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Network analysis of H. pylori effect on AGS human gastric adenocarcinoma cells gene expression profile

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ABSTRACT

Aim: To better understand the molecular mechanism of Helicobacter pylori (H. pylori) in adenocarcinoma, the gene expression profile of AGS cells was analyzed by complementary study.

Background: Gastric cancer, as one of the most lethal malignancies in the world, is important to be studied in terms of biomarkers. On the other hand, Helicobacter pylori is one of the key risk factors in this type of disease.

Methods: In this cross-sectional study, we evaluated the seroprevalence of total and IgM anti-HAV antibodies of 254 institutionalized people with intellectual disabilities. Total and IgM anti-HAV antibodies of the blood samples of these people were determined by ELISA method. Protein-protein interaction (PPI) network analysis is a bioinformatic study with validation values for biomarker identification and clarification of molecular mechanisms. Cytoscape V 3.10.2 and its application identified potential central elements of the PPI network and its corresponding roles.

Results: GAPDH and P53 are the most promising candidates in this study. In addition, the microRNA signatures assessment provided more information about these biomarkers and added more value.

Conclusion: Consequently, a new outlook for the relationship between gastric cancer and H. pylori was explored based on the new key biomarkers.

Keywords: Helicobacter pylori, Human gastric adenocarcinoma, Gene expression, Biomarker, Network analysis.

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Introduction

Helicobacter pylori is a cause of many gastric diseases, including peptic ulcer (1), chronic gastritis, and gastric cancer (GC) (2). An infection with this gram-negative bacterium is a prevalent stomach disease worldwide (3, 4). As mentioned, one of the diseases is gastric cancer, and gastric adenocarcinoma H. pylori plays a role in its pathogenicity and shows a strong relationship; however, not many patients get cancer. Gastric cancer is

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known as the major cause of cancer death in the world and is rated for high prevalence in Eastern Asia (5, 6). The number of young patients with gastric cancer has increased in recent years (5). Treatment approaches for gastric cancer include endoscopy, chemotherapy, and surgery, which are the standards (7). Early detection, eradication of H. pylori, quitting smoking, and consumption of alcohol could be beneficial for decreasing the probability of getting cancer (5, 6). The effort to reduce the prevalence of H. pylori should be considered as it is an essential factor in gastric cancer development (8). The risk of carcinogenesis varies depending on the strain of the bacteria and host response and interactions (3).

The previous studies highlighted the complexity of interaction between the host and bacteria (9). Adenocarcinoma classification depends on different factors, including the tumor's location and the lesion's shape (9). Therefore, as Adenocarcinomas are the most common type of gastric cancer, it has been chosen for more evaluation in terms of complementary study. Gene expression profiles of AGS Cells uninfected and infected with H. pylori were compared to evaluate the differential regulation profile. The physical interaction analysis can assist in finding the fundamental genes in terms of the network structure's stability by applying centrality analysis. These key genes are vital for determining the molecular mechanism of the related gene profile in the state of health condition (10). By the application of these findings, early detection and therapeutic approaches facilities. In this view, it is valuable to better understand the nature of H. pylori's effects on gene expression profiles to reveal information related to the underlying mechanism of this association and ultimately for clinical goals. This study aims to decipher the underlying mechanism of H. pylori carcinogenesis by studying AGS gene expression changes.

Methods

Data collection

Differentially expressed genes (DEGs) from the microarray study were derived from a series of GSE264263 using the platform GPL6244 in the GEO database (https://www.ncbi.nlm.nih.gov/geo/). This study was “Expression data from AGS cells with Helicobacter pylori infection”. It should be mentioned that there is another gene series about the relationship between H. pylori and gastric cancer in different conditions. Here, GSE264263 is selected to avoid possible mistakes due to variable conditions.

Pre-evaluation analysis

GEO2R was applied as an online analyzer, available in GEO, for this purpose. A comparison of DEGs in uninfected and infected samples of n=3 for each was conducted, and statistically significant genes were identified for further analysis. For data visualization, different sets of plots, including the volcano, Uniform Manifold Approximation and Projection (UMAP), and Moderated t Statistics, are provided in this study.

PPI network analysis

Genes with significant differences were then chosen based on adjusted p-value < 0.05 and fold change > 2. In the network analysis, the role of these significant genes and the potential contribution of neighbor genes could be considered. Cytoscape version 3.10.2 detected these genes' interaction network using the STRING database (https://string-db.org/). The protein query extracts data by considering a confidence score off= 0.5. The network was further analyzed for centrality features, and two popular parameters were chosen. Degree and betweenness centrality were the important keys for the network topological analysis. Nodes with high values of these two elements are called hub bottlenecks. For this network, hub-bottlenecks, non-hub-bottlenecks, and hub-non-bottlenecks (11) were measured. In a way,10% of the queried DEGs with the highest values of degree and betweenness centrality can be identified as hubs and bottlenecks, respectively (12). In the next step, by application of AutoAnnotate Plug-in (13), the network can undergo further analysis in terms of clustering measurements. To interpret more information from our network, the miRDB Tool (https://mirdb.org/cgi-bin/mining.cgi) was applied to annotate target miRNAs.

Results

Infected and uninfected cells with helicobacter pylori were compared regarding gene expression profile with the GEO2R analyzer. The data obtained from GEO2R was visualized using different data visualization methods, including Boxplot, Venn diagram, UMAP, moderated t statistic, and Volcano plot obtained from the GEO Database. Box plot visualization can help determine whether the samples are comparable in terms of differential expressions (see Figure 1). As sample

groups are comparable when median-centered, this analysis can confirm that they follow this rule.

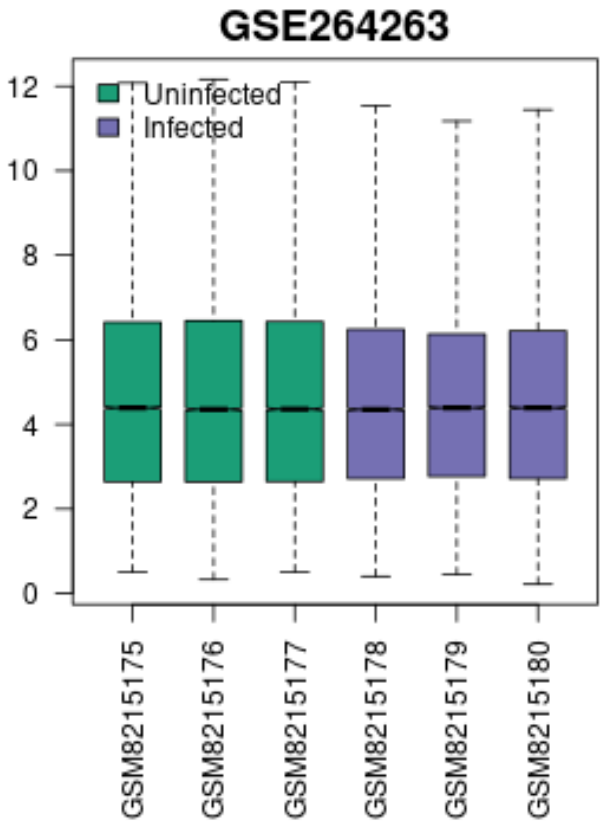

Figure 1. Boxplot view of sample values distribution. Each group is colored differently.

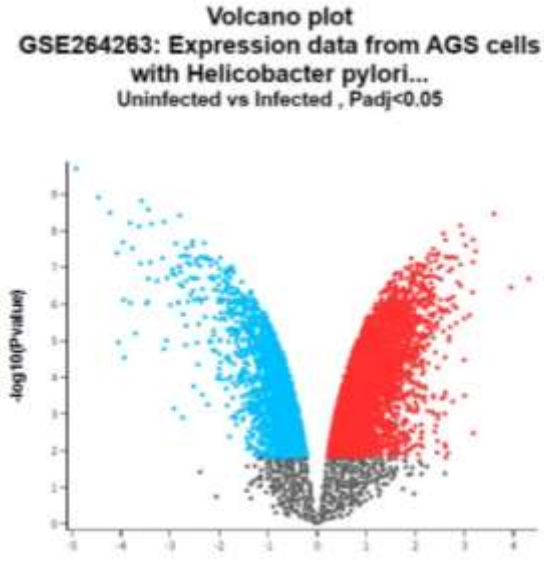

Figure 2. In this volcano plot, the Y axis shows (-log10 P value) while the X axis indicates (log2 fold change). Differential expressions of genes are shown here as blue and red dots.

In groups of samples, overlap between groups in terms of significant DEGs can be visualized by Venn Diagram (See supplementary Figure S1).

UMAP is used for visualization of sample relationships or, in other words, dimension reduction. Grouping of samples before the study is not required (See supplementary Figure S2). As depicted in Figure S2, each sample is compared with three neighbors to find similarities between them. The samples are divided into two groups of cells, including infected and uninfected individuals.

Assessing the quality of limma test results, alignment of points with the straight line could indicate the correct prediction (See supplementary Figure S3)

The volcano plot showed many significant DEGs (see Figure 2). The expressed genes are marked with different colors indicating expressional differentiation at a significant level. Upregulation is shown with red dots, while down-regulation is with blue dots.

The GEO2R data analysis identified 250 IDs that were then searched against Cytoscape via STRING Plug-in. Among 250 IDs for significant DEGs, there were repeated genes with individual IDs; therefore, only 212 genes resulted in this query. In the first network query, 212 genes with 225 connections with a confidence score cut off= 0.5 were determined. By adding 50 neighbor genes, several 262 genes and 1696 links were obtained. The next step was to analyze network centrality regarding degree and betweenness parameters. The second network was used for this purpose. This network then underwent further processing, extracting a subnetwork of 197 nodes and 1693 connections. The distribution of centrality parameters (degree and betweenness centrality) is analyzed and viewed in Figure 3. Color tone increases with relation to degree value increment in the scatter plot. In other words, the higher the degree value, the node is darker. As depicted in Figure 3, there are limited genes with higher values of the described centrality parameters. These genes can be considered as the central genes of the PPI network.

In the Table 1, GAPDH, RPS27A, TP53, POLR1B, and ACTB are Hub-Bottlenecks whereas RPS9, RPS2, RPS6, and PDCD11 are hub-non-bottlenecks. GAPDH has the highest degree and betweenness centrality value and represents the most potential hub-bottleneck of the network.

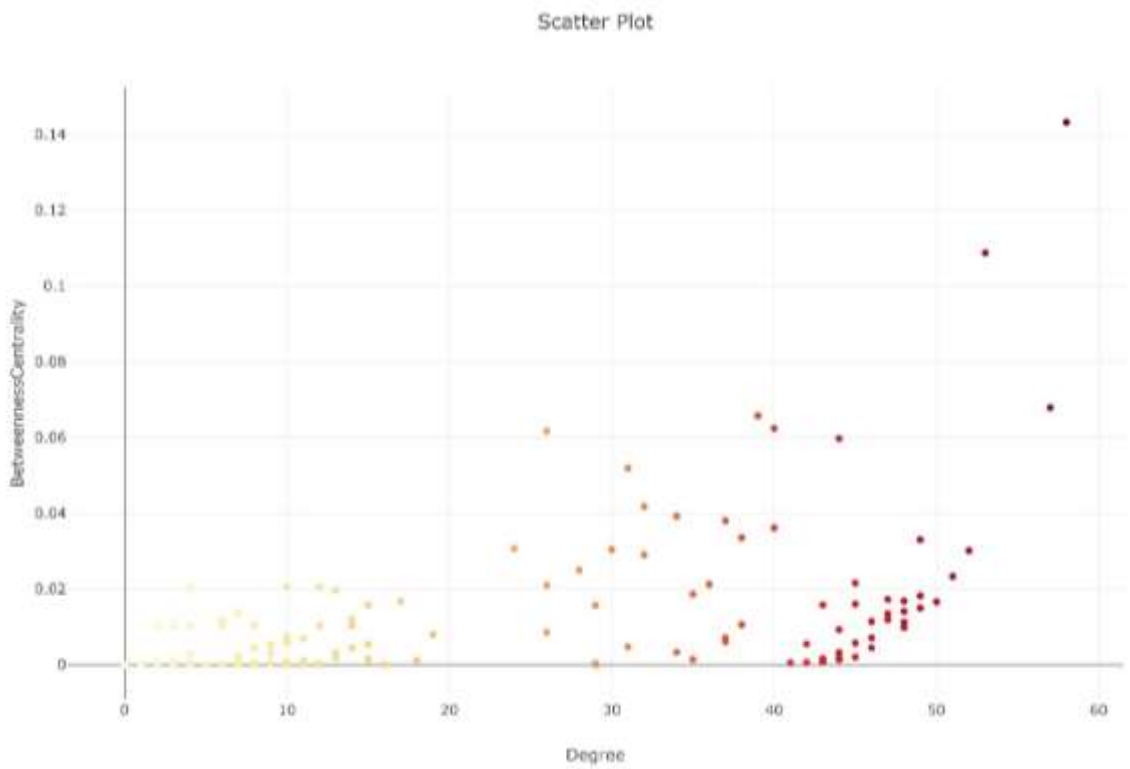

Figure 3. In the distribution of degree versus betweenness centrality, nodes are differentiated based on color changes, and the x-axis is degree while the y-axis is betweenness centrality.

Table 1. List of top hub-bottlenecks and hub-non-bottlenecks of the AGS network. Genes with stars are the DEGs.

Row	Degree	Display name	Normalized betweenness centrality
1	58	GAPDH	1.00
2	57	RPS27A	0.42
3	53	TP53*	0.67
4	52	RPS6	0.08
5	51	RPS9	0.00
6	50	RPS2*	0.00
7	49	PDCD11	0.08
9	48	POLR1B	0.42
10	44	ACTB	0.33

The network in Figure 4, is derived from the second network with consideration of clustering based on the description of sets of genes. These descriptions involve RNA polymerase ribosomal, cell eco, cholesterol coa fatty, ubiquitin linked lys, max recognizes ahr, rejecting amino trna, chloride enac, monophosphate dctp triphosphates, valyl tRNA seryl, and dendric immature c1q. As depicted in Table 1 and Figure 4, ribosome is a critical targeted organelle by H. pylori. miRNA annotation with miRDB for the key genes introduced some microRNAs. Several 57 targeting microRNAs were identified.

Discussion

The underlying mechanism and effects of H. pylori on gastric cancer have not yet been fully understood. In this regard, previous studies suggested that viral factors, cytotoxin-associated gene A (CagA), and abnormal DNA methylation have to do with gastric cancer risk (14). The process by which Cag A introduces its pathogenicity is by activation of NLRP3 inflammasome (15). In addition, based on other studies, H. pylori can dysregulate apoptosis in gastric cells (16). The association between gastric cancer and infection with helicobacter pylori as a spiral-shaped bacteria was

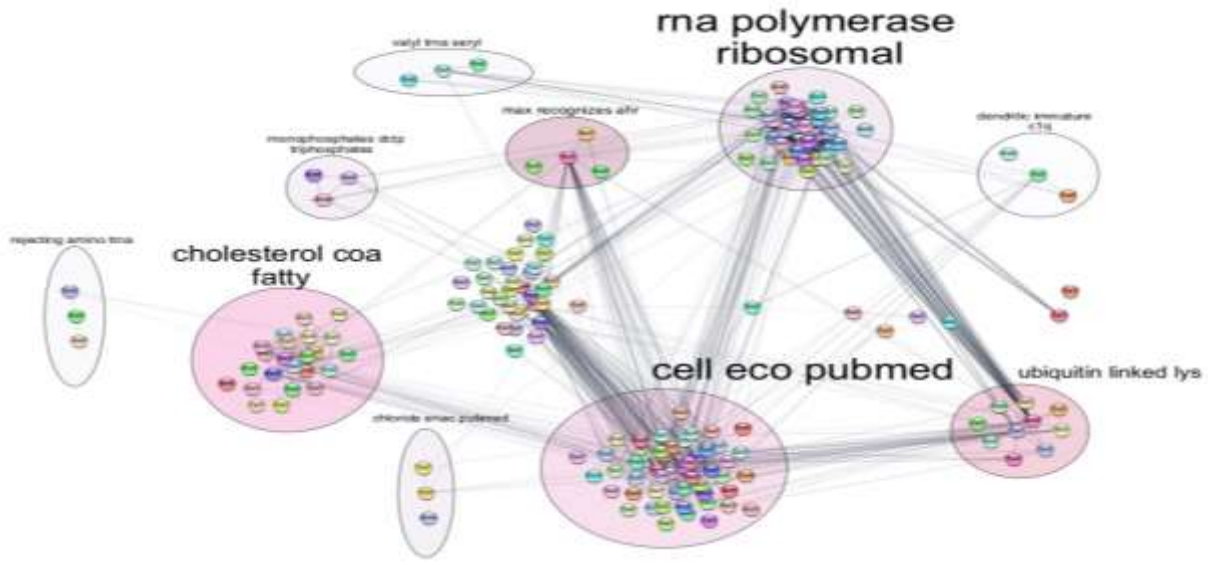

Figure 4. Graphical representation of subnetwork clustering annotated with gene description. "Cell eco PubMed" and "RNA polymerase ribosomal" appeared as the critical clusters related to the studied genes.

studied by expression profiling by the array in the main study. In a way, samples of AGS cells with and without Helicobacter pylori (H. pylori) infection were compared by microarray. Comparison of sample groups handled by data visualization analysis implies that samples are comparable in terms of expressional profile.

In the original study and a proteomics approach of gastric cancer with H. pylori, the interest genes were highly overexpressed by the verification methods (14). Differentially expressed genes were then considered for protein-protein interaction network analysis by Cytoscape. The PPI network analysis indicated that this network is scale-free and central nodes are present, so more evaluation is worthy of our biomarker study. Centrality analysis suggested that several 10 genes that were characterized with distinct degree values from others could be potential key genes, namely hub-bottlenecks and hub-non-bottlenecks. These genes include GAPDH, RPS27A, TP53, RPS6, RPS9, RPS2, PDCD11, POLR1B, and ACTB. Among these identified genes, TP53 and RPS2 are from the queried DEGs. The role of these genes in gastric cancer can be better understood by literature surveys.

The first gene is GAPDH, glyceraldehyde-3-phosphate dehydrogenase, which is known as a housekeeping gene and is popular in tumorigenesis. Many cancers, including gastric cancer, have been reported for dysregulation of this gene. Overexpression of GAPDH in most cancers has been identified (17). It is important in cellular metabolism as a catalyst in the glycolysis process. Other processes that GAPDH participates in include RNA transport, DNA replication, cytoskeleton organization, and more (17). The next gene is ribosomal protein S27a (RPS27A). Its linkage with gastric cancer is not yet recognized; other cancers of cervical and lung adenocarcinoma demonstrated associations (18, 19). The next one is the p53 tumor suppressor, also determined by proteomics study (14). H. pylori is revealed to play a role in degrading p53 as a tumor suppressor by a series of processes (20). It is also downregulated in infected AGS cells with the bacteria in the main microarray study. Tumorigenesis of ribosomal protein S6 (RPS6) is the next gene its dysregulation has been referred for gastric cancer in other studies (21). Tumorigenesis of Ribosomal protein S9 (RPS9), Ribosomal protein S2 (RPS2), programmed cell death 11 (PDCD11), and RNA polymerase I subunit B (POLR1B) as the next central genes did not provide any correlation with gastric cancer based on previous studies. The last gene is beta (β)-actin (ACTB), and its correlation with gastric cancer has been proven. Its structural instability in this type of cancer is determined (22). Overall, GAPDH and P53 were the only genes previously identified as target genes of H. pylori in gastric cancer pathogenicity. RPS6 was also recognized as a gastric

cancer-related gene while not any evidence of the bacteria effects on this gene yet. There was no report of RPS2 role in gastric cancer development before while in the original study this gene was identified as a dysregulated gene.

The description clustering analysis shows that most network genes are involved in these three categories: RNA polymerase ribosomal, cell eco, and cholesterol coa fatty. Furthermore, microRNA targets central genes and identifies elements corresponding to these sets. Target microRNAs were assessed as a validation test to better understand the role of the most promising central genes, which are GAPDH and p53, which are also confirmed as correlative markers with H. pylori in gastric cancer based on previous studies and network analysis. MicroRNAs have a fundamental role in tumor development (23). On the other hand, the bacteria and host relationship can be regulated by microRNA changes (24). Thus, microRNAs of these two genes are selected for more evaluations and possible background in H. pylori-positive gastric cancer. For the GAPDH: hsa-miR-942-3p and hsa-miR-3175 and for p53: hsa-miR-491-5p, hsa-miR-223-3p, hsa-miR-622, hsa-miR-504-5p, hsa-miR-4677-3p, hsa-miR-330-3p, hsa-miR-374a-3p, hsa-miR-1285-3p, hsa-miR-1972, hsa-let-7f-5p, hsa-let-7e-5p, hsa-miR-98-5p, hsa-let-7c-5p, hsa-miR-421, hsa-let-7i-5p, hsa-miR-320e, hsa-let-7a-5p, hsa-let-7b-5p, hsa-miR-608, and hsa-let-7g-5p are the related microRNAs. The first GAPDH microRNA, hsa-miR-942-3p, is a gastric cancer prognostic biomarker that regulates GAPDH by influencing MAPK/ERK signaling (23). hsa-miR-3175 is another important element; its down-regulation is reported in gastric cancer (25). For p53, hsa-miR-491-5p is related to resistance against Cisplatin in gastric cancer (26). H. pylori increases the level of hsa-miR-223-3p in gastric cancer; moreover, it is known as a diagnostic biomarker of gastric cancer (27, 28). hsa-miR-622, as a tumor advancing in gastric cancer, can be related to inflammatory response initiated by H. Pylori infection (24). hsa-miR-504-5p, the next microRNA, is also essential in gastric cancer based on previous genomic studies (29), while hsa-miR-4677-3p, hsa-miR-374a-3p ,hsa-miR-330-3p,hsa-miR-374a-3p, hsa-miR-1285-3p, hsa-miR-1972, hsa-let-7f-5, hsa-let-7e-5p, hsa-let-7i-5p, hsa-miR-320e, and hsa-let-7g-5p have not yet determined as a correlating element in gastric cancer. The other microRNA, hsa-miR-98-5p by regulating other genes, shows anticancer properties in gastric cancer (30). hsa-let-7c-5p is also another reported microRNA in gastric cancer (31). One of the promising biomarkers for gastric cancer is hsa-miR-421 which indicates diagnostic values (28), its up-regulation has been identified in gastric cancer (32). The next one, hsa-let-7b-5p which has high prognostic value in gastric cancer (33). The next one is a cancer inhibitor, hsa-miR-608, through MAPK signaling activation (34). Finally, as depicted in Table 1, GAPDH, TP53, RPS27A, and POLR1B, and ACTB where appeared as the potent hub bottlenecks.

Conclusion

It can be concluded that H. pylori targets many genes in AGS human gastric adenocarcinoma cells, including crucial individuals like GAPDH, TP53, RPS27A, POLR1B, and ACTB. The studied microRNA showed a correlation between H.pylori infection and gastric cancer incident. However, here the role of the critical genes was highlighted. It can be suggested that the mentioned critical genes are suitable candidate genes for drug targeting to prevent the associated possible gastric cancer. The present study's role of hubs was valid via a literature survey. Experimental validation in future complementary studies is suggested.

Conflict of interests

The authors declare that they have no competing interests.

References

1. Majumdar D, Looi S. Helicobacter pylori infection and peptic ulcers. Medicine 2024.

2. Shao Y, Lin Y, Fang Z, Yan J, Zheng T, Ye G. Analysis of Helicobacter pylori resistance in patients with different gastric diseases. Sci Rep 2024;14:4912.

3. Kim N, Marcus EA, Wen Y, Weeks DL, Scott DR, Jung HC, et al. Genes of Helicobacter pylori regulated by attachment to AGS cells. Infect Immun 2004;72:2358-68.

4. Polk DB, Peek Jr RM. Helicobacter pylori: gastric cancer and beyond. Nat Rev Cancer 2010;10:403-14.

5. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. CA Cancer J Clin 2021;71:264-79.

6. Boubrik F, Belmouden A, El Kadmiri N. Potential non-invasive biomarkers of helicobacter pylori-associated gastric cancer. J Gastrointest Cancer 2022;53:1113-20.

7. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020;396:635-48.

8. Suzuki H, Iwasaki E, Hibi T. Helicobacter pylori and gastric cancer. Gastric Cancer 2009;12:79-87.

9. Smith MG, Hold GL, Tahara E, El-Omar EM. Cellular and molecular aspects of gastric cancer. World J Gastroenterol 2006;12:2979.

10. Safari-Alighiarloo N, Taghizadeh M, Rezaei-Tavirani M, Goliaei B, Peyvandi AA. Protein-protein interaction networks (PPI) and complex diseases. Gastroenterol Hepatol Bed Bench 2014;7:17.

11. Nithya C, Kiran M, Nagarajaram HA. Dissection of hubs and bottlenecks in a protein-protein interaction network. Comput Biol Chem 2023;102:107802.

12. Arjmand B, Jahani Sherafat S, Ahmadzadeh A, Zamanian-Azodi M, Khodadoost M. Onion extract on cell gene expression profile: a system biology approach. Res J Pharmacognosy 2023;10:19-27.

13. Kucera M, Isserlin R, Arkhangorodsky A, Bader GD. AutoAnnotate: A Cytoscape app for summarizing networks with semantic annotations. F1000Research. 2016;5:1717.

14. Zhou J, Wang W, Xie Y, Zhao Y, Chen X, Xu W, et al. Proteomics-based identification and analysis of proteins associated with Helicobacter pylori in gastric cancer. PloS One 2016;11:0146521.

15. Zhang X, Li C, Chen D, He X, Zhao Y, Bao L, et al. H. pylori CagA activates the NLRP3 inflammasome to promote gastric cancer cell migration and invasion. Inflamm Res 2022:1-15.

16. Konturek P, Pierzchalski P, Konturek S, Meixner H, Faller G, Kirchner T, et al. Helicobacter pylori induces apoptosis in gastric mucosa through an upregulation of Bax expression in humans. Scand J Gastroenterol 1999;34:375-83.

17. Guo C, Liu S, Sun M-Z. Novel insight into the role of GAPDH playing in tumor. Clin Transl Oncol 2013;15:167-72.

18. Li H, Zhang H, Huang G, Bing Z, Luo H, Xu D, et al. Loss of RPS27a expression regulates cell cycle, apoptosis, and proliferation via the RPS27a-RPL11-MDM2-p53 pathway in lung adenocarcinoma cells. J Exp Clin Cancer Res 2021;41:33.

19. Wang Q, Cai Y, Fu X, Chen L. High RPS27A expression predicts poor prognosis in patients with HPV type 16 cervical cancer. Frontiers in Oncology. 2021;11:752974.

20. Wei J, Nagy TA, Vilgelm A, Zaika E, Ogden SR, Romero–Gallo J, et al. Regulation of p53 tumor suppressor by Helicobacter pylori in gastric epithelial cells. Gastroenterology 2010;139:1333-43.

21. Sadeghi M, Ghorbanpour N, Barzegar A, Rafiei I. Exploring gene signatures in different molecular subtypes of gastric cancer (MSS/TP53+, MSS/TP53-): a network-based and machine learning approach. J Genet Resour 2020;6:195-208.

22. Kit O, Vodolazhsky D, Kutilin D, Gudueva E. Changes in the number of copies of genetic loci in gastric cancer. Mol Biol 2015;49:589-97.

23. Liu W, Ying N, Rao X, Chen X. MiR-942-3p as a potential prognostic marker of gastric cancer associated with AR and MAPK/ERK signaling pathway. Curr Issues Mol Biol 2022;44:3835-48.

24. Zabaleta J. MicroRNA: a bridge from H. pylori infection to gastritis and gastric cancer development. Front Genet 2012;3:294.

25. Zhang H-H, Gu G-L, Zhang X-Y, Li F-Z, Ding L, Fan Q, et al. Primary analysis and screening of microRNAs in gastric cancer side population cells. World J Gastroenterol 2015;21:3519.

26. Zhang Y, Xu W, Ni P, Li A, Zhou J, Xu S. MiR-99a and MiR-491 regulate cisplatin resistance in human gastric cancer cells by targeting CAPNS1. Int J Biol Sci 2016;12:1437.

27. Pachathundikandi SK, Blaser N, Backert S. Mechanisms of inflammasome signaling, microRNA induction and resolution of inflammation by Helicobacter pylori. Curr Top Microbiol Immunol 2019;421:267-302.

28. Xu Y, Wang G, Hu W, He S, Li D, Chen P, et al. Clinical role of miR-421 as a novel biomarker in diagnosis of gastric cancer patients: A meta-analysis. Medicine 2022;101:29242.

29. Xiao J, Zhang F, Liu W, Zang W. Construction of epithelial-mesenchymal transition related miRNAs signatures as prognostic biomarkers in gastric cancer patients. bioRxiv 2022:2022.09.02.506322.

30. Zhan P, Shu X, Chen M, Sun L, Yu L, Liu J, et al. miR-98-5p inhibits gastric cancer cell stemness and chemoresistance by targeting branched-chain aminotransferases 1. Life Sci 2021;276:119405.

31. Yan L-r, Ding H-x, Shen S-x, Lu X-d, Yuan Y, Xu Q. Pepsinogen C expression–related lncRNA/circRNA/mRNA profile and its co-mediated ceRNA network in gastric cancer. Funct Integr Genomics 2021;21:605-18.

32. Kim YJ, Hwang K-C, Kim SW, Lee YC. Potential miRNA-target interactions for the screening of gastric carcinoma development in gastric adenoma/dysplasia. Int J Med Sci 2018;15:610.

33. Liang Y, Zhao Y, Li L, Wei H, Huang T, Zhang H, et al. MicroRNA profiles in five pairs of early gastric cancer tissues and adjacent non-cancerous tissues. Oncol Lett 2021;22:1-12.

34. Xu Q, Yao Y, Ni H, Gu J, Wang X, Jiang L, et al. Hsa-circ-0052001 promotes gastric cancer cell proliferation and invasion via the MAPK pathway. Cancer Med 2023;12:7246-57.