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Bioinformatics-based analysis of PTGIS gene expression and clinical significance in colon adenocarcinoma

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Abstract

Aim: To analyze the expression of PTGIS in colon adenocarcinoma and its relationship with clinical prognosis using multiple databases.

Materials and Methods: By mining the data of Timer and GEPIA databases on PTGIS studies, the changes of its expression level in colon adenocarcinoma were analyzed. The GEPIA database was used to analyze the relationship between PTGIS expression levels and survival prognosis of colon adenocarcinoma patients. the Linked Omics database was used to analyze the correlation between PTGIS gene expression and clinicopathological features of colon adenocarcinoma. The Genecards database was used to collect proteins related to PTGIS gene, and the STRING data platform was used to construct protein interactions network of PTGIS-related proteins and analyze the physiological process of protein enrichment.

Results: The study of Timer database and GEPIA database regarding the differential expression of PTGIS genes in colon adenocarcinoma and normal tissues of colon glands showed that the expression of PTGIS genes in colon adenocarcinoma tissues was significantly lower than that in normal tissues of colon glands ($p < 0.05$). The overall survival rate of patients with low PTGIS gene expression was significantly higher than that of patients with high PTGIS gene expression, and the prognosis of patients with low PTGIS gene expression was better ($p < 0.05$), according to the survival analysis of the GEPIA database. PTGIS gene expression levels were lower in colon adenocarcinoma stages I and IV and higher in colon adenocarcinoma stages II and III. Twenty-five proteins related to PTGIS were collected through Genecards database, including LSS, SIGMAR1, FDFT1, etc. The results of their related protein enrichment analysis showed that they were mainly enriched in Cholesterol biosynthetic process, B cell chemotaxis and other biological processes.

Conclusion: PTGIS gene is lowly expressed in colon adenocarcinoma and its expression level correlates with survival prognosis. PTGIS gene can provide bioinformatics guidance for the later laboratory experiments.

Introduction

Colorectal adenocarcinoma (COAD) are malignant tumors that start in the cells of the colon. The exact cause of this type of cancer is unknown, but several factors have been associated with an increased risk of developing it [1]. These include a family history of bowel cancer, a diet high in fat and red meat, obesity, smoking, a sedentary lifestyle and long-term use of certain medications [1-2]. The incidence of COAD tumors is increasing, with approximately 140,000 cases diagnosed each year in the US alone. The majority of cases are diagnosed in people over the age of 50, and the risk increases with age [3]. Treatment for COAD tumors typically involves a combination of surgery, chemotherapy and radiation. Surgery is the primary treatment for early-stage tumors, while chemotherapy and radiotherapy are used to treat more advanced tumours [4-5]. In some cases, targeted therapies such as immunotherapy may be used to reduce the risk of recurrence. The overall prognosis for COAD tumors depends on the stage of the cancer when it is diagnosed, as well as the age and general health of the patient [6].

PTGIS (Prostaglandin I2 Synthase) is a Protein Coding gene. Diseases associated with PTGIS include Hypertension, Essential and Childhood-Onset Schizophrenia [7]. Among its related pathways are Synthesis of bile acids and bile salts and Oxidation by cytochrome P450 [8].

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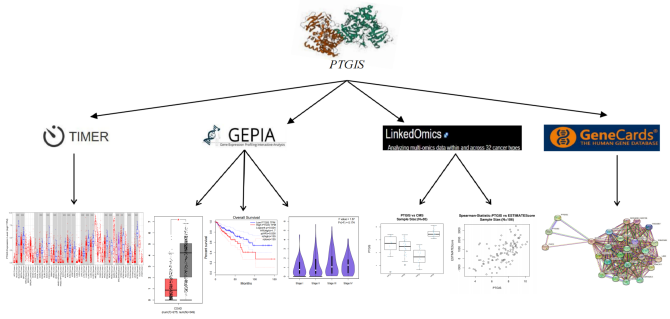

Figure 1. The workflow to study the expression and clinical significance of the PTGIS gene in COAD.

This paper explores the expression and clinical significance of the PTGIS gene in colon adenocarcinoma through several web-based databases (Figure 1) [9].

Materials and Methods

Timer database mining

TIMER database(http://timer.cistrome.org/) [10] was used to systematically analyze the tumor-infiltrating immune cells (TIICs) in 32 cancer types using more than 10,000 samples from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/) [11]. TIMER determines the abundance of tumor-infiltrating immune cells (TIICs) based on the statistical analysis of gene expression profiles.I analysed the expression of the PTGIS gene between tumour tissue and normal tissue using the Diff Exp module of the Timer database [10].

GEPIA database mining

The GEPIA data analysis platform (http://gepia.cancer-pku.cn/) [12], is a web-based tool that provides fast and customizable functionality based on TCGA and GTEx data. It includes differential expression analysis, contour mapping, patient survival analysis, and similar gene detection [13]. It is used to analyze expression differences between colon adenocarcinoma and normal tissue, prognosis, and overall survival and pathological staging.

Differential expression of PTGIS in colon adenocarcinoma and normal colonic glandular tissues

Searches were performed in the Box Plots module of the GEPIA data analysis platform. The search criteria were:①Gene:PTGIS;②log2FC|Cutoff:2, P-valueCutoff:0.001;③Cancer name: COAD;④Log Scale:Yea; ⑤Jitter Size:0.4;⑥Matched Normal data: Match TCGA normal and GTEx data [11].

Relationship between PTGIS expression and prognosis of colonic adenocarcinoma

The search was performed in the Survival Analysis module of the GEPIA data analysis platform. The search criteria were:①Gene:PTGIS;②Methods:Overall Survival;③Group Cutoff:Median;④Cutoff-High(%)&Low(%):50;⑤95% Confidence Interval:Yes;⑥Hazards Ratio (HR):Yes;⑦Axis Units:Months;⑧Cancer name:COAD.

Relationship between PTGIS expression and pathological stage of colon adenocarcinoma patients

Searches were performed in the Stage Plot module of the GEPIA data analysis platform. The search criteria were:①Gene:PTGIS; ②Use major stage:YES; ③Cancer name:COAD; ④Log Scale:YES.

Relationship between PTGIS expression and clinicopathological features of colonic adenocarcinoma

The Linked Omics database (http://Linked Omics.org/) [14] contains multi-omics and clinical data for 32 cancers and 11,158 patients from the The Cancer Genome Atlas (TCGA) project. It is also a global multi-omics database for proteomics data.The Linked Omics database has developed three analysis modules, the LinkFinder module, the LinkCompare module, and the LinkInterpreter module, to analyse and compare multi-omics data within and between tumours [14-15]. The Linked Omics database was used to analyze the relationship between PTGIS gene expression and clinicopathological features of colon adenocarcinoma.Searches were performed in the Linked Omics data analysis platform. The search criteria were ①Select Cancer Cohort:COAD; ②Select Search Dataset: Datastype:RNAseq; ③Select Search Dataset attribute:PTGIS; ④Select Target Dataset: Clinical; ⑤Select statistical method:Non-Parametric Test [12-13].

GO function and KEGG pathway analysis

The Genecards database (https://www.genecards.org/) [16] was used to search for relevant information using "PTGIS" as the keyword. The PTGIS-related proteins were imported to the String analysis website, and the target was set as "homo sapiens" with the highest confidence level of 0.900, and the free gene nodes were hidden to obtain the results of protein interactions and GO and KEGG analysis. The results of the PPI analysis were downloaded as "TSV" files and imported into Cytospace (3.9.1) by selecting "network Analyzer", obtaining the network topology parameters, and analyzing and calculating the PPI network The network topology parameters are obtained and the PPI network is analysed to calculate the degree, betweenness centrality (BC) and closeness centrality (CC) of the nodes.

Results

PTGIS gene expression in tumour and normal tissues

Mining of the Timer database revealed that, as shown in Figure 2A, the PTGIS gene was expressed in ACC, BRCA-Basal, BRCA-Luminal, CESC, DLBC, GBM, LAML, LGG, MESO, OV, PAAD, PCPG, SARC, TGCT, THYM, USC, UVM tumors, while it was not expressed in the PTGIS gene was low in BLCA, BRCA, COAD, ESCA, HNSC, KICH, KIRP, LIHC, LUAD, LUSC, PRAD, READ, SKCM, STAD, THCA, UCEC tumors and high in related normal tissues. Gene expression was slightly higher in CHOL tumors than in normal tissues. Further validation analysis using the GEPIA database revealed that in 624 samples from the database source, including 275 colon adenocarcinoma tissues and 349 normal colon glandular

Table 1. Association result.

Query	Statistic	P-value	FDR (BH)
Stromal Score (Spearman Correlation)	7.83E-01	3.37E-23	7.42E-22
ESTIMATE Score (Spearman Correlation)	6.27E-01	6.68E-13	4.90E-12
Tumor Purity (Spearman Correlation)	-6.27E-01	6.68E-13	4.90E-12
CMS (Kruskal-Wallis Test)	5.20E+01	3.00E-11	1.65E-10
UMS (Kruskal-Wallis Test)	3.46E+01	3.12E-08	1.38E-07
ProS (Kruskal-Wallis Test)	3.27E+01	1.38E-06	5.05E-06
Immune Score (Spearman Correlation)	3.51E-01	2.26E-04	7.10E-04
Polyps_History (Wilcox Test)	-3.10E-01	1.26E-03	3.40E-03
Stage (Kruskal-Wallis Test)	1.56E+01	1.39E-03	3.40E-03
pathology_T_stage (Kruskal-Wallis Test)	1.21E+01	2.32E-03	5.10E-03
pathology_N_stage (Kruskal-Wallis Test)	8.16E+00	1.69E-02	3.39E-02
Polyps_Present (Wilcox Test)	-1.81E-01	2.45E-02	4.49E-02
Mucinous (Wilcox Test)	1.10E-01	3.34E-02	5.66E-02
CEA (Spearman Correlation)	2.13E-01	1.06E-01	1.66E-01
Vascular_Invasion (Wilcox Test)	-9.12E-02	1.41E-01	2.07E-01
Age (Spearman Correlation)	-1.42E-01	1.51E-01	2.08E-01
Synchronous_Tumors (Wilcox Test)	-1.02E-01	2.38E-01	3.08E-01
Subsite (Kruskal-Wallis Test)	7.42E+00	2.84E-01	3.35E-01
Lymphatic_Invasion (Wilcox Test)	-3.18E-02	2.89E-01	3.35E-01
Perineural_Invasion (Wilcox Test)	-1.67E-01	4.20E-01	4.62E-01
Tumor.Status (Wilcox Test)	-8.43E-02	5.63E-01	5.90E-01
mutaiton_rate (Spearman Correlation)	-1.31E-02	8.94E-01	8.94E-01

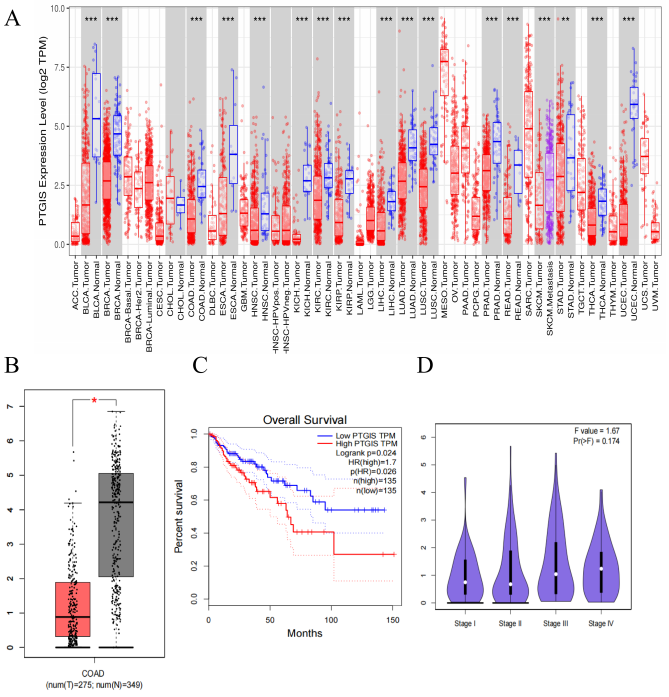

Figure 2. A) Expression of PTGIS gene in tumour and normal tissues, B) Expression of PTGIS gene in colon adenocarcinoma and normal colon glandular tissue, C) The relationship between PTGIS gene expression and overall patient survival, D) Relationship between PTGIS gene expression and the pathological stage of colon adenocarcinoma.

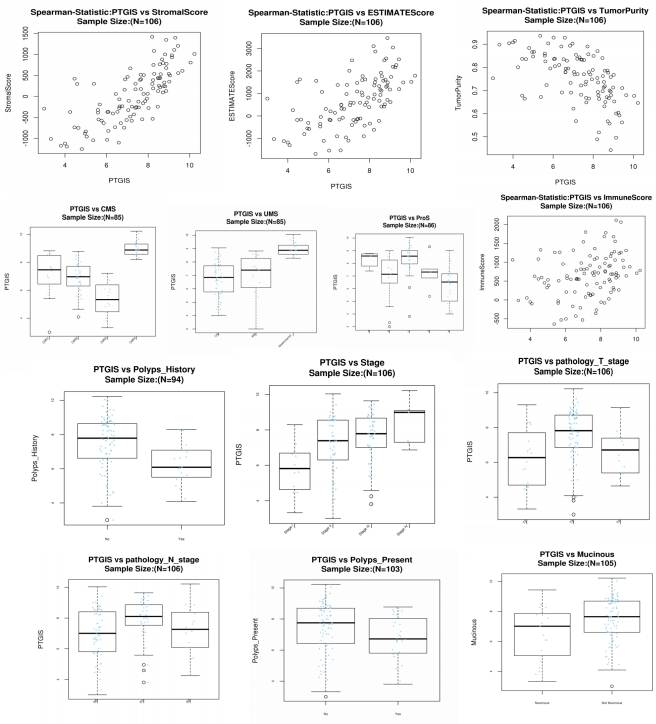

Figure 3. Relationship between PTGIS expression and multiple clinical features of COAD.

tissues. The expression of PTGIS gene in colon adenocarcinoma was significantly lower than that in normal colon glandular tissues (as shown in Figure 2B), and the difference was statistically significant ($p < 0.05$), which was consistent with the Timer database.

Table 2. Analysis of the top five GOs of the PTGIS gene.

BP	MF	CC
Cholesterol biosynthetic process via lathosterol	3-beta-hydroxy-delta5-steroid dehydrogenase activity	Smooth endoplasmic reticulum membrane
Cholesterol biosynthetic process via desmosterol	C-4 methylsterol oxidase activity	Nuclear outer membrane
B cell chemotaxis	Cholesterol dehydrogenase activity	Lipid droplet
Mineralocorticoid biosynthetic process	delta14-sterol reductase activity	Nuclear inner membrane
Cyclooxygenase pathway	Prostaglandin-endoperoxide synthase activity	Caveola

Table 3. Analysis of the first five KEGGs of the PTGIS gene.

Pathway ID	Pathway Name	Count	Strength
hsa00100	Steroid biosynthesis	9 of 20	2.53
hsa00120	Primary bile acid biosynthesis	2 of 17	1.95
hsa04913	Ovarian steroidogenesis	4 of 50	1.78
hsa00140	Steroid hormone biosynthesis	3 of 59	1.58
hsa00590	Arachidonic acid metabolism	3 of 61	1.57

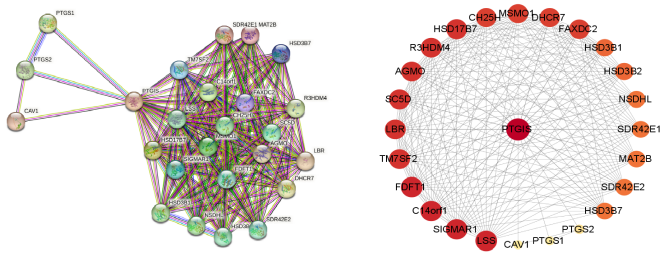

Figure 4. PPI analysis of PTGIS gene-related proteins.

Relationship between PTGIS expression and the pathological stage and prognosis of patients with colon adenocarcinoma

The relationship between PTGIS gene expression and the prognosis and pathological staging of colon adenocarcinoma patients was analyzed in the GEPIA database. Based on the data analysis of colon adenocarcinoma patients from the TCGA database source, we could obtain the overall survival (OS) curves and pathological staging of each 135 patients with high and low PTGIS expression. As shown in Figure 2C, the overall survival rate of patients with low PTGIS gene expression in the cancerous tissues of colon adenocarcinoma patients was significantly higher than that of patients with high expression. The overall survival rate of patients with low PTGIS gene expression from the onset of colon adenocarcinoma was not significantly different from that of patients with high expression in the short term, but was consistently higher than that of patients with high expression after a short period of time. As shown in the figure: logrank p=0.024, risk ratio HR(high)=1.7, P(HR)=0.026. Figure 2D demonstrates the relationship between PTGIS gene expression and pathological stage in patients with colon adenocarcinoma. The PTGIS gene expression level gradually increased from stage 1 to stage 2 in patients with colon adenocarcinoma. In stage II and III colon adenocarcinoma patients, PTGIS gene expression levels were slightly reduced. The PTGIS gene expression level was significantly reduced in patients with stage III to stage IV colon adenocarcinoma [F value=1.67, Pr(>F)=0.174]. In these results, lower PTGIS gene expression levels were found in stages I and IV, and higher PTGIS gene expression levels in stages II and III. The expression of PTGIS gene in colon adenocarcinoma can be used as an indicator to distinguish stage I and IV from stage II and III colon adenocarcinoma.

Correlation between PTGIS gene expression and clinicopathological features of colonic adenocarcinoma

We used the Linked Omics database to search for correlations between PTGIS gene and clinicopathological features of colon adenocarcinoma. The search results showed that PTGIS gene expression was associated with Stromal Score, ESTIMATE Score, Tumor Purity, CMS, UMS, ProS, Immune Score Polyps History, Stage, Pathology T stage, Pathology N stage, Polyps Present and Mucinous. Not related to CEA, Vascular Invasion, Age, Synchronous Tumors, Subsite, Lymphatic Invasion, Perineural Invasion, Tumor Status, mutation rate (Table 1).

In the Stromal Score and ESTIMATE Score plots, the higher the expression levels of PTGIS gene, the greater the Stromal Score and ESTIMATE Score. In the Tumor Purity plot, the higher the expressionlevel of PTGIS gene, the lower the Tumor Purity. In the CMS plot, PTGIS gene expression was lowest in CMS3 and highest in CMS4. In the UMS plot, PTGIS gene expression was highest in Mesenchymal, with little difference in expression in CIN and MSI. In the ProS plot, PTGIS gene expression was highest in C and lowest in E, but the overall expression difference was small. In the Immune Score plot, PTGIS gene expression showed little relationship with Immune Score. In the Polyps History plot, PTGIS gene expression was found to be lower in the presence of Polyps. Combined with the previous analysis that low PTGIS expression is associated with colon adenocarcinoma, it can be assumed that there is a higher incidence of colon adenocarcinoma with a history of colon polyps. In the Stage graph, we can see that the higher the Stage, the higher the PTGIS gene expression level. In the pathology T stage graph, the highest expression of PTGIS gene was found in T3 stage, while the expression of PTGIS gene in pathology N stage was not significantly different. PTGIS gene expression was lower in the presence of polyps, suggesting that the presence of colon polyps is related to colon adenoma. In the Mucinous map, PTGIS gene expression was lower in the presence of Mucinous in the colon, suggesting that Mucinous is closely related to colon adenocarcinoma and may be a cause of colon adenocarcinoma (Figure 3).

GO and KEGG analysis and PPI analysis of PTGIS gene related proteins

The PTGIS gene-related proteins were found in the Genecards database and imported into the String website for PPI, GO, and KEGG analysis. The PPI results were imported into Cytoscape software to create a network diagram based on Degree values (Figure 4). The main proteins that interacted with PTGIS in the network diagram were LSS, SIGMAR1, C14orf1, FDFT1, TM7SF2, LBR, etc. The results of String GO analysis (Table 2) showed that the Biological Process of PTGIS-related proteins mainly interacted with Cholesterol The results of String GO analysis (Table 2) showed that the Biological Process of PTGIS-related proteins was mainly related to Cholesterol biosynthetic process, B cell chemotaxis, Mineralocorticoid biosynthetic process and Cyclooxygenase pathway. beta-hydroxy-delta5-steroid dehydrogenase activity, C-4 methylsterol oxidase activity, Cholesterol dehydrogenase activity, delta14-sterol The Cellular Component of PTGIS-related proteins is mainly associated with the endoplasmic reticulum membrane, the nuclear outer membrane, the Lipid droplet membrane, and the endoplasmic reticulum membrane. Ovarian steroidogenesis, Steroid hormone biosynthesis, Arachidonic acid metabolism, etc.

Discussion

In this paper, we used bioinformatics methods to analyze data from several databases on colon adenocarcinoma. First, the Timer database was used to screen that PTGIS showed low expression in colon adenocarcinoma, and further validation analysis using the GEPIA database revealed that in 624 samples with 275 colon adenocarcinoma tissues and 349 normal colon glandular tissues, the expression of PTGIS gene in colon adenocarcinoma was significantly lower than that in normal bladder tissues. The relationship between PTGIS gene expression level and survival prognosis of colon adenocarcinoma patients was analyzed using the GEPIA database, and the results showed that the overall survival rate of patients with low expression was significantly higher than that of patients with high expression, and the PTGIS gene could be used as an indicator to judge their prognosis. The PTGIS gene expression levels were lower in colon adenocarcinoma stages I and IV, and higher in colon adenocarcinoma stages II and III. Second, the LinkedOmics database was used to analyze the correlation between PTGIS gene expression and clinicopathological features of colon adenocarcinoma. The results showed that the expression of PTGIS gene was correlated with Stromal Score, ESTIMATE Score, Tumor Purity, CMS, UMS, ProS, Immune Score, Polyps History , Stage, pathology T stage, pathology N stage, Polyps Present and Mucinous. Patients with colon polyps were also found to be at risk of developing adenocarcinoma of the colon even after surgical treatment. Finally, the Genecards database was used to collect proteins associated with PTGIS gene, and the interaction of PTGIS gene related proteins was analysed by STRING and GO and KEGG analysis. The results showed that PTGIS gene-related proteins were mainly enriched for the main biological processes involved in Cholesterol biosynthetic process, B cell chemotaxis, Mineralocorticoid biosynthetic process and Cyclooxygenase Arachidonic acid metabolism.

Conclusion

The PTGIS gene is lowly expressed in colon adenocarcinoma and its expression level correlates with survival prognosis. The PTGIS gene may provide a reference for the treatment of colon adenocarcinoma, providing a bioinformatic guide for later laboratory experiments.

Acknowledgments

Nil.

Conflicts of interest

Nil.

Ethical approval

Study that does not require an ethics committee.

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