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PRECLINICAL STUDIES

A comprehensive analysis of different gene classes in pancreatic cancer: SIGLEC15 may be a promising immunotherapeutic target

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Summary

Background. Pancreatic cancer (PC) is one of the most lethal cancer types with an extremely poor diagnosis and prognosis. This study aimed to comprehensively analyze the relationships between PC and different gene classes. *Methods*. Numerous genes from different categories were selected from the UALCAN database. Expression and survival analysis of these genes were performed via GEPIA, starBase and Kaplan–Meier Plotter tools. The correlations between PC-related genes and frequently mutated genes in PC as well as myeloid-derived suppressor cells (MDSCs) infiltration levels were explored by TIMER tool. The associations between PC-related genes, immune checkpoints and 182 core cancer-intrinsic CTLs-evasion genes were analyzed by R software. Besides, KEGG analysis were performed for the PC-related genes. *Results*. 14 genes were identified to be highly expressed in pancreatic cancer and significantly associated with poor prognosis. Besides, high expression of these genes were observed in patients with KRAS or TP53 mutations. Most genes were significantly positively associated with immune checkpoint SIGLEC15, however, showed negative relations to PDCD1, CTLA4, LAG3, TIGIT, PDCD1LG2. In addition, all 14 genes exhibited close relationships with MDSC infiltration levels and various core cancer-intrinsic CTLs-evasion genes, especially DNTTIP1, FADD, ARF6, BCL2L1, CEP55, GALE, PDCD6IP, and RCE1. We also explored the most related pathways with these genes to further reveal the pathogenesis and metastatic mechanisms of PC. *Conclusion*. Our study analyzed the relationships between 14 PC-related genes and pancreatic cancer from different angles, which may contribute to a better understanding of unsolved mystery in PC.

Keywords Pancreatic cancer · Expression · Prognosis · SIGLEC15 · Immune escape

Introduction

The incidence of pancreatic cancer (PC) has largely increased over the past few years, especially in developed countries [1, 2]. Pancreatic cancer is one of the most lethal cancers and notorious for its extremely poor prognosis [1]. As of 2020, pancreatic cancer has become the seventh cause of cancer-related death with a 5-year survival rate of approximately 8% [3]. Ductal adenocarcinoma is the most common histological type among pancreatic cancers, accounting for more than 90% of all patients [4]. Early diagnosis and treatment of pancreatic cancer is still difficult, a deeper understanding of the invasive and metastatic mechanisms of pancreatic cancer is urgently in need. Although various previous studies have revealed multiple pathophysiological mechanisms underlying pancreatic cancer pathogenesis, the biology of pancreatic cancer remains unknown [5, 6]. The growth and metastasis of tumors are pretty complex and influenced by a wide variety of factors. For example, dysregulation of kinases and phosphatases activity is common in many diseases including cancer. Various cancer signaling pathways that regulate cell growth, differentiation, proliferation, and metastasis are mediated by the synergistic action of kinases and phosphatases, which are often destroyed or dysregulated in cancer [7, 8]. Besides, the p53 pathway, as a typical tumor inhibitor, is able to prevent eukaryotic cells from DNA damage or deficient oxygenation [9]. The function of the p53 pathway alters in most human cancers due to mutations in the p53 gene itself or other genes in

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this pathway [10]. The Hedgehog signaling pathway also controls cell proliferation and differentiation, and previous studies have reported that the aberrant activation of Hedgehog signaling pathway is a potential mediator of pancreatic carcinogenesis and growth [11, 12]. Proteases, which are mainly classified into secreted proteases and intracellular proteases, have been demonstrated to be involved in many processes of cancer progression from initiation to metastasis [13, 14]. In addition, the abnormal of ubiquitin ligase (E3s) has been proved to be significantly correlated with various cancers, such as breast cancer, colon cancer, prostate cancer, etc. [15]. The activity of ubiquitin ligases regulates lots of cellular processes including homeostasis, metabolism, and cell cycle progression [16–18]. In some cases, the stability and activity of ubiquitin ligase substrates altered leading to the downregulation of tumor suppressor and upregulation of oncogenic activities [19]. Integrins are transmembrane receptors consisting of two subunits, called α and β, which seem to play a critical role in cancer biology. Increasing studies have indicated that the composition of integrins is altered in the tumor microenvironment [20, 21].

Our study aimed to explore the relationships between different gene classes and the prognosis of pancreatic cancer. We attempted to identify the pathogenesis of pancreatic cancer from diverse perspectives and find potential interconnections among them. Additionally, it is well-known that KRAS, TP53, CDKN2A, and SMAD4 mutations have been identified in pancreatic cancer. Thus, we analyzed the gene differential expression levels in patients with mutations and without mutations. Meanwhile, the relationships between gene expression levels and common immune checkpoints including SIGLEC15, IDO1, CD274, HAVCR2, PDCD1, CTLA4, LAG3, and PDCD1LG2 were analyzed. Besides, we also explored the association between genes and 182 core cancer-intrinsic CTLs-evasion genes as well as immune suppressive cells. Meanwhile, the correlations between genes and signaling pathways deserve further investigation. We hope our research can provide more novel strategies for the treatment of pancreatic cancer.

Materials and methods

Data acquisition

UALCAN is an online tool for facilitating tumor subgroup gene expression and survival analysis (http://ualcan.path.uab.edu/) [22]. Genes with diverse biological functions were selected from the UALCAN database. Besides, the genes were mainly divided into 25 classes, which are mainly kinase coding and related genes, cell cycle pathway and related genes, P53 signaling pathway and related genes, apoptosis pathway and related genes, hedgehog signaling pathway and related genes, metastasis associated genes, protease coding and related genes, circardian clock genes, tumor suppressors and related genes, oncogenes and related genes, DNA damage response genes, deubiquitinase coding and related genes, ubiquitin ligase coding and related genes, ubiquitin-conjugating enzyme coding genes, histone methyltransferase coding and related genes, histone deacetylases and related genes, histone acetyltransferases and related genes, histone demethylase coding and related genes, integrin coding and related genes, collagen synthesis and modifying enzymes, extracellular matrix protelglycans, immune regulatory genes, phosphatase coding and related genes, cell surface receptors and extracellular matrix components, and unfolded protein response genes. Only high expression of genes significantly correlated with the overall survival of PAAD patients can be collected.

Gene expression level and survival analysis

GEPIA is a web resource for gene expression profiling and interactive analysis between tumor and normal tissues (http://gepia.cancer-pku.cn/) [23]. We use it to analyze the expression levels of different gene categories between tumor and normal tissues. In addition, overall survival differences were also explored by GEPIA. To further ensure the accuracy of the conclusions, we utilized the starBase database (http://starbase.sysu.edu.cn/) [24] to validate our results. Pancreatic ductal adenocarcinoma (PDAC) is the most frequent and aggressive histological type of pancreatic cancer. Overall survival (OS) and corresponding hazard ratio (HR) with 95% confidence interval (CI) of different gene expressions in PDAC were evaluated by the Kaplan–Meier (K-M) Plotter (www.kmplot.com) [25].

Relationship between diverse gene types and KRAS, TP53, CDKN2A, and SMAD4 mutations in PC patients

Frequent mutations of KRAS, TP53, CDKN2A, and SMAD4 occur in pancreatic cancer and are correlated with poor prognosis [26]. KRAS mutations are observed in more than 90% of patients [27], while TP53 mutations are detected in up to 75% of pancreatic cancers, followed by CDKN2A and SMAD4 [28]. Differentially expressed genes were performed in patients with 4 gene mutations and without mutations via TIMER database [29]. Besides, interactions between diverse genes were identified by STRING database (http://string-db.org) [30].

The correlations between genes with different expression and immune checkpoints as well as infiltration of suppressive cells

Immune checkpoints are regulatory molecules of the immune system and take a crucial part in maintaining immune homeostasis and self-tolerance [31]. Upregulation of immune

checkpoint molecules is a strategy that tumors utilize to escape attack by host immune cells. CD274, CTLA4, HAVCR2, LAG3, PDCD1, PDCD1LG2, TIGIT, and SIGLEC15 were all immune-checkpoint-relevant transcripts and to explore the linkage between different gene classes and checkpoints may help identify wether patients will benefit from immune checkpoint inhibitors or not. All statistical analysis was conducted by the R software.

Myeloid-derived suppressor cells (MDSC), as immune-suppressive cells, were found to be significantly elevated in pancreatic cancer and become one of the obstacles that hinder immunotherapy responses [31]. We investigated the correlations between gene expression and MDSC infiltration levels in pancreatic cancer by TIMER tool. Besides, to further identify the function of these genes, KEGG pathway enrichment analysis was conducted.

The association between genes and 182 core cancer-intrinsic CTLs-evasion genes

Immune escape is one of the main causes for the progression of cancer and the poor therapeutic effect of immunotherapy. Multiple biological functions are performed by various genes and their counterpart proteins. Negative and positive correlations suggested synergistic or antagonistic relationships between the two gene proteins. 182 core cancer-intrinsic CTLs-evasion genes were selected from a study published in Nature in 2020 [32]. The relationships between cancer-intrinsic CTLs-evasion genes and cancer-related genes were determined via the R software package pheatmap.

Statistical analysis

Analysis of variance (ANOVA) was used to compare the expression levels of different genes between normal and tumor tissues. Survival curves were generated by the GEPIA and starBase database and differences between survival outcomes were evaluated using the Log-rank test. Heatmaps and statistical analysis were implemented by R foundation for statistical computing (2020) version 4.0.3 and the software packages ggplot2 and pheatmap. Spearman's correlation analysis was used to describe the correlation between quantitative variables without a normal distribution. P value < 0.05 was regarded as statistically significant.

Results

The mRNA expression levels of different gene classes and their impact on prognosis in PC patients

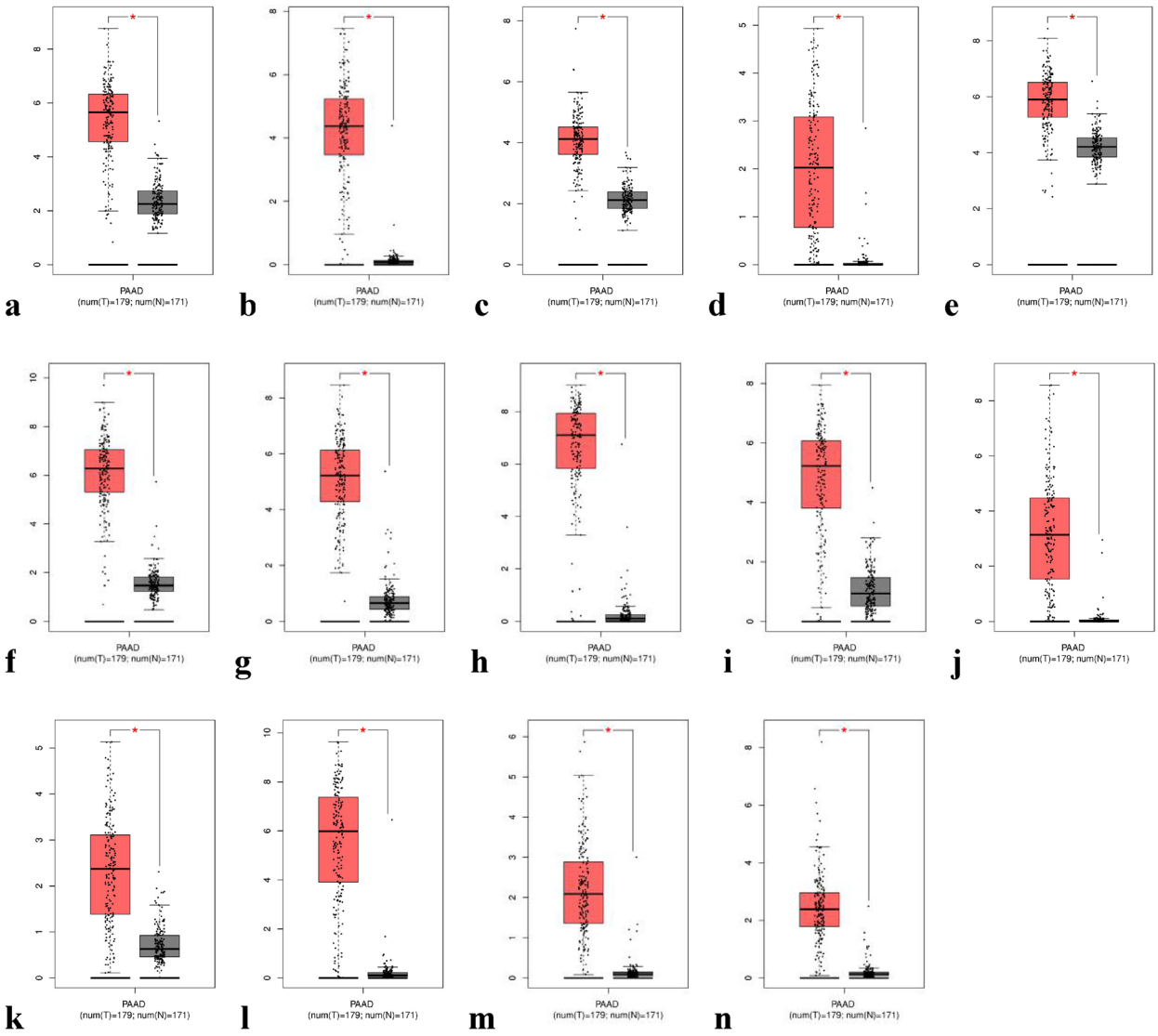
Numerous genes from 25 gene classes were listed in Supplementary Table 1. We analyzed these genes expression in pancreatic cancer via the GEPIA database. Only genes with significant differential expression were used for further survival analysis. EPHA2, PRKCI, SERPINB5, WNT7A, ITGA6, LAMA3, MMP28, TMPRSS4, FAM83D, MYEOV, FAM83A, RNF39, COL17A1, PTPRR were significantly highly expressed in pancreatic cancer patients and high expression of these genes were all associated with poor prognosis (Figs. 1 and 2). Meanwhile, similar results were obtained using the starBase database analysis. To further investigate whether 14 genes were correlated with the prognosis of PDAC patients, the survival time and hazard ratio of 171 PDAC patients with different gene expression levels were performed via K-M Plotter (Table 1). High levels of all genes were significantly related to the unfavorable prognosis of PDAC patients ($P < 0.05$). Among these genes, patients with high expression of LAMA3 indicated the worst prognosis, while low expression of MYEOV showed the longest overall survival with 67.87 months. In conclusion, high expression of LAMA3 (HR = 3.86, 95%CI: 2.09–7.11), MYEOV (HR = 3.24, 95%CI: 2.03–5.19), SERPINB5 (HR = 2.89, 95%CI: 1.79–4.65), WNT7A (HR = 2.72, 95%CI: 1.77–4.17), and FAM83A (HR = 2.58, 95%CI: 1.69–3.94) exhibited higher hazard ratio than other 10 genes.

Differential expression of 14 genes between patients with 4 gene mutations and without mutations

KRAS, TP53, CDKN2A, and SMAD4 are widely known to be frequently altered in pancreatic cancer and often predict poor prognosis. Following the analysis, high expressions of all 14 genes were observed in patients with KRAS and TP53 mutations (Fig. 3). The difference was especially striking among patients with KRAS mutation ($P < 0.001$). However, no significant differences were found in the expression of PTPRR, WNT7A, FAM83D between patients with CDKN2A mutation and without CDKN2A mutation. Besides, expression of PRKCI, SERPINB5, WNT7A, LAMA3, FAM83D, and FAM83A did not show notable differences between SMAD4-mutant patients and SMAD4-wild patients. Moreover, strong associations were found among LAMA3, ITGA6, and COL17A1. The highest correlation coefficient between LAMA3 and ITGA6 was 0.976, followed by LAMA3 and COL17A1 (cor = 0.970), ITGA6 and COL17A1 (cor = 0.966) (Table 2).

Associations between immune checkpoints and different kinds of gene classes

Immune checkpoints are a vital component of the immune system, which are often exploited by tumor cells to evade

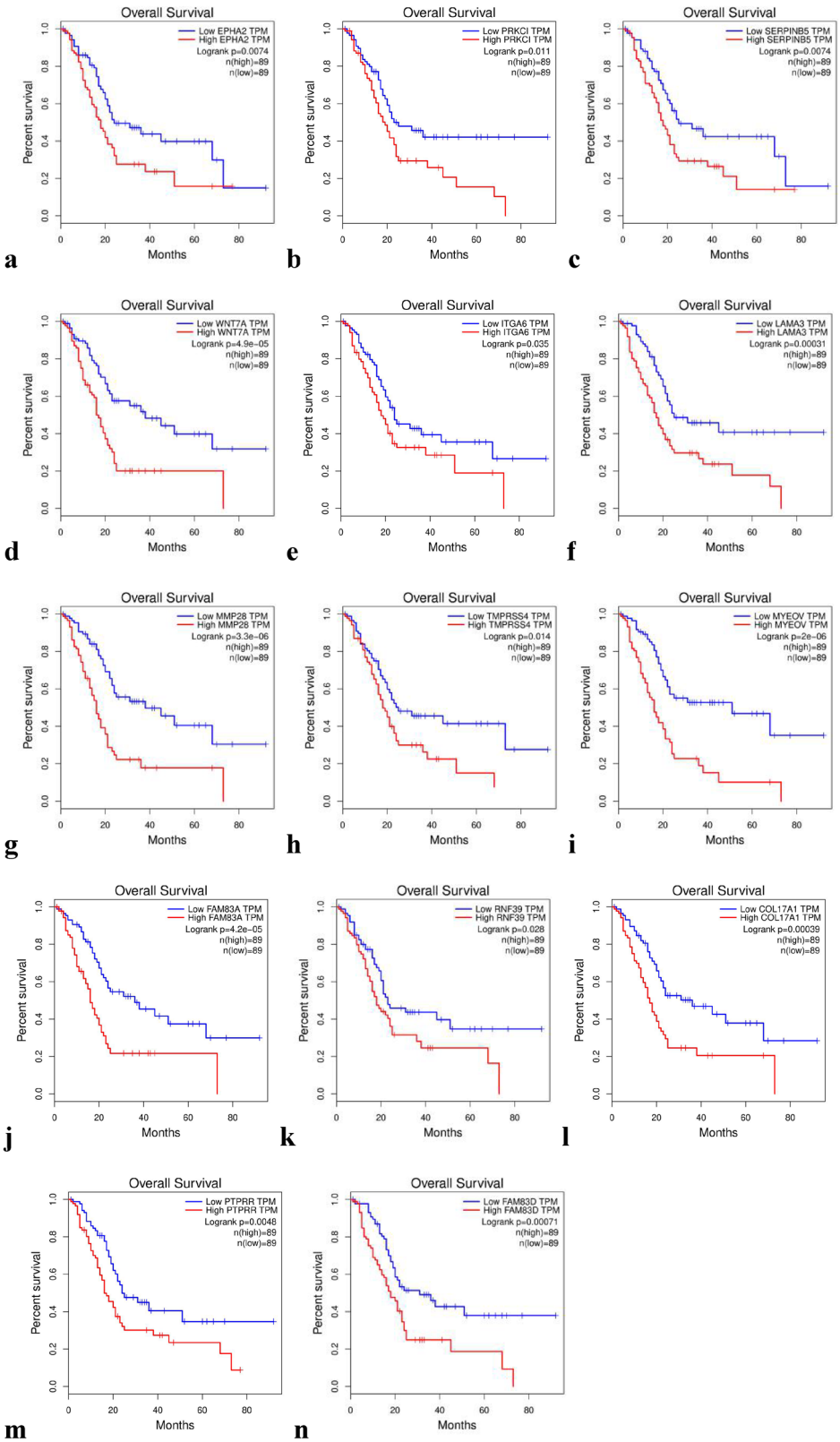


a: EPHA2; **b**: PRKCI; **c**: SERPINB5; **d**: WNT7A; **e**: ITGA6; **f**: LAMA3; **g**: MMP28; **h**: TMPRSS4; **i**: MYEOV; **j**: FAM83A; **k**: RNF39; **l**: COL17A1; **m**: PTPRR; **n**: FAM83D

Fig. 1 Differences in expression of different gene classes between pancreatic cancer tissues and paired adjacent normal tissues

antitumor immunity. CD274, CTLA4, HAVCR2, LAG3, PDCD1, PDCD1LG2, TIGIT, and SIGLEC15 are very common immune checkpoints and we evaluated the associations between different gene categories and these immune checkpoints (Supplementary Fig. 1). All genes all represented significant positive correlations with SIGLEC15 in pancreatic cancer patients except for PTPRR and FAM83A ($P < 0.05$). Meanwhile, PRKCI, ITGA6, and LAMA3 showed positive relevance with CD274 ($P < 0.05$). However, significant negative correlations were found between immune checkpoints including PDCD1, CTLA4, LAG3, TIGIT, PDCD1LG2, and many genes, such as EPHA2, SERPINB5, MMP28, TMPRSS4, MYEOV, RNF39, and COL17A1 ($P < 0.05$). Besides, no notable relationship was observed between any immune checkpoints and PTPRR or FAM83A ($P > 0.05$).

Meanwhile, the relations between the expression of 14 genes and the infiltration level of MDSC were also analyzed. The results indicated that all 14 genes were significantly positively associated with MDSC infiltration ($P < 0.05$) (Supplementary Fig. 2). Among them, SERPINB5 showed the highest association (cor = 0.498), followed by EPHA2 (cor = 0.489), FAM83D (cor = 0.485), TMPRSS4 (cor = 0.431), RNF39 (cor = 0.401), FAM83A (cor = 0.398), ITGA6 (cor = 0.393), MMP28 (cor = 0.385),



a: EPHA2; **b**: PRKCI; **c**: SERPINB5; **d**: WNT7A; **e**: ITGA6; **f**: LAMA3; **g**: MMP28; **h**: TMPRSS4; **i**: MYEOV; **j**: FAM83A; **k**: RNF39; **l**: COL17A1; **m**: PTPRR; **n**: FAM83D

Fig. 2 Comparison of survival times between the different expression level of differentially expressed genes

Table 1 The survival difference of different expression levels of 14 genes in pancreatic cancer

Genes	Low expression cohort (months)	High expression cohort (months)	HR (95% CI)	P value
EPHA2	35.30	17.27	2.04 (1.29–3.23)	0.002
PRKCI	35.30	16.20	2.17 (1.43–3.32)	P < .001
PTPRR	23.40	15.67	1.92 (1.27–2.90)	0.0016
SERPINB5	35.30	15.77	2.89 (1.79–4.65)	P < .001
WNT7A	37.67	15.67	2.72 (1.77–4.17)	P < .001
ITGA6	35.30	19.73	2.19 (1.22–3.95)	0.0074
LAMA3	20.23	9.77	3.86 (2.09–7.11)	P < .001
MMP28	37.67	15.57	2.60 (1.69–4.00)	P < .001
TMPRSS4	23.03	14.33	2.20 (1.42–3.42)	P < .001
FAM83D	23.40	15.67	2.31 (1.52–3.49)	P < .001
MYEOV	67.87	15.53	3.24 (2.03–5.19)	P < .001
FAM83A	35.30	15.57	2.58 (1.69–3.94)	P < .001
RNF39	22.80	15.67	1.83 (1.20–2.79)	0.0046
COL17A1	23.40	15.33	2.19 (1.44–3.33)	P < .001

MYEOV (cor = 0.385), COL17A1 (cor = 0.383), PRKCI (cor = 0.374), LAMA3 (cor = 0.349), and WNT7A (cor = 0.336). The lowest correlation was observed for PTPRR (cor = 0.291).

14 genes and their related pathways

Many signaling pathways have been demonstrated to play crucial roles in the pathogenesis and metastasis of pancreatic cancer. Thus, we further performed KEGG pathway enrichment analysis on all 14 genes (Supplementary Table 2). According to the results, EPHA2 and PTPRR were correlated with MAPK signaling pathway, while EPHA2 and PRKCI both had relevance with rap 1 signaling pathway. Other than that, EPHA2 is also involved in PI3K-Akt signaling pathway and ras signaling pathway. WNT7A was significantly associated with hippo signaling pathway like PRKCI, as well as Wnt signaling pathway, mTOR signaling pathway. ITGA6 and LAMA3 were neighboring genes and shared three same pathways including PI3K-Akt signaling pathway, ECM-receptor interaction and focal adhesion. Moreover, SERPINB5 has been implicated in two pathways including p53 signaling pathway and microRNAs in cancer. No significantly enriched pathways among other genes. To further clarify the correlations between genes and pathways in pancreatic cancer, SangerBox software (http://sangerbox.com/) was utilized to perform the analysis. The cor cut-off was set to 0.1 and P value was set to 0.05 (Supplementary Fig. 3). Pathway analysis exhibited that EPHA2 was most strongly associated with axon guidance with a correlation coefficient of 0.419 and the most significantly correlated pathway related to the PRKCI was tight junction (cor = 0.353). SERPINB5 was found most highly related to the p53 signaling pathway (cor = 0.56). The most closely related pathway of WNT7A was basal cell carcinoma (cor = 0.532), followed by wnt signaling pathway (cor = 0.381), and pathways in cancer (cor = 0.325). ECM-receptor interaction was the most relevant pathway both in ITGA6 (cor = 0.221) and LAMA3 (cor = 0.254), followed by focal adhesion.

Correlations between PC-related genes and 182 core cancer-intrinsic CTLs-evasion genes

A study published in Nature in 2020 has revealed 182 core cancer-intrinsic cytotoxic T lymphocytes-related genes and we listed them in Supplementary Table 3. We explore the relevance between these 182 genes and 14 PC-related genes. The results showed that close proximity existed between many genes (Supplementary Fig. 4). 15 genes were all significantly correlated with CFLAR, CHIC2, DNTTIP1, EMC8, FADD, PPP2R2A, TAP1, TAP2, ACTB, ARF6, ATXN7L3, BCL2L1, CEP55, CHMP5, EMC4, TMEM127, VDAC2, VPS35, GALE, HEXIM1, MTA2, PDCD6IP, PKN2, PPP1CA, and RCE1 (P < 0.01). High correlations were especially observed in DNTTIP1, FADD, ARF6, BCL2L1, CEP55, GALE, PDCD6IP, and RCE1. However, negative associations were found between several pancreatic cancer-related genes and FITM2, SOCS1, DPH5, and WDR7. We also counted the number of CTLs-evasion genes which had significant positive correlations with each pancreatic cancer related gene. FAM83D was notably related to 141 CTLs-evasion genes, followed by PRKCI (140), ITGA6 (140), SERPINB5 (125), LAMA3 (120), PTPRR (118), EPHA2 (111), TMPRSS4 (104), MYEOV (101), COL17A1 (99), WNT7A (90), RNF39 (87), MMP28 (80), and FAM83A (77).

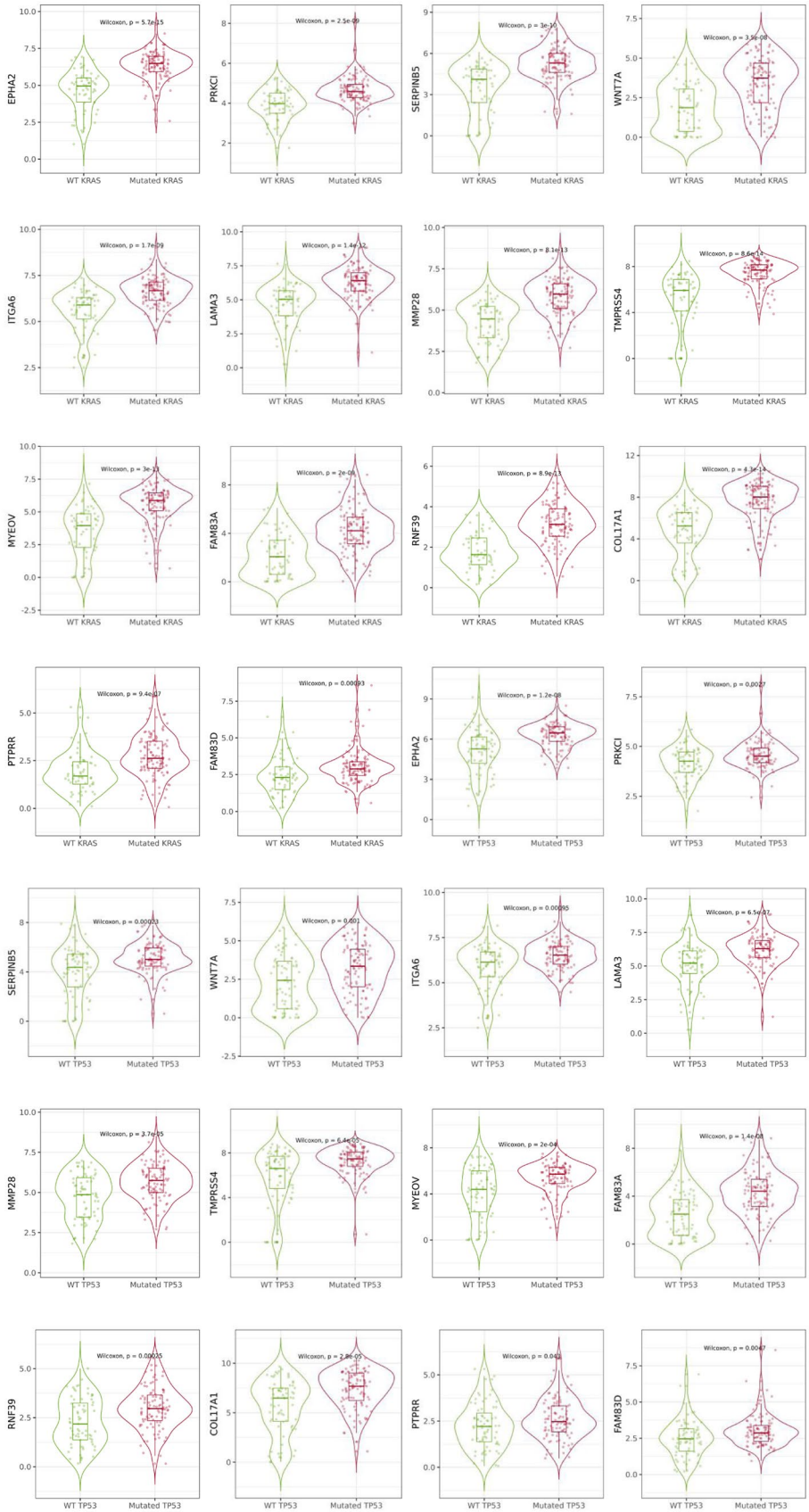


Fig. 3 Expression levels of different gene classes between patients with KRAS/TP53 mutations and wild-type

Table 2 The correlation coefficient between 14 genes and 4 mutated genes

Genes	Log2 (Fold change)			
	KRAS P	TP53 P	CDKN2A P	SMAD4 P
EPHA2	0.458 ***	0.327 ***	0.258 ***	0.160 *
PRKCI	0.253 ***	0.137 **	0.117 **	0.075 0.37
PTPRR	0.537 ***	0.221 *	0.174 0.09	0.252 *
SERPINB5	0.609 ***	0.356 ***	0.278 *	0.187 0.12
WNT7A	0.866 ***	0.478 **	0.280 0.074	0.291 0.089
ITGA6	0.243 ***	0.145 ***	0.106 *	0.109 **
LAMA3	0.430 ***	0.283 ***	0.172 *	0.097 0.23
MMP28	0.456 ***	0.269 ***	0.220 **	0.175 **
TMPRSS4	0.540 ***	0.324 ***	0.217 **	0.257 ***
FAM83D	0.308 ***	0.272 **	-0.042 0.80	0.042 0.45
MYEOV	0.695 ***	0.391 ***	0.267 **	0.252 **
FAM83A	0.935 ***	0.791 ***	0.531 ***	0.139 0.42
RNF39	0.816 ***	0.402 ***	0.346 **	0.334 **
COL17A1	0.695 ***	0.382 ***	0.322 **	0.272 **

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Discussion

Pancreatic cancer is one of the most challenging cancer types characterized by early metastasis and dismal prognosis without effective therapeutic methods. In this study, we aimed to analyze the underlying relationships between pancreatic cancer and different gene classes. After analyzing the expression levels and prognostic impact of numerous genes included in 25 gene classes in pancreatic cancer, EPHA2, PRKCI, PTPRR, SERPINB5, WNT7A, ITGA6, LAMA3, MMP28, TMPRSS4, FAM83D, MYEOV, FAM83A, RNF39, and COL17A1 were all highly expressed in pancreatic cancer and were associated with unfavorable prognosis. Although some of them have been revealed to be closely relevant to the pathogenesis, prognosis, and chemoresistance of pancreatic cancer more or less, our research aimed to investigate the correlations among them more comprehensively and deeply.

KRAS and TP53 mutations are the most common events in the development of pancreatic cancer, followed by CDKN2A and SMAD4. We further analyzed the relationships between 14 PC-related genes and 4 mutated genes. High expressions of 14 genes were observed in patients with KRAS and TP53 mutations. Several PC-related genes were highly expressed in patients with CDKN2A or SMAD4 mutations. For example, a study has reported that KRAS activation of the ERK pathway induces EPHA2 expression in lung cancer cells [33]. Thus, the exploration of EPHA2 in PC patients based on their function in KRAS-associated signaling dysregulation is in need. However, the interactions between most high-expressed genes and mutated genes in PC patients remain unclear. To unravel the mysteries between these correlations may shed light on the pathogenesis or metastatic mechanisms of PC.

Immunotherapy has emerged as a major therapy in oncology, which has shown great success in multiple cancer types. Immune checkpoint inhibitors (ICIs) are effective immunotherapies that block inhibitory immune checkpoint pathways to reactivate immune responses against cancer. However, although immunotherapy with checkpoint blockade has displayed a remarkable and durable response in many cancers, the application of checkpoint inhibitors in PC is still unsatisfactory [34]. PD-1/PD-L1 inhibitors have a poor curative effect on pancreatic cancer. Not only because immune cell infiltrations are sparse in PC, but also an abundance of T cell-suppressive myeloid cells interfere antitumor immune responses [35]. Thus, we investigated the relationship between the expression levels of 14 genes and immune checkpoints in PC patients. Most genes showed negative relationships with PDCD1, CTLA4, LAG3, TIGIT, PDCD1LG2 but had significantly positive correlations with SIGLEC15. SIGLEC15 was first characterized by Dr.Takashi Angata in 2007 as one of the most evolutionarily conserved Siglecs in vertebrates [36]. Recently, it has been identified as a vital immune suppressor which is widely upregulated on human cancer cells and tumor-infiltrating myeloid cells. Moreover, SIGLEC15 has unique molecular characteristics and shows a mutually exclusive expression with PD-L1, indicating that it might be a supplementary therapeutic target for PD-L1-negative patients [37]. Hence, SIGLEC15 could be a potential target for immunotherapy of PC. In addition, PRKCI, ITGA6, and LAMA3 demonstrated significant association with the expression of CD274. Thus PD-L1 might also become a promising target for specific patients. MDSC is widely known as an important mediator of tumor progression in pancreatic cancer. Expression of 14 genes exhibited significant positive relationships with infiltrating levels of MDSC in PC. The finding suggested that these genes played a specific role in immune infiltration in PC. For instance, EPHA2 has been identified as a tumor cell intrinsic factor that could regulate immune infiltration in the tumor microenvironment and response to immunotherapy [38]. Thus, EPHA2 inhibition may help diminish MDSC immunosuppression and enhance the blockade efficacy of immune checkpoints. Subsequent in-depth research into this area is required.

The occurrence of pancreatic cancer is pretty complex and many signaling pathways involved in this disease, such as PI3K/AKT, TGF-β, and STAT3 signaling pathways, etc. The most associated signaling pathways with PC-related genes have been detected. Axon guidance is a process by which axons stretch to their correct targets and genes in this pathway have been implicated in cancer cell growth, proliferation, and invasion in PC [39]. Thus, the genetic role of

EPHA2 in axon guidance pathway is worth being studied in the future. Tight junction, as a vital intercellular junction, turns out to be important in the inhibition of tumor progression [40]. We speculated that overexpression of PRKCI disrupted the activation of the tight junction pathway in PC, leading to the fast growth and proliferation of cancer cells. It was worth mentioning that ITGA6 and LAMA3 shared the same pathways including ECM-receptor interaction and focal adhesion, which were significantly associated with tumor occurrence and metastasis [41, 42]. The interactions between ITGA6 and LAMA3 in these pathways need further investigation.

Besides, immune escape happens to be an important mechanism in cancer development and metastasis. To explore the strategies for tumor immunotherapy depends on the recognition of molecular mechanisms of immune evasion. After analyzing the associations between 14 PC-related genes and 182 cancer-intrinsic CTLs-evasion genes, we found that PC-related genes showed tight links with numerous CTLs-evasion genes. The loss of CTLs-evasion genes would enhance the T cells attack by tumor or render resistance in cancer cells [32]. Our study showed that DNTTIP1, FADD, ARF6, BCL2L1, CEP55, GALE, PDCD6IP, and RCE1 were highly significantly correlated with PC-related genes, which may be regarded as potential targets for immunotherapy. Besides, FAM83D had close links with the highest number of CTLs-evasion genes, which may assist the tumor in immune escape. Nevertheless, further exploration of the cross-talk between these genes is necessary, which is essential for the pathogenesis and therapy of pancreatic cancer.

Conclusions

This study analyzed the relationships between 14 PC-related genes and pancreatic cancer from different angles, which may help us better understand the pathogenesis and progression of PC. Besides, we also found that SIGLEC15 may be a promising target of immunotherapy of PC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10637-021-01176-5.

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Authors' contributions Ji-li Xu: Conceptualization, Formal analysis and investigation, Writing-original draft preparation, Yong Guo: Conceptualization, Methodology, Writing-review and editing, Supervision.

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The datasets are available in the TCGA database (https://tcga-data.nci.nih.gov/tcga) and genes were selected from the UALCAN database (http://ualcan.path.uab.edu/)

Code availability Not applicable.

Declarations

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent to publication Not applicable.

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