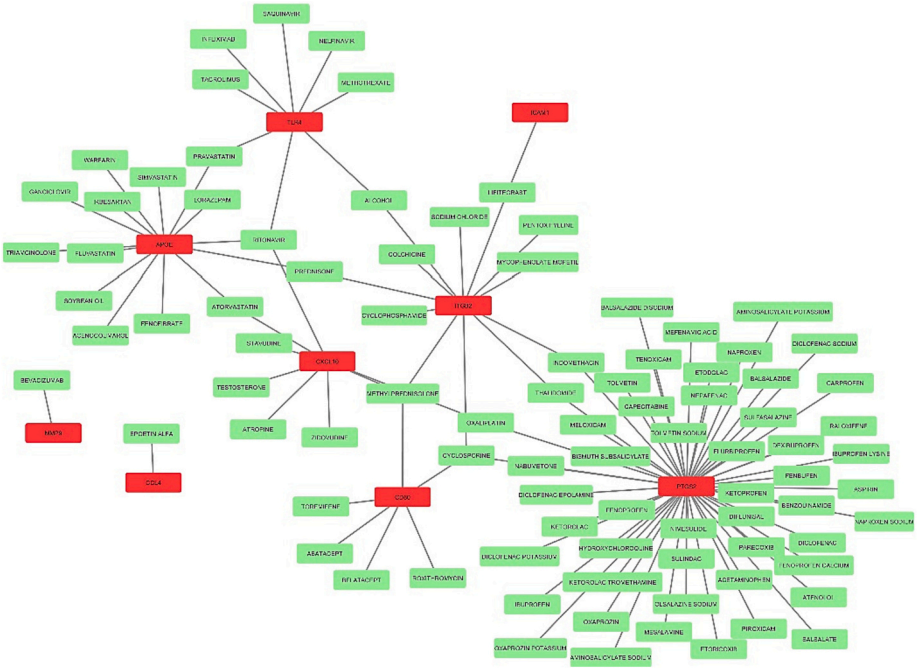

Fig. 7. The drug-hub genes interaction network. The green rectangle represents hub genes, and the red represents drugs targeting hub genes.

mucosa. Also, other research showed that ICAM-1 serum concentrations are considerably higher in GC patients than in healthy controls (Lian et al., 2020; Velikova et al., 1997).

CXCL10 is a member of the C-X-C motif chemokine family. An essential function of a chemokine is its vital role in certain immune cells' migration to the place of inflammation or infection, thereby impacting how the body responds to infection and inflammation outcomes. Chronic inflammation has been associated with an enhanced risk of cancer development. Chemokines are the main chemicals that attract leukocytes to local inflammatory regions. Chemokine receptors have been proven to have a significant role in developing GC. As a result, overexpression of CXCL10 and its receptor, CXCR3, may have a role in *H. pylori associated* GC development (Jalalpour et al., 2021).

The CCL family of chemokines has been reported to have a significant function in the pathogenesis of GC. CCL4 is a beta-chemokine that has been reported to be overexpressed in GCs of the diffuse type.

According to research conducted by Baj-Krzyworzeka et al. (2016), substantial variations in plasma CCL2, CCL4, and CCL5 levels have been observed in GC patients and healthy controls (Baj-Krzyworzeka et al., 2016). It has been shown that higher levels of these chemokines stimulate GC cell migration and invasiveness (Pawluczuk et al., 2020; Rajkumar et al., 2010).

In this study, hsa-mir-146a-5p interacted with 9 hub genes. MicroRNAs, such as miR146a-5p regulate gene expression by binding to the 3'UTR section of the genes. Research has shown an association between mir-146a-5p and gastric, pancreatic, breast, lung, and esophageal squamous cancers. In the aforementioned cancers, up- and down-regulation of miRNA-146a have been reported. Multiple studies have reported the relation of miR-146a-5p to cancer risk, invasiveness, and metastatic potential in various cancers. For example, according to the results, the expression of hsa-mir-146a-5p was downregulated in gastric cancers, and the low hsa-mir-146a-5p expression group showed greater venous invasion than the high-expression group (Min et al., 2017).

Furthermore, miR-146a-5p has been shown to target Smad4 and TNF receptor-associated factor 6 (TRAF6), which are critical TGF-β pathway mediators. A broad range of cellular processes is regulated by TGF-β, including cell growth, differentiation, migration, apoptosis, and the creation of an extracellular matrix. This cytokine inhibits the growth of epithelial cells and is, therefore, a potent anti-tumor cytokine. Numerous studies have reported that miR-146a-5p is a carcinostatic miRNA in breast, prostate, pancreatic, and gastric cancers. As a result, miR-146a-5p has a significant role in various cancers (Sokolova and Naumann, 2017; Li et al., 2014).

In our study, RELA regulates 9 of the hub genes. The NF-κB family consists of five members in mammals: NF-κB1 p50, NF-κB2 p52, c-Rel, RELA, and RELB. These proteins form various dimeric complexes that transactivate many genes by binding to the κB enhancer. They control a wide variety of biological processes, such as inflammation and cancer, as dimeric transcription factors. Tumor advancement, cell proliferation, and apoptosis may be affected differently by NF-κB activation in different species and cell types (Sasaki et al., 2001).

In our study, the NF-κB signaling pathway emerges as a common pathway shared between the KEGG and MSigDB analyses. This pathway is recognized for its pivotal role in inflammation, immunity, and cell survival. The NF-κB pathway's activation by *H. pylori* and its connection to inflammation align with the chronic inflammatory environment associated with GC development. NF-κB has a critical role in promoting cytokine expression and GC development; also, activation of NF-κB is associated with chronic inflammation and tumorigenesis caused by *H. pylori* in GC (Sasaki et al., 2001; Oeckinghaus and Ghosh, 2009; Huang et al., 2016). Recent research shows that NF-κB is constitutively active in cancers, including pancreatic and breast cancer. The NF-κB signaling pathway is involved in gastric tumorigenesis. The role of the RELA protein (a NF-κB pathway component), mainly its expression and function in GC, is yet not well characterized (Sasaki et al., 2001; Oeckinghaus and Ghosh, 2009; Huang et al., 2016).

5. Conclusion

Our findings from this study increase our understanding of the underlying causes of GC incidence, which can ultimately help us identify effective GC malignancy biomarkers and particular treatment approaches according to key regulatory pathways. In total, we identified 10 upregulated common genes (such as TLR4, MMP9, ICAM1, CXCL10, and CCL4) in *H. pylori* infection and GC and their associated miRNAs and TFs, including hsa-mir-146a-5p and RELA. Further investigation of these factors and inflammatory pathways, including NF-κB and their regulatory factors, could help treat *H. pylori infection* and prevent GC development.

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Not Applicable for this study.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

Credit author statements

Reza Maddah conceived the study, performed the analysis, and contributed to the design of the methodology. He also supervised the manuscript's final revision.

Zahra Molavi and Hadi Mohammed Ehymayed were responsible for the writing and manuscript editing, ensuring the clarity and coherence of the text.

Farzaneh Miri4 played a crucial role in manuscript editing and supervised the final revision of the manuscript to maintain its quality.

Parvin Shariati contributed to both writing and editing, enhancing the overall readability and accuracy of the manuscript.

Maziyar Veisi conducted the statistical analysis of the data, providing valuable insights into the research findings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

Not Applicable for this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humgen.2023.201237.

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