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Correlation analysis of PBX family with immune invasion and drug sensitivity in colon adenocarcinoma

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ABSTRACT

Objedtive: Pre-B cell leukemia (PBX) has been found to be associated with cancer, but poorly studied with colon adenocarcinoma (COAD). In this study, the correlation between PBX family and COAD pathogenesis and immune cytokine infiltration was further explored by analyzing online tumor databases, in order to find new biomarkers for the diagnosis of COAD.
Methods: The online database was used to analyze gene differential expression, methylation level, gene mutation rate, immune infiltration difference, drug sensitivity, and so on.
Results: PBX1 and PBX3 decreased in COAD. PBX2 and PBX4 increased. The expression of PBX1 and PBX2 in different clinical stages was different. PBX4 was valuable for the prognosis of COAD. PBX family has correlation between COAD and immune infiltration. PBX2 was correlated with different pathological stages. PBX3 had the highest gene mutation rate, followed by PBX1, PBX2 and PBX4. PBX1, PBX2 and PBX4 were correlated with the sensitivity of multiple drugs.
Conclusion: The PBX family is differentially expressed in COAD and has a genetic mutation, and its protein network is closely related to the HOX family and is associated with immune infiltration of COAD.

1. Introduction

Colorectal cancer is recognized as one of the malignant tumors with high incidence rate, and its mortality is also high, which has attracted extensive attention [1]. Colon adenocarcinoma (COAD) is the main type of colorectal cancer and can be difficult to diagnose early. COAD is often found to be in the middle and late stages, missing the optimal treatment period, and surgery does not improve survival [2]. Therefore, early diagnosis of COAD is very important. At present, it is considered that COAD often forms malignant tumors due to changes in tumor microenvironment and gene mutations [3]. If COAD-targeting markers can be found, it will help improve the survival rate of patients and become a hot spot and demand for COAD treatment in the future. Pre-B cell leukemia (PBX) family is a group of transcription factors with four members [4]. Since abnormal expression of PBX is associated with multiple diseases, including cancer, it is considered a biomarker available [5]. The study found that PBX1 was upregulated in breast cancer and was considered an important biomarker and prognostic factor [6]. PBX1 is also involved in mechanistic regulation of cervical cancer [7], while PBX3 is considered a biological marker for prostate cancer [8]. The expression of PBX2 in gastric cancer is increased, and the invasion of gastric cancer cells can be reduced by inhibiting PBX2 [9]. It can be seen that there is a correlation between PBX family and cancer, but there are few studies on PBX family and COAD, and the mechanism is unclear. In this study, we will use the online public database to further study the correlation between PBX family and COAD through analysis, and explore the correlation between PBX

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family and immune cell infiltration in COAD patients, so as to clarify the possibility of PBX family as COAD biomarkers.

2. Materials and methods

2.1. Ethics statement

This study is a biological information analysis. The databases used are all online. The databases are public databases, which have passed the informed consent of patients and meet the ethical requirements. In this statistical analysis, the node of statistical difference is 0.05.

2.2. TIMER database

TIMER (https://cistrome.shinyapps.io/timer/) uses the data of TCGA database for analysis, which can analyze the gene differential expression, immune cell infiltration and survival of different tumors. TIMER is an online database, in which the correlation analysis of immune cells mainly includes six types of immune cells. We search the database for PBX families and needed immune cells, and with systematic analysis, scatterplots will appear to represent the relationship between infiltration estimates and gene expression.

2.3. UALCAN database

Ualcan database is analyzed based on TCGA database. It can easily and quickly obtain tumor related data, conduct gene level analysis, survival analysis, and further verify biological indicators. In this database (http://ualcan.path.uab.edu), after we enter the gene of interest, we can statistically analyze the different expression levels of the relevant cancer in this data and perform further survival analysis.

2.4. GEPIA database

GEPIA database is an online database. Its functions include differential gene expression analysis, survival analysis, dimensionality reduction analysis, co-expression gene analysis and transcription analysis. The database is located at http://gepia.cancer-pku.cn/. By searching for the target gene, you can obtain gene expression differences in different tumor types, gene expression differences at different clinical stages, etc. through this website analysis. At the same time, we can also obtain survival analysis maps.

2.5. STRING database

STRING database can be used for protein-protein interaction analysis with powerful functions. Through database analysis, the

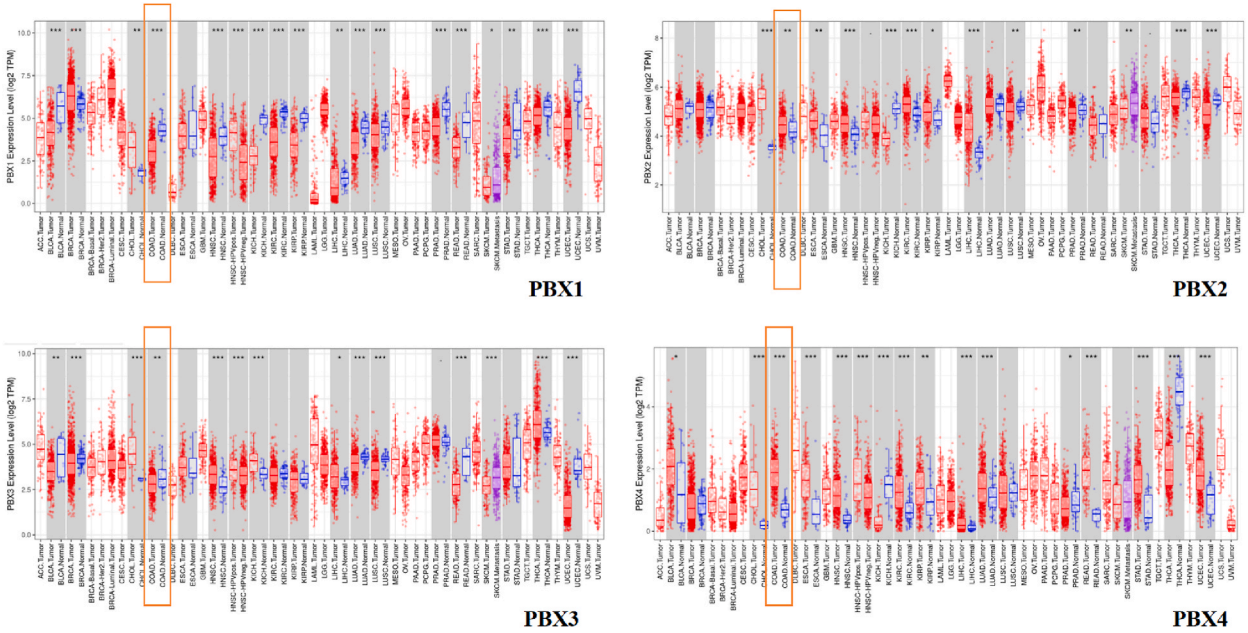


Fig. 1. Differential expression of PBX family in various cancers and COAD. PBX1 and PBX3 decreased significantly in COAD ($p < 0.05$). PBX2 and PBX4 in COAD significantly increased ($p < 0.05$). P: $0 \leq$ *** $< 0.001 \leq$ ** $< 0.01 \leq$ * $< 0.05 \leq$. < 0.1.

protein network related to this protein can be obtained. At the same time, it can provide sequence information and structure information of protein. The database is located at http://string-db.org. This database enables the acquisition of protein networks that are closely related to the target gene.

2.6. GSCA database

GSCA database integrates the contents of TCGA database on immune infiltration, gene expression, methylation and gene mutation, and can also conduct gene related drug sensitivity analysis. The database is located at http://bioinfo.life.hust.edu.cn/web/GSCALite/. By searching for target genes, we are able to obtain PBX-related drug susceptibility analysis.

3. Results

3.1. Differential expression of PBX family in tumor tissues

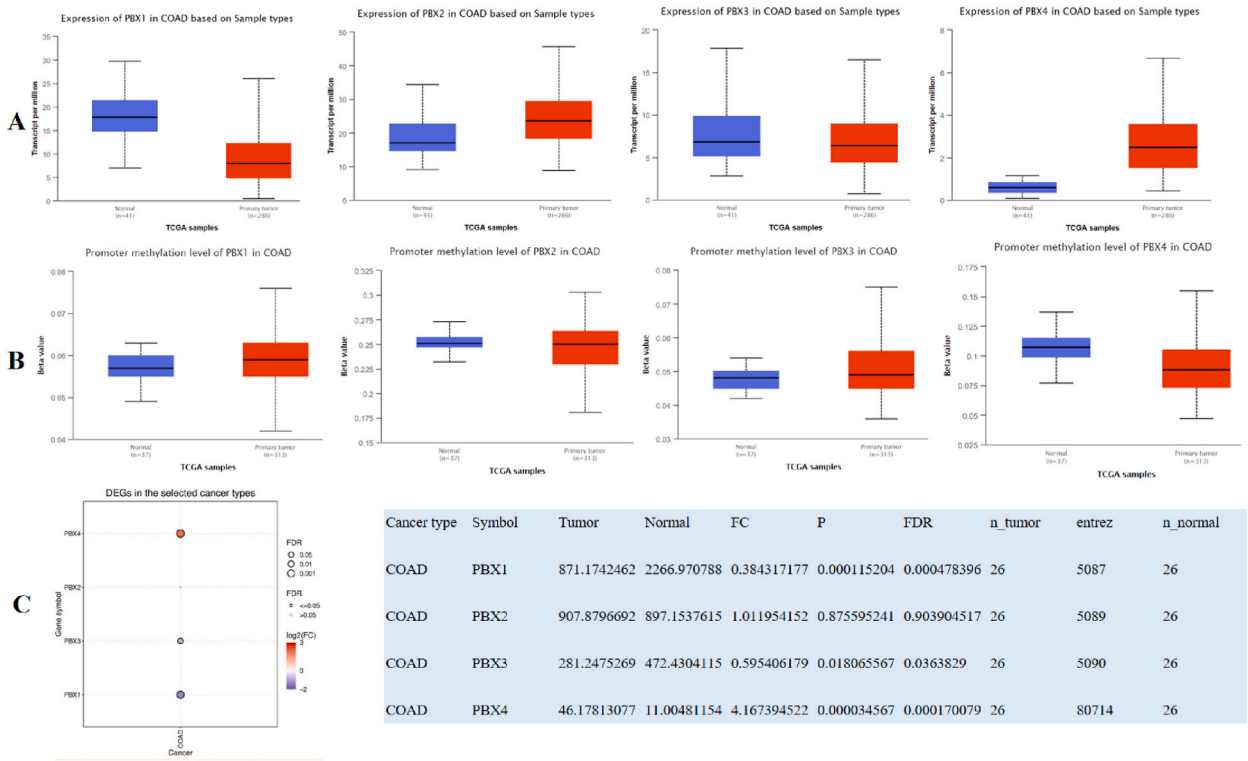
PBX1-4 expression was analyzed and Fig. 1 showed that PBX family has differential expression in various cancers. The red box showed the differential expression of PBX family in COAD. From the results, we found that the expression of PBX1 and PBX3 decreased significantly in COAD ($p < 0.05$). The expression of PBX2 and PBX4 in COAD significantly increased ($p < 0.05$).

3.2. Differential expression and methylation level of PBX family in COAD

TCGA database was used to analyze the expression and methylation correlation. Compared between normal tissues ($n = 41$) and COAD tissues ($n = 286$), the expression of PBX1 and PBX3 decreased in COAD ($p < 0.05$), and the expression of PBX2 and PBX4 increased in COAD ($p < 0.05$) (Fig. 2A). The methylation levels of PBX1 and PBX3 in COAD increased ($p < 0.05$), PBX4 decreased ($p < 0.05$) ($p > 0.05$) (Fig. 2B). We further analyzed 26 cases of COAD tissues and 26 cases of normal tissues. Fig. 2C showed that PBX1, PBX3 and PBX4 had significant differences in COAD.

3.3. Expression of PBX family in different clinical stages of COAD and survival analysis

We analyzed the online database and found that there were significant differences in the expression of PBX1 and PBX2 in different



Cancer type	Symbol	Tumor	Normal	FC	P	FDR	n_tumor	entrez	n_normal
COAD	PBX1	871.1742462	2266.970788	0.384317177	0.000115204	0.000478396	26	5087	26
COAD	PBX2	907.8796692	897.1537615	1.011954152	0.875595241	0.903904517	26	5089	26
COAD	PBX3	281.2475269	472.4304115	0.595406179	0.018065567	0.0363829	26	5090	26
COAD	PBX4	46.17813077	11.00481154	4.167394522	0.000034567	0.000170079	26	80714	26

Fig. 2. Expression correlation and methylation level of PBX family in COAD. A: Differential expression of PBX family in COAD; B: Methylation level of PBX family in COAD; C: Expression correlation of PBX family in COAD (Red represents positive correlation and blue represents negative correlation. The darker the color, the stronger the correlation. Black circles represent statistical differences).

clinical stages of COAD ($p < 0.05$). The results of survival analysis showed that PBX4 was valuable for the prognosis of COAD (Fig. 3).

3.4. Correlation between PBX family and immune cell infiltration in COAD

We analyzed the level of infiltration of six immune cells (B cells, $CD4^+$ T cells, Neutrphils, $CD8^+$ T cells, Dendritic cells and Macrophages) (Fig. 4). In COAD, PBX1 was connected with the level of cell infiltration: $CD4^+$ T cells (R = 0.496, P = 2.25e-26), Dendritic cells (R = 0.202, P = 4.53e-05), B cells (R = 0.154, P = 1.92e-03) and Macrophages (R = 0.365, P = 3.32e-14). PBX2 was connected with the level of cell infiltration: Neutrphils (R = 0.166, P = 8.46e-04), $CD4^+$ T cells (R = 0.5, P = 8.55e-27), Dendritic cells (R = 0.231, P = 3.00e-06), $CD8^+$ T cells (R = 0.148, P = 2.82e-03) and Macrophages (R = 0.27, P = 3.64e-08). PBX3 was connected with the level of cell infiltration: Neutrphils (R = 0.446, P = 5.67e-21), $CD4^+$ T cells (R = 0.426, P = 4.07e-19), Dendritic cells (R = 0.448, P = 2.74e-21), B cells (R = 0.157, P = 1.52e-03), $CD8^+$ T cells (R = 0.308, P = 2.34e-10) and Macrophages (R = 0.606, P = 6.22e-42). PBX4 was connected with the level of cell infiltration: $CD8^+$ T cells (R = −0.178, P = 3.14e-04) and Macrophages (R = −0.207, P = 2.67e-05).

3.5. Evaluation of PBX family related immune infiltration level in COAD

In order to better understand the degree of immune infiltration, we conducted a more in-depth analysis. Analysis from the degree of infiltration (Fig. 5A), it was showed that PBX1 could significantly affect the infiltration of immune cells (Dendritic cells, B cells and $CD8^+$ T cells). PBX2 could significantly affect the infiltration of immune cells (B cells, $CD8^+$ T cells and $CD4^+$ T cells). PBX3 could significantly affect the infiltration of immune cells ($CD4^+$ T cells). PBX4 could significantly affect the infiltration of immune cells (Dendritic cells, B cells and $CD8^+$ T cells). From the correlation analysis of immune infiltration, we expanded the scope of immune cell analysis (Fig. 5B). The infiltration score of PBX3 was significantly higher than that of the other three. In addition to the six types of immune cells previously analyzed, PBX family was also associated with other immune cells in COAD.

3.6. Correlation between PBX family and different pathological stages of COAD and its protein network

The different pathological stages of COAD was analyzed and showed that only PBX2 was correlated with different pathological stages of COAD. From the expression trend, the expression of PBX2 increased with the increase of pathological stage. Protein related network analysis showed that PBX family and HOXA family were closely related (Fig. 6).

3.7. Gene mutations and mutation sites of PBX family in COAD

Gene mutation analysis showed that in COAD, PBX3 had the highest single nucleotide variation frequency of 8%, followed by PBX1 (6%), PBX2 (4%), PBX4 (3%) (Fig. 7A). In COAD, PBX3 had the highest gene mutation rate of 42%, followed by PBX1 (32%), PBX2 (21%) and PBX4 (16%) (Fig. 7B). Fig. 7C showed the mutation sites of PBX family genes.

3.8. Correlation between PBX family expression and the sensitivity of GDSC drugs (top 30) in COAD

Drug sensitivity was analyzed and the top 30 drugs of the tumor drug sensitivity multiomics database (GDSC) were mainly

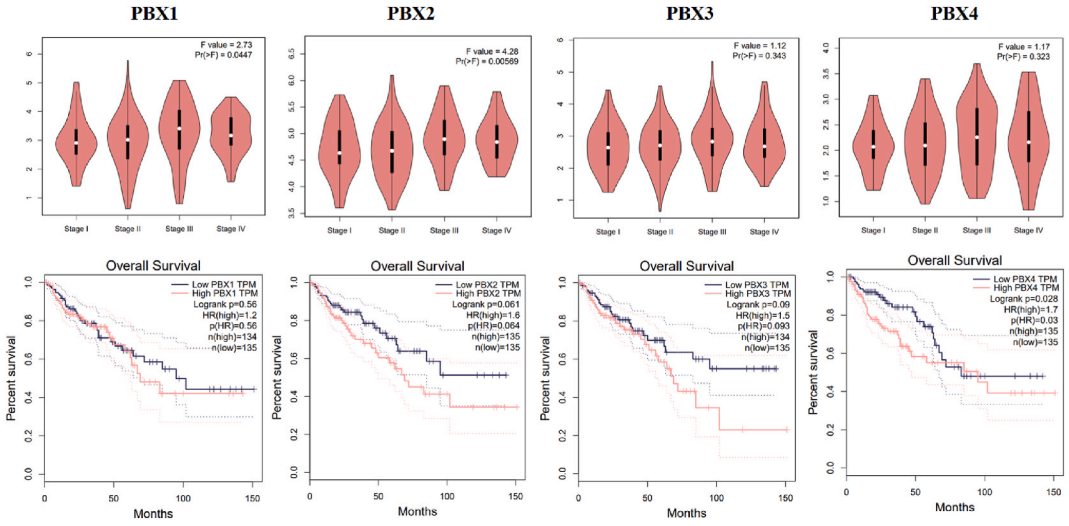


Fig. 3. Expression of PBX family in different clinical stages of COAD and survival analysis. PBX4 was valuable for the prognosis of COAD.

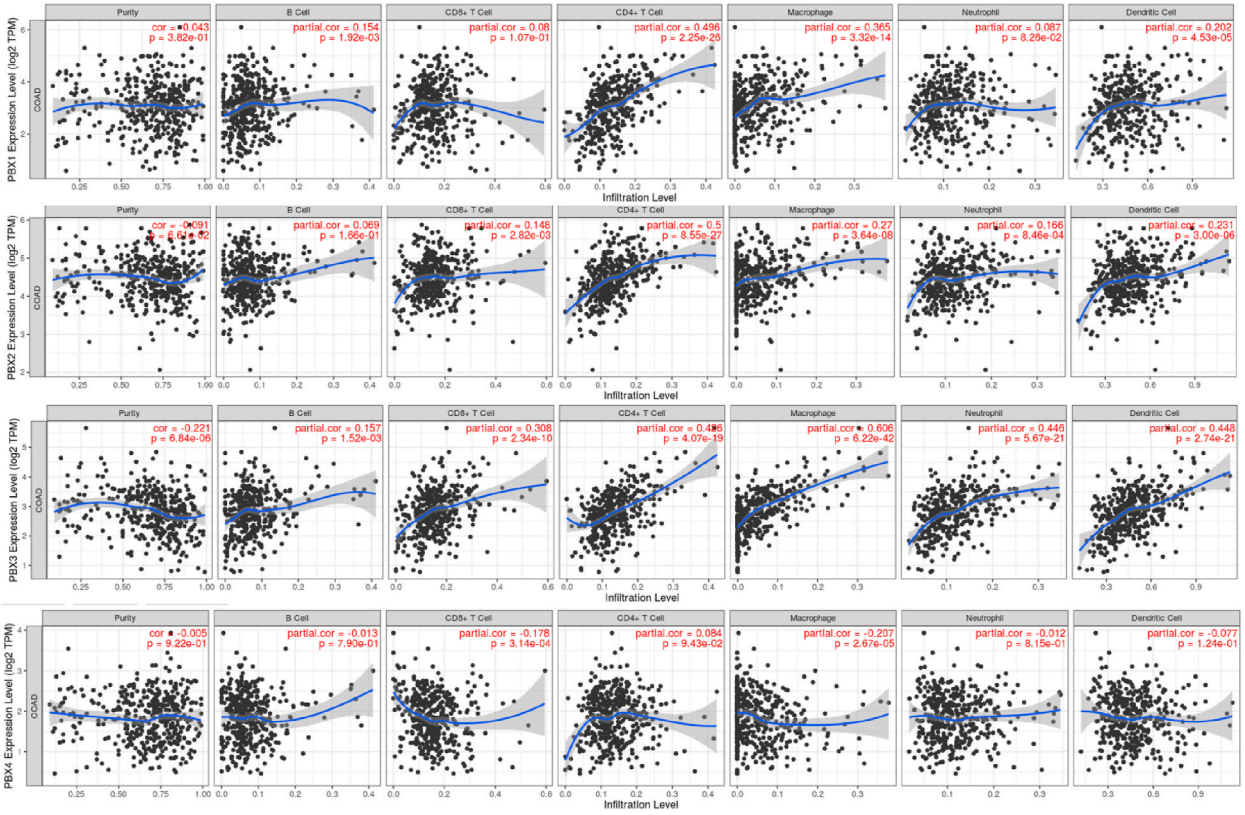


Fig. 4. Correlation between PBX family and immune cell infiltration in COAD. PBX1 was connected with the level of cell infiltration: $CD4^+$ T cells (R = 0.496, P = 2.25e-26), Dendritic cells (R = 0.202, P = 4.53e-05), B cells (R = 0.154, P = 1.92e-03) and Macrophages (R = 0.365, P = 3.32e-14). PBX2 was connected with the level of cell infiltration: Neutrphils (R = 0.166, P = 8.46e-04), $CD4^+$ T cells (R = 0.5, P = 8.55e-27), Dendritic cells (R = 0.231, P = 3.00e-06), $CD8^+$ T cells (R = 0.148, P = 2.82e-03) and Macrophages (R = 0.27, P = 3.64e-08). PBX3 was connected with the level of cell infiltration: Neutrphils (R = 0.446, P = 5.67e-21), $CD4^+$ T cells (R = 0.426, P = 4.07e-19), Dendritic cells (R = 0.448, P = 2.74e-21), B cells (R = 0.157, P = 1.52e-03), $CD8^+$ T cells (R = 0.308, P = 2.34e-10) and Macrophages (R = 0.606, P = 6.22e-42). PBX4 was connected with the level of cell infiltration: $CD8^+$ T cells (R = −0.178, P = 3.14e-04) and Macrophages (R = −0.207, P = 2.67e-05).

included. Bubble plot showed the relationship between PBX family expression and drug sensitivity. The color of bubbles represented the correlation between PBX expression and IC50. Studies showed that PBX1, PBX2 and PBX4 were correlated with the sensitivity of multiple drugs (Fig. 8).

4. Discussion

Colon cancer is one of the most common cancers in the world, especially in the late stage, it is prone to the problem of chemotherapy resistance, and the recurrence rate is high [10]. COAD is a common pathological type of colon cancer and a common digestive tract tumor, and it not only poses a great threat to the lives of patients, but also causes a huge economic burden to society and families [11]. After distant metastasis of COAD, the mortality of patients will increase significantly [12]. At this stage, no biological markers of significant value for the treatment and prognosis of COAD have been found. Therefore, the search for targeted genes has become the focus of clinical and basic research of COAD.

The PBX family currently studied has four members (PBX1-4). Our study found that PBX family was differentially expressed in a variety of cancers, and the differential expression of PBX1-4 was more obvious in COAD. In the same group of COAD, the expression of PBX4 was the highest, while PBX1 was the lowest. At the same time, we also analyzed the methylation level. Except for PBX2, other family members were differentially expressed. These expression differences indicate that PBX has different potential functions in different cancers, and different PBX members have different potential functions in COAD. Recent studies have found a strong relationship between PBX4 and colorectal cancer cell cycle and cell proliferation [13]. Recent studies have pointed out that PBX3 is involved in the occurrence and development of gastric cancer and colorectal cancer [14]. PBX3 is considered to be related to lymph node invasion and distant metastasis of colorectal cancer, and can activate the mechanism of invasion and metastasis of colorectal cancer through the regulation of PBX3 [15]. However, our analysis showed that the expression of PBX3 was decreased in COAD, which seemed to contradict the results of the literature. It was considered that the analysis object we selected was simple COAD, and the sample size was limited. From the abnormal expression of PBX family and the change of methylation level, we can determine the

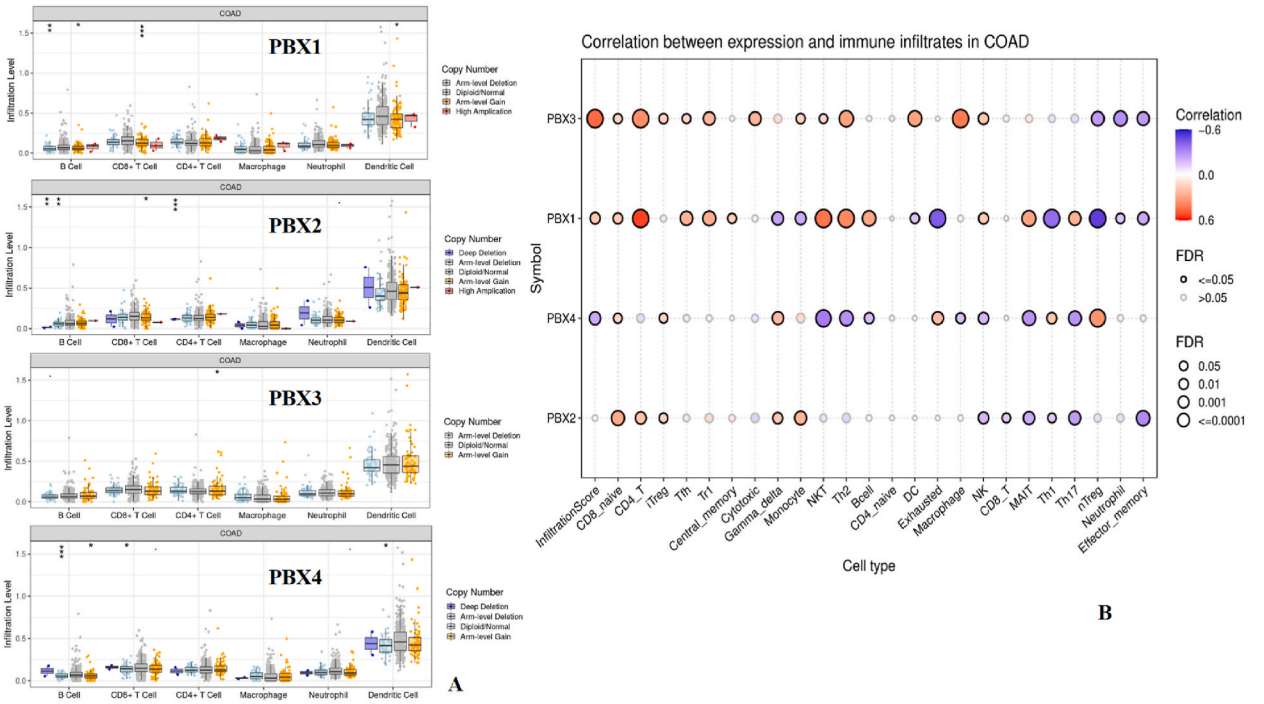


Fig. 5. Correlation between expression and immune infiltration in COAD. A: Infiltration level connected with PBX family in COAD. B: Correlation between expression and immune infiltration (Black circles represent statistically significant. Red represents positive correlation and blue represents negative correlation. The darker the color, the stronger the correlation).

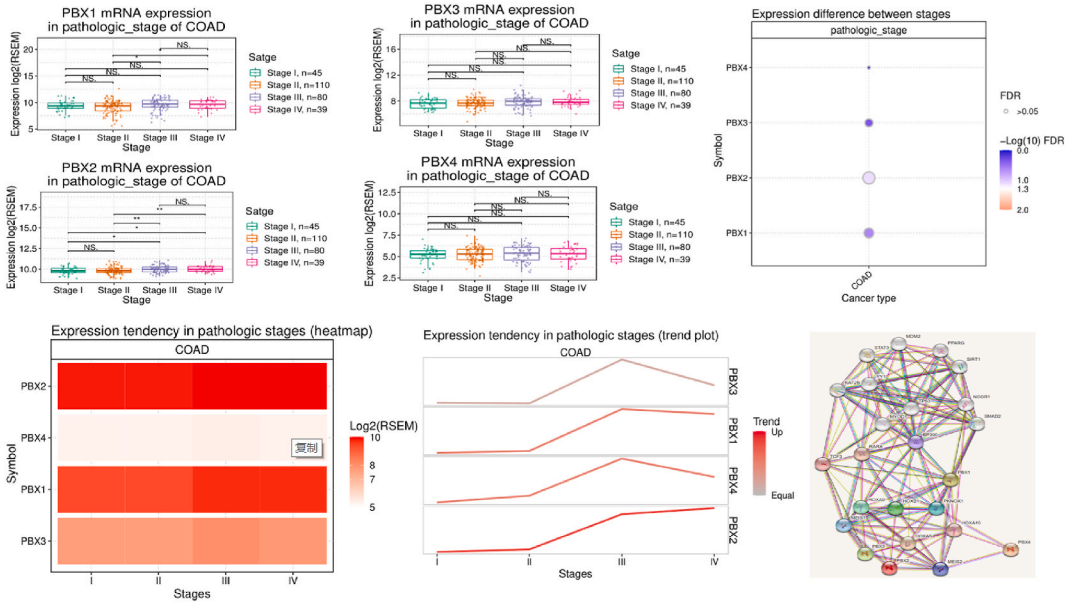


Fig. 6. Correlation between PBX family and different pathological stages of COAD and protein PBX2 was correlated with different pathological stages of COAD. From the expression trend, the expression of PBX2 increased with the increase of pathological stage. PBX family and HOXA family were closely related.

mechanism of PBX participating in the occurrence and development of COAD.

In the analysis of protein interaction network, it was found that the mechanism network of PBX was most closely related to HOX protein, followed by MEIS. Scholars have pointed out that PBX is a cofactor of HOX, and HOX/PBX dimer is also considered a potential therapeutic target for malignant tumors [16]. Some scholars have also proposed that HOX/PBX dimer is related to the mechanism of

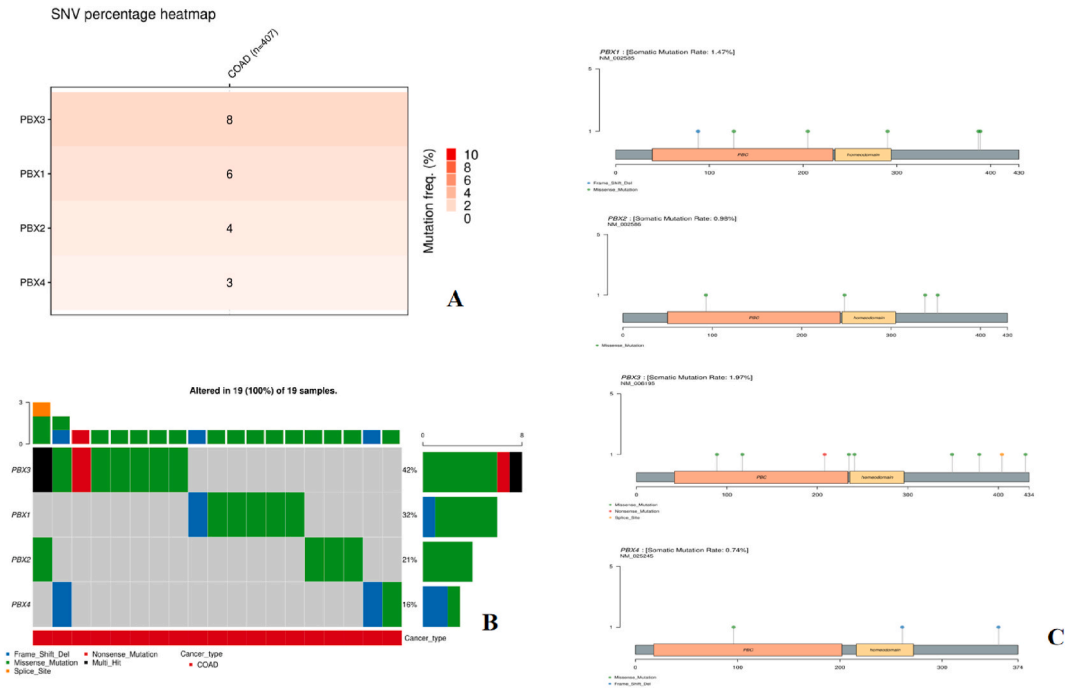


Fig. 7. Gene mutations and mutation sites of PBX family in COAD. A: Single nucleotide variation frequency of PBX family; B: Gene mutation rate of PBX family; C: Mutation sites of PBX family.

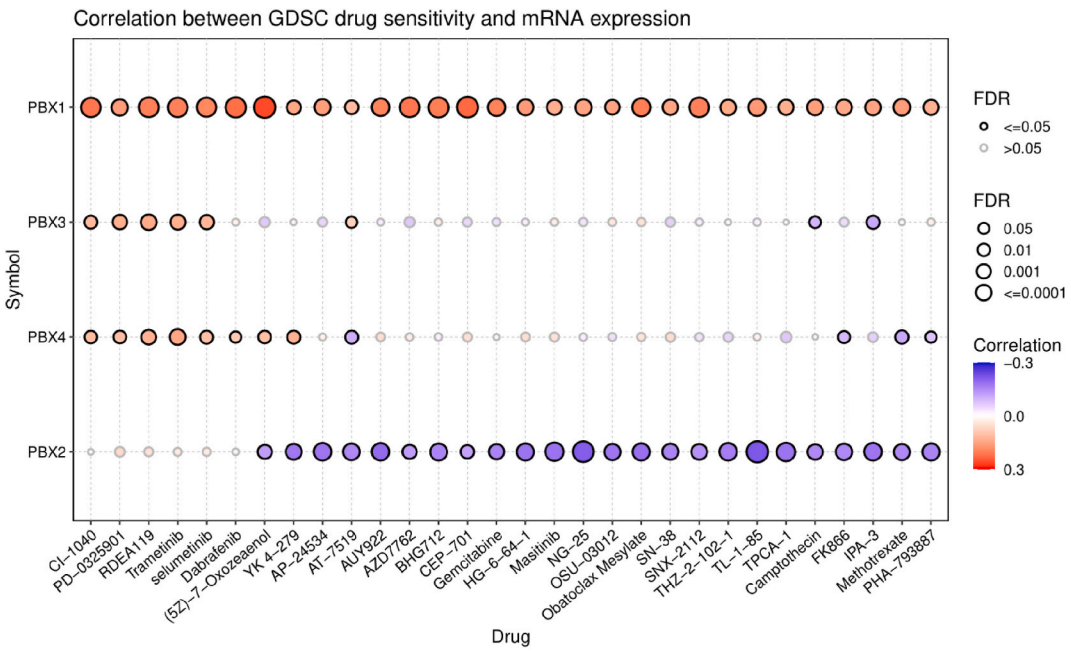


Fig. 8. Correlation between PBX family expression and the sensitivity of GDSC drugs (top 30) in COAD. Bubble size is positively correlated with FDR significance, and the starting point of black contour coil indicates FDR < 0.05.

apoptosis in tumor cells [17]. The PBX-HOX protein can act as an oncogene or tumor suppressor in the microenvironment of different tumors [18]. Based on the fact that various types of tumors are not simply regulated by a single gene, and some genes are relatively conserved, it is impossible to achieve tumor cell inhibition by simply regulating a single gene, and it is often necessary to achieve regulation through the relevant associated gene network. Therefore, according to the relevant literature and PBX protein network mechanism, we believe that HOX/PBX dimer may also be a potential target for regulating the inhibition of colon adenocarcinoma cells.

Scholars have proposed that studying the gene modules of different stages of COAD can help to understand the progression of colon cancer and find prognostic markers [19]. Therefore, after understanding the differential expression, methylation level and related proteins of PBX in COAD, we analyzed the role of PBX family in different clinical and pathological stages of COAD, and performed survival analysis. The results of this study showed that PBX1 and PBX2 were associated with different clinical stages of COAD, PBX2 may be associated with different pathological stages, and PBX4 was associated with survival and prognosis of COAD. The PBX family is thought to be associated with clinical staging and is important for prognosis [20]. This result is consistent with our findings and further demonstrates that PBX can be an effective gene to guide the clinical practice of COAD.

The tumor microenvironment is a hot spot in current research. Studies have found that the tumor microenvironment can activate humoral immunity, secrete inflammatory factors and recognize antigens, and interact with other immune cells [21], which is thought to be related to the balance of tumor cells and the invasion and growth of tumor cells [22]. Some researchers have also proposed that dendritic cells can exert antitumor effects by activating $CD8^+$ T cells [23]. This suggests that tumors are immune-related, and recent studies have shown that patients with COAD are characterized by abnormal immune system function [24]. Therefore, we also conducted the analysis of immune cell infiltration, and found that there was a significant correlation between the PBX family and immune cell infiltration in COAD, which once again suggested the importance of immunity in COAD. Immune cell infiltration has been shown to inform the prognosis of colon cancer [25]. The behavior of tumor cells changes with the degree of immune cell infiltration [26]. Immunoinfiltration with a good prognosis is characterized by high levels of plasma cells, mast cells, and dendritic cells, and low levels of $CD4^+$ T cells and macrophages [27]. Combined with the results and related literature, given the infiltration relationship between the PBX family and related immune cells, we can infer that the PBX family may change the degree of immune invasion by regulating the signaling pathways associated with the PBX family, thereby improving the tumor microenvironment and becoming an important target for COAD therapy.

As mentioned earlier, colon cancer has a higher mortality rate and a poor prognosis, in which chemotherapy drug sensitivity has become one of the important factors determining prognosis. Researchers believe that the chemosensitivity of colon cancer is related to many factors, including genetic factors and the nature of the cancer [28]. To this end, we further used the database to analyze the susceptibility of chemotherapy drugs and found that PBX1, PBX2 and PBX4 were associated with the sensitivity of multiple drugs. At the same time, studies have confirmed that chemotherapy resistance is the main cause of poor prognosis in colon cancer patients, and have pointed out that the sensitivity of colon cancer cells to certain chemotherapy drugs should be regulated by CerS5, and the mechanism is also related to autophagy and decreased mitochondrial respiration [29]. PBX is thought to be associated with esophageal cancer chemotherapy drug sensitivity [30], but whether PBX is associated with COAD chemotherapy drug susceptibility has not been reported. It can be seen that genes are closely related to the sensitivity of chemotherapy drugs. Our results suggest that PBX may affect the drug sensitivity of COAD chemotherapy, and by adjusting PBX, it may be able to change the drug treatment effect and become an effective adjuvant therapeutic target for COAD. However, the mutational burden of tumor-associated genes is an independent factor in assessing the efficacy of immunotherapy [31]. The researchers compared colon adenomas with colon cancer and found that no genetic mutations occurred in colon adenomas [32], whereas PBX was present in our study COAD. Therefore, we speculate that the gene mutation rate of the PBX family in COAD indicates that PBX may be an important target for the invasion and progression of COAD tumor cells, which needs to be confirmed by further studies. Our results obtained more information about the correlation between PBX family and COAD, suggesting that PBX family may be the key biomarker of COAD. However, there are still some limitations in our study: (1) Our study used an online database, and the sample size could not be controlled; (2) The number between the control group and the tumor group could not reach a good match; (3) The mechanism was not verified by basic research and clinical research. In view of the limitations of this study, further research is needed to further confirm the important role of PBX family as a biomarker in COAD.

5. Conclusion

The PBX family is differentially expressed in COAD and has a genetic mutation whose protein network is closely related to the HOX family. The PBX family is associated with immune infiltration of COAD. PBX1, PBX2 and PBX4 are correlated with the sensitivity of multiple drugs. Therefore, it is inferred that the PBX family may be a key biomarker of COAD and an important target for exploring COAD therapy.

Author contribution statement

Guanqun Chao Conceived and designed the experiments; Guanqun Chao and Lan Zhang analyzed and interpreted the data; Guanqun Chao wrote the paper.

Data availability statement

Data will be made available on request.

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.

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