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Introducing Prostaglandin Endoperoxide Synthase-2 as a Remarkable Player in the Development of Gastroesophageal Reflux Disease

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Abstract

Background: Gastroesophageal reflux disease (GERD), a common disorder of the upper gastrointestinal tract, is associated with abdominal pain and acid regurgitation. GERD is considered a risk factor for esophageal adenocarcinoma. In this study, the key genes associated with GERD are determined and discussed.

Methods: Gene expression profiles of GERD samples and controls were obtained from the Gene Expression Omnibus (GEO) database and assessed via PPI network analysis to find crucial genes. These crucial genes were validated using the GeneCards database by comparison with the top GERD-related genes. The crucial genes are evaluated via directed PPI network analysis, and the key genes are determined.

Results: A total number of 104 central significantly differentially expressed genes (DEGs) were identified as separators of GERD samples of controlled individuals. GeneCards analysis demonstrated that *ACE, COL5A1, IL1A, IL1B, NGF, POSTN*, and *PTGS2* are the crucial genes. Findings showed *PTGS2* and *IL1B* are two key genes that promote GERD development.

Conclusion: The results of the current study suggest that PTGS2 inhibition may represent a potential therapeutic strategy that requires further experimental validation**.**

Keywords: Gastroesophageal reflux disease, Prostaglandin endoperoxide synthase-2, Gene expression, Network analysis

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Introduction

Gastroesophageal reflux disease (GERD), which is associated with abdominal pain and acid regurgitation, is a common disorder of the upper gastrointestinal tract. The reflux of gastric contents into the esophagus is the main feature of GERD (1-3). There is a high prevalence (13% to 20%) of GERD in the USA compared to the lower rates in Asia (2.5% to 4.8%). Family history of reflux disease, obesity, chronic consumption of certain drugs, and in-

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Key Messages:

↑What is "already known" in this topic:

GERD is a prevalent upper gastroesophageal disorder associated with esophageal adenocarcinoma. Multiple genes, including IL1B and PTGS2, contribute to GERD pathogenesis through complex inflammatory pathways.

→What this article adds:

This study identifies IL1B and PTGS2 as key genes using bioinformatic analysis, showing their central roles in GERD development. It highlights PTGS2 as a promising therapeutic target and demonstrates that gene expression relationships involving ENG and HGF are complex, suggesting further research is needed for clinical application.

creasing age are noteworthy risk factors for GERD (4).

Barrett's esophagus, non-erosive gastroesophageal reflux disease (including abnormal and normal acid exposure), and erosive esophagitis are the clinical endoscopic phenotypes of GERD. Researchers have demonstrated upregulation of IL8, *IL10, MMP3*, and *MMP9* in Barrett's esophagus, and increased levels of *IL1B, IL6, and IL10* in erosive esophagitis (5). Barrett's esophagus and GERD are considered risk factors for esophageal adenocarcinoma (6). There are various medical treatments for GERD, such as potassium-competitive acid blockers, proton pump inhibitors, histamine receptor antagonists, mucosal protectants, and prokinetics, each with its own benefits and disadvantages (7). It is reported that several single-nucleotide polymorphisms in genes such as *CCND1, FOXF1*, anti-inflammatory cytokine, *HCH*, and DNA repair genes significantly increase GERD risk (8). Results of a genome-wide association study (GWAS) indicate a positive correlation between smoking initiation, cigarettes smoked per day, ever smoking, and GERD. A negative correlation between GERD and never smoking, as well as age of smoking initiation, is confirmed. Three genes (*MAML3, HIST1H2BO, and MED27*) were identified as pleiotropic genes between GERD and the mentioned smoking conditions (9). The investigation by Zamanian-Azodi et al. (10) showed that *IL4, ALB, TP53, IL6, TNF, INS, VEGFA, CXCL8, PTGS2, ADIPOQ*, and *EGFR* are dysregulated in patients with GERD. The involvement of the "*IL17* signaling pathway" in GERD is highlighted in this document. Bioinformatics, as a powerful tool, is applied to interpret gene expression changes in many diseases. Screening many genes to identify a few critical genes related to a certain disease can provide new diagnostic or therapeutic biomarkers (11). In the present study, gene expression changes in GERD samples relative to control individuals are derived from the GEO database and analyzed via bioinformatics methods to find the critical genes involved in the initiation and progression of GERD.

Methods

Data collection

Gene expression profiles of patients with eosinophilic esophagitis (EoE) and gastro-esophageal reflux disease (GERD) versus controls are available in GSE148381 from the GEO database. In the present analysis, six GERD samples and seven controls were selected for evaluation using the GEO2R program. As depicted in the recorded report, the samples were evaluated via endoscopic and histological methods. The studied RNAs were extracted from proximal esophageal biopsy samples (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE148381).

Pre-evaluation analysis

The gene expression profiles were assessed using the GEO2R program to explore the comparative characteristics of the studied samples. Eligible samples for further analysis were selected based on the UMAP plot assessment. Due to the inequality of patient and control samples, significant DEGs were identified based on an adjusted p-value < 0.05 via the provided Venn diagram by using the GEO2R program. To increase confidence in the analysis, significant DEGs were further limited by a fold change > 2 criterion.

Undirected PPI network analysis

The significant DEGs were assessed via an undirected PPI network to find the central genes using the "Protein query" of the STRING database through Cytoscape software v 3.10.1. The PPI network was constructed based on a confidence score = 0.4 and was analyzed by the "Network analyzer" application of Cytoscape software to identify the central nodes. Hub nodes were identified considering a cutoff value of degree = (average + 2(standard deviation)). Degree value distribution of nodes and the correlation between degree values and betweenness centralities of nodes were provided to visualize the importance of the hub nodes.

GeneCards analysis

To find the gastro-esophageal reflux disease-associated genes, the phrase "gastro-esophageal reflux disease" was searched in the GeneCards database (https://www.genecards.org/Search/Keyword?queryString=%22gastro-esophageal%20reflux%20disease%22), and the identified genes were assessed based on GIFtS criterion (GeneCards Inferred Functionality Scores). This score is a quantitative measure that assesses the degree of known functionality of human genes. It integrates extensive annotation from multiple sources within the GeneCards database. The selected genes were compared with the introduced hubs from the undirected PPI network analysis using Excel software. The common genes between these two analyses were designated as critical genes.

Directed PPI network analysis

The hub genes were further evaluated via directed PPI network analysis using the CluePedia plugin of Cytoscape software. Nodes were connected by expression action to identify co-expression relationships among the hub genes. The critical genes and their first neighbors were extracted from the main connected component of the directed PPI network.

The Human Protein Atlas analysis

Expression of the top key protein was searched in The Human Protein Atlas, as an open-access resource for human proteins (https://www.proteinatlas), to determine its expression level in the esophagus relative to other tissues.

Results

Pre-evaluation analysis

The UMAP plot comparing six gene expression profiles of GERD samples (GSM4485322-4 and GSM4485346-8) with seven control individuals (GSM4485325-7, GSM4485329, and GSM4485349-51) is illustrated in Figure 1. The findings indicate that GSM4485347-8 are not eligible for further analysis because they are not separated from the control individuals (Figure 2). This contrast be-

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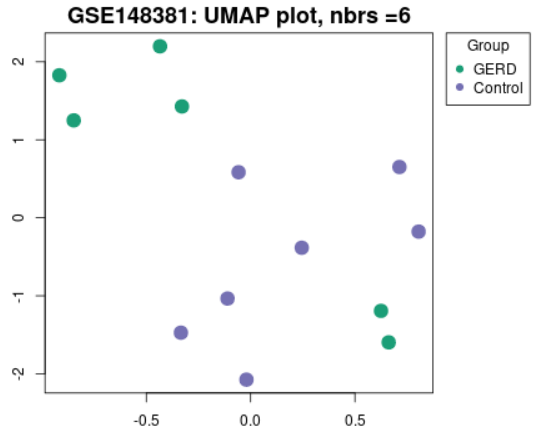

Figure 1. UMAP plot of gene expression profile comparison between GERD and control samples. Each sample is compared with six neighbors (nbrs=6).

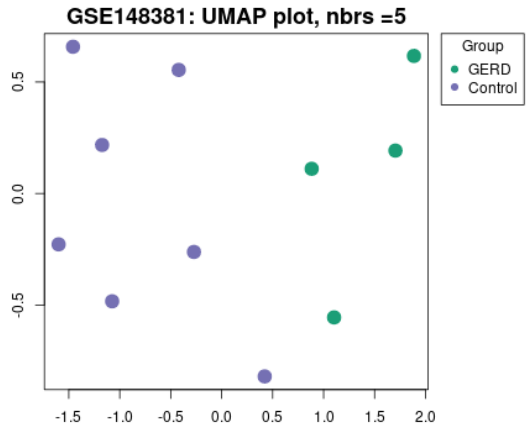

Figure 2. UMAP plot of gene expression profile comparison between GERD and control samples (GSM4488347-8 are ignored). Each sample is compared with five neighbors (nbrs=5).

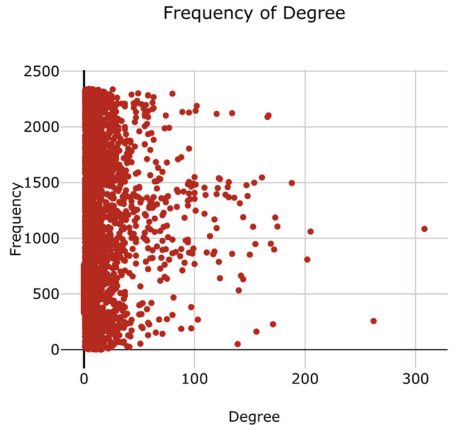

Figure 3. Node degree distribution for the constructed PPI network. The potent hubs appeare on the right side of figure.

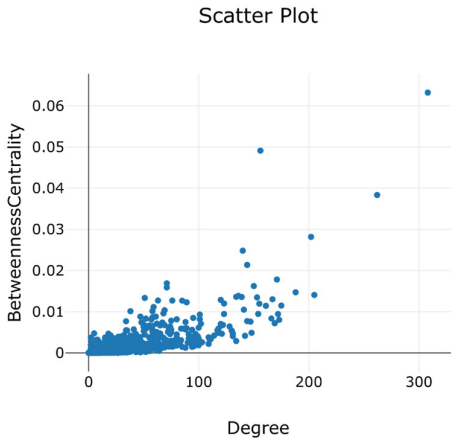

Figure 4. Correlation between degree values and betweenness centrality of nodes.

tween GSM4485347-8 and other gene expression profiles of patients may be attributed to the early stage of disease in the two mentioned patients. Because the samples show more similarity to controls relative to patients. As demonstrated in Figure 2, excluding GSM4488347-8 led to the complete separation of GERD samples from the control samples. Analysis revealed that among a total of 23526 dysregulated genes, 4939 significant DEGs separate GERD samples from controls. Considering a fold change > 2 and excluding uncharacterized individuals, a total number of 2789 significant DEGs were pointed out for further investigations. The created PPI network was so large, and its visualization was not informative. Therefore, it was not presented.

Undirected PPI network analysis

The 2789 significant DEGs were evaluated via undirected PPI network analysis. The network was constructed from 2342 recognized genes and 21114 edges. As depicted in Figure 3, the node degree distribution shows a few nodes with higher degree values to a large number of genes with lower degree values. A cutoff of 72 was calculated to identify the hub nodes. A total of 104 hubs were identified in the analyzed PPI network (Table 1). As depicted in Figure 4, there is a strong correlation between degree values and betweenness centrality of nodes (three triplet sub-networks were excluded from visualization to improve clarity).

GeneCards analysis

A total of 96 gastroesophageal reflux disease-associated genes were found in the GeneCards database. The distribution of these genes based on GIFtS is presented in Figure 5. As shown in Figure 5, the gastroesophageal reflux disease-associated genes with GIFtS higher than 50 (Table 2) follow a similar trend. Comparison between Tables 1 and 2 indicates that *ACE, COL5A1, IL1A, IL1B, NGF, POSTN,* and *PTGS2* are critical genes that distinguish the gene expression profiles of patients from controls.

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Table 1. List of hub nodes of the analyzed PPI network

No.	Display name	Degree	No.	Display name	Degree	No.	Display name	Degree
1	FN1	308	36	BGN	122	71	LGALS3	94
2	IL1B	262	37	CXCL10	122	72	SELE	94
3	MMP9	205	38	POSTN	121	73	COL4A1	94
4	EGF	202	39	CDH5	120	74	ENG	94
5	COL1A1	188	40	LOX	120	75	SPARC	94
6	PECAM1	175	41	ITGB3	120	76	TGFBR2	92
7	CCL2	173	42	FGF7	118	77	SELP	91
8	FGF2	172	43	DCN	118	78	SELL	91
9	TLR4	171	44	FGF10	117	79	FGF13	90
10	MMP2	169	45	HGF	114	80	CDH17	89
11	CXCR4	167	46	CD163	111	81	NFKBIA	89
12	ITGAM	166	47	SERPINE1	110	82	VIM	88
13	IGF1	161	48	THY1	109	83	EPCAM	88
14	CALML5	156	49	MMP3	109	84	CCR2	88
15	PXDN	155	50	IL18	103	85	FGFR1	87
16	COL1A2	154	51	NGF	102	86	COL6A3	85
17	KDR	153	52	BMP2	101	87	PRKCA	85
18	APOE	150	53	TGFB2	101	88	COL4A2	84
19	CXCL12	148	54	NT5E	101	89	IGF2	84
20	THBS1	147	55	COL5A1	100	90	TIMP3	83
21	PPARG	144	56	COL5A2	100	91	CD33	81
22	CD34	144	57	ELN	100	92	SERPINA1	80
23	IL1A	142	58	CXCL1	100	93	TEK	80
24	PDGFRB	141	59	THBS2	99	94	ACE	80
25	APP	140	60	FBN1	99	95	ITGA1	80
26	PTGS2	139	61	FGF9	98	96	TAGLN	78
27	BMP4	136	62	IL7R	97	97	NES	77
28	VCAM1	134	63	COL6A1	97	98	MRC1	77
29	NCAM1	134	64	CTLA4	97	99	NRXN1	76
30	TIMP1	131	65	MMP1	96	100	CD28	76
31	COL3A1	131	66	WNT5A	95	101	REN	75
32	SPP1	130	67	COL6A2	95	102	IRS1	75
33	FCGR3A	128	68	CD80	95	103	CACNA1C	75
34	CD36	123	69	CCR7	95	104	CXCR2	75
35	LUM	123	70	ITGA5	95			

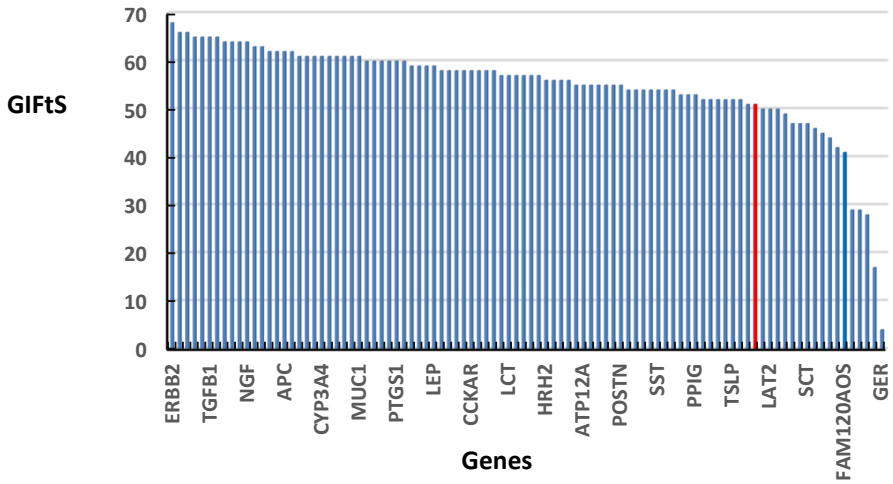

Figure 5. Distribution of gastro-esophageal reflux disease-associated genes from GeneCards based on GIFtS criterion.

Directed PPI network analysis

The 104 hub nodes were included in a directed PPI network based on co-expression action. *Col5A1* appeared as an isolated node, and the other six critical genes with their first neighbors were extracted as a sub-network (see Figure 6). As depicted in Figure 6, the critical hubs play a key role as actor genes in the directed PPI network.

The Human Protein Atlas analysis

Expression of the *PTGS2* was searched in The Human Protein Atlas (https://www.proteinatlas.org/ENSG00000073756-PTGS2/tissue), and findings from the GTEx dataset and consensus dataset across various tissues

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Table 2. List of gastro-esophageal reflux disease-associated genes with GIFtS > 50.

No	Gene symbol	GIFtS	No.	Gene symbol	GIFtS	No.	Gene symbol	GIFtS
1	ERBB2	68	28	IL1B	60	55	TFF1	55
2	TP53	66	29	GRM5	60	56	ATP12A	55
3	CFTR	66	30	IL10	60	57	S100A8	55
4	RPS6KA3	65	31	PTGS1	60	58	GCG	55
5	TNF	65	32	TMPRSS2	60	59	GPT	55
6	TGFB1	65	33	ABCC8	59	60	IL17A	55
7	CTSD	65	34	ADIPOQ	59	61	POSTN	55
8	IL6	64	35	IL4	59	62	TFF3	54
9	CDKN2A	64	36	LEP	59	63	ATP4A	54
10	ACE	64	37	CYP2C19	58	64	CDX2	54
11	NGF	64	38	ABAT	58	65	GHRL	54
12	CD4	63	39	CRP	58	66	SST	54
13	IFNG	63	40	IL5	58	67	MUC5B	54
14	PTGS2	62	41	CCKAR	58	68	TAC1	54
15	CDH1	62	42	CCL11	58	69	ACTL6A	53
16	APC	62	43	IL1A	58	70	NTS	53
17	GDNF	62	44	AKR1C2	58	71	PPIG	53
19	TRPV1	61	46	LCT	57	73	TFF2	52
20	ALB	61	47	IL13	57	74	MLNR	52
21	CYP3A4	61	48	VIP	57	75	RNASE2	52
22	CD8A	61	49	EPX	57	76	TSLP	52
23	HTR2A	61	50	CALCA	57	77	CCN1	52
24	INS	61	51	HRH2	56	78	GEMIN4	51
25	MIF	61	52	CCK	56	79	GIT2	51
26	MUC1	61	53	PYY	56			
27	COL5A1	60	54	AKR1B10	56			

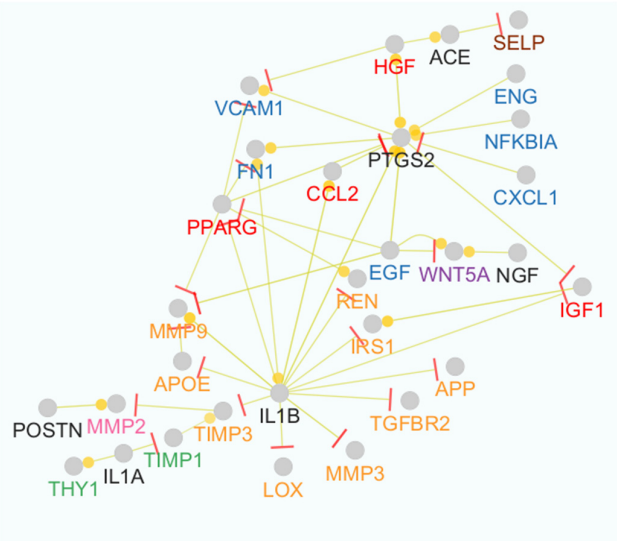

Figure 6. A sub-network including ACE, IL1A, IL1B, NGF, POSTN, PTGS2, and their first neighbors. The critical genes are presented in black, and the first neighbors of two critical genes are shown in red.

are shown in Figure 7. As depicted in Figure 7, the level of *PTGS2* expression in the esophagus is above the median compared to other tissues.

Discussion

Results indicate that six critical genes play a crucial role in GERD progression. As shown in Figure 6, *IL1B* and *PTGS2* are the key genes among the identified critical DEGs because *IL1B* acts as an important regulatory gene, while *PTGS2* appears as the most controlled gene. The role of interleukin 1 beta in many diseases, such as cancers, radiation effects on skin, and major depression, has been confirmed and discussed (12-14). An increased level of *IL1B* in GERD was reported by Zavala-Solares and colleagues (15). As demonstrated in Figure 6, *IL1B* controls the expression of 14 genes while its own expression is controlled by only one gene. It inhibits expression of *LOX, MMP3, TGFBR2, APP, IGF1, IRS1, REN, PPARG, APOE*, and *TIMP3*, and upregulates *PTGS2, CCL2, MMP9,* and *FN1*. *IL1B* is upregulated by approximately a 2-fold change in the studied gene expression profile of GSE148381. Therefore, overexpression of *IL1B* implies downregulation of the 10 genes mentioned above. Surprisingly, except for *REN*, the other nine controlled genes are upregulated in GERD. It can be concluded that overex-

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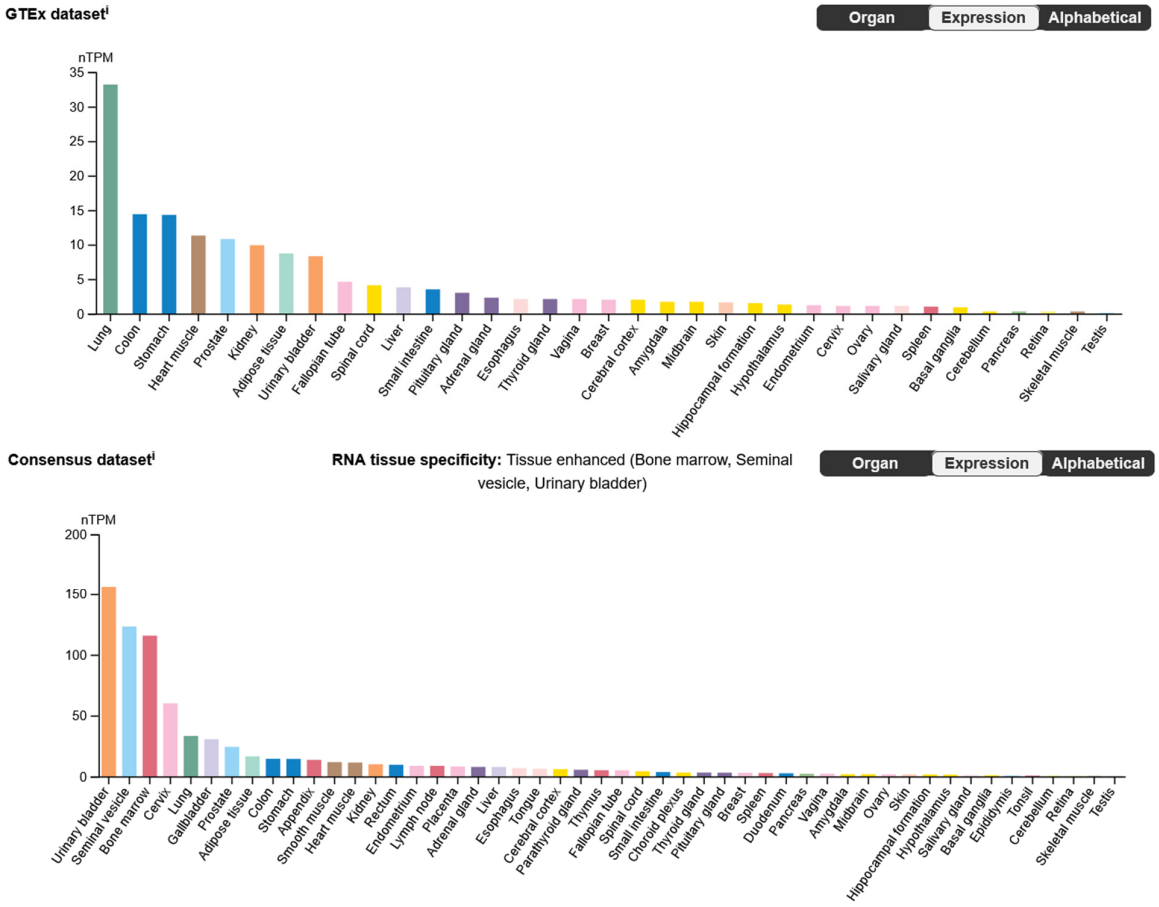

Figure 7. Rate of PTGS2 expression in the esophagus relative to other tissues from The Human Protein Atlas. Data are extracted from the GTEx and Consensus datasets.

pression of *IL1B* is a beneficial process in GERD for maintaining gene expression activities in patients.

Prostaglandin endoperoxide synthase 2 (cyclooxygenase 2) (*PTGS2*), which is upregulated in GERD, is an important player in inflammatory signaling pathologies. It is reported that prostaglandin E2 is the main product of activation and expression of *PTGS2/COX2*, a process involved in diabetogenic conditions. *PGE2* is known as both a consequence and a cause of inflammation (16). A positive co-expression relationship between *IL1B* and *PTGS2* suggests a destructive role for *IL1B* in GERD. This effect is further intensified by the involvement of *EGF, ENG, NFKBIA, and HGF. ACE, NGF, IL1A,* and *POSTN* (the other four critical genes) have no direct effect on *IL1B* and *PTGS2*. It seems that controlling *IL1B* expression does not have exclusively beneficial effects on GERD progression, as *IL1B* exhibits dual roles, both constructive and injurious, in the development of GERD.

It appears that *PTGS2* is a key enzyme associated with GERD. Nonsteroidal anti-inflammatory drugs, such as aspirin, are known inhibitors of *PTGS2* (17). As demonstrated in Figure 7, the level of *PTGS2* expression in the esophagus is higher than the median relative to other represented tissues. Experiments have demonstrated that EGFR-signaling inhibitors, together with *PTGS2* inhibitors, prevent tumorigenesis of transformed P53-deficient oligodendrocyte precursor cells in Mice and human glioma-initiating cells (18, 19). As mentioned earlier, *EGF, ENG, NFKBIA*, and *HGF* have a positive co-expression relationship with *PTGS2*; however, *EGF* and *NFKBIA* are downregulated genes, while *ENG* and *HGF* appear as upregulated genes. *ENG* and *HGF* appear to upregulate *PTGS2* and may influence GERD progression, but their roles are complex and incompletely characterized. While inhibition of HGF could potentially reduce *PTGS2* expression and inflammation, studies in animal models show that *HGF* can promote healing and epithelial regeneration (20). This suggests that *HGF* inhibition might have unintended negative effects. Similarly, *ENG* is involved in endothelial cell functions; however, evidence indicates that its inhibition may only partially control *PTGS2* expression without directly affecting tumor cell proliferation. Therefore, any therapeutic targeting of *ENG* and *HGF* should consider complex functions in GERD, indicating the importance of additional experimental studies to define their therapeutic value. Hepatocyte growth factor

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(*HGF*) is overexpressed with an 8-fold change in GERD. *HGF* is one of the factors that promotes the proliferation of hepatocytes (21). It can be concluded that inhibition of *HGF* leads to downregulation of *PTGS2* and may be a suitable strategy to prevent GERD progression.

Results of an investigation showed that treatment of rats with induced esophageal ulcers via intraperitoneal administration of *HGF* led to a considerable decrease in the ulcerative area and enhanced proliferation of esophageal epithelial cells (22). Therefore, inhibition of *HGF* is a complex intervention and cannot be directly proposed for the inhibition of *PTSG2* expression. Endoglin (*ENG*) is another upregulated gene that enhances the expression of *PTGS2*. *ENG* is known for its role in regulating the proliferation and migration of endothelial cells (23). Investigation of *ENG* expression in patient-derived cell lines from patients with esophageal squamous cell carcinoma (ESCC) demonstrated that *ENG* does not influence the migration or proliferation of squamous cell carcinoma cells (24). It seems that inhibition of *ENG* expression may partially control *PTGS2* expression. The finding can be used to determine possible drug targets to treat the disease.

This study has some limitations that should be considered. The gene expression analysis was limited by a small sample size, only using six GERD samples and seven controls. This may constrain the generalizability of the findings. While the bioinformatic analysis revealed that *PTGS2* is a promising therapeutic target in GERD, future experimental studies with larger cohorts will be important to validate these gene expression patterns. This would refine the understanding of underlying mechanisms and the potential role of *IL1B, PTGS2*, and related pathways as therapeutic targets in GERD.

Conclusion

GERD is associated with the dysregulation of a large number of genes, including critical individuals such as *ACE, COL5A1, IL1A, IL1B, NGF, POSTN*, and *PTGS2*. Analyses revealed the remarkable roles of *IL1B* (as a regulatory actor with complex functions) and *PTGS2* (as a controlled gene with a destructive role) in the progression of GERD. Inhibition of *PTGS2* has been recommended as an effective method to counter GERD development. However, future experimental and clinical trial investigations are required to validate these findings.

Acknowledgment

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Conflict of Interests

The authors declare that they have no competing interests.

Authors' Contributions

M.R.T. was responsible for conceptualization and writing the original draft. B.A. conducted the formal investigation. Z.R. performed validation and data analysis. F.B. handled data curation. F.B., F.R., and Z.R. contributed to the review of the manuscript. Visualization was carried out by M.R., R.M.R., and F.R. Supervision was provided by F.R.

Ethical Considerations

This study received approval from the ethics committee of the School of Medicine at Iran University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1403.839).

Funding Support

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Data Availability

All data used in this study were obtained from the GEO database. No new datasets were generated during this study.

AI Use Statment

No artificial intelligence (AI) was used in the design, analysis, and interpretation of this manuscript.

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