Original Article

Identification of key genes and pathways at the downstream of S100PBP in pancreatic cancer cells by integrated bioinformatical analysis

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Background: The aim of the present study was to identify key genes and pathways downstream of S100PPBP in pancreatic cancer cells.

Methods: The microarray datasets GSE35196 (S100PBP knockdown) and GSE35198 (S100PBP overexpression) were downloaded from the Gene Expression Omnibus (GEO). Differentially expressed genes (DEGs) were obtained separately from GEO2R, and heatmaps showing clustering analysis of DEGs were generated using R software. Gene Ontology and pathway enrichment analyses were performed for identified DEGs using the Database for Annotation, Visualization, and Integrated Discovery and Kyoto Encyclopedia of Genes and Genomes, respectively. A protein-protein interaction (PPI) network was created using the Search Tool for the Retrieval of Interacting Genes and Cytoscape software. Relevant expression datasets of key identified genes were downloaded from The Cancer Genome Atlas, and overall survival (OS) analysis was performed with R software. Finally, Gene Expression Profiling Interactive Analysis was used to evaluate the expression of key DEGs in pancreatic cancer tissues.

Results: A total of 34 DEGs (11 upregulated and 23 downregulated) were screened out from the two datasets. Gene Ontology enrichment analysis revealed that the identified DEGs were mainly functionally enriched in ATPase activity, production of siRNA involved in RNA interference, and production of miRNAs involved in gene silencing by miRNA. The pathway enrichment analysis of the identified DEGs showed enrichment mainly in apoptosis, non-homologous end-joining, and miRNA pathways in cancer. The protein–protein interaction network was composed of 21 nodes and 30 edges. After survival analysis and gene expression analysis, 4 genes associated with poor prognosis were selected, including LMNB1, PRKRA, SEPT2, and XRCC5.

Conclusions: LMNB1, PRKRA, SEPT2, and XRCC5 could be key downstream genes of the S100PBP gene in the inhibition of pancreatic cancer cell adhesion.

Keywords: Pancreatic cancer; S100PBP; bioinformatical analysis; overall survival (OS)

Submitted Jul 14, 2020. Accepted for publication Dec 11, 2020.
doi: 10.21037/tcr-20-2531
View this article at: http://dx.doi.org/10.21037/tcr-20-2531

Introduction

Pancreatic cancer is a highly malignant tumor and the seventh leading cause of cancer-related mortality worldwide (1). Due to the difficulty in detecting aggressive biologic properties and early signs of pancreatic cancer, most patients are at a locally advanced or metastatic stage when they are first diagnosed; consequently, the 5-year survival rate stands at less than 7% (2,3). Despite the effort that has been invested into their development, treatment modalities are still insufficient. Therefore, it is important to investigate the key molecules in pancreatic cancer progression and to identify potential biomarkers for early diagnosis and therapeutic strategies.

S100PBP, located at 1p34.3, encodes a protein that is a binding partner of S100P and shares no sequence or structural similarity with any other protein. S100PBP is a widely expressed protein detected in normal brain, breast, spleen, and lung tissue, whereas its expression is decreased in pancreatic cancer (4). Studies have reported that S100PBP can inhibit the adhesion of pancreatic cancer cells through the S100PBP/CTSZ/RGD αvβ5 pathway (5).

In recent years, high-throughput platforms, such as microarrays, have been widely used in the analysis of gene expression and genetic alteration in tumorigenesis (6). Bioinformatics methods for processing and analyzing a great amount of data generated by microarray technology have been used to explore key genes and potential molecular mechanisms for the diagnosis and treatment of pancreatic cancer. Given the function of S100PBP in pancreatic cancer, the microarray datasets GSE35196 (S100PBP knockdown) and GSE35198 (S100PBP overexpression) in the present study were downloaded from the Gene Expression Omnibus (GEO) database, and the differentially expressed genes (DEGs) were analyzed. Functional enrichment and protein-protein interaction (PPI) network analyses were also applied in order to identify the key pathways that the DEGs are involved in. To further explore the impact of node genes on pancreatic cancer, overall survival (OS) analysis and gene expression analysis were also employed.

We present the following study in accordance with the MDAR checklist (available at http://dx.doi.org/10.21037/tcr-20-2531).

Methods

Microarray data

The GEO (http://www.ncbi.nlm.nih.gov/geo) is a public storage library from which microarray, next-generation sequencing, and other high-throughput data are freely available. The SuperSeries GSE35199, which comprises GSE35196 and GSE35198, was based on the GPL570 platform and downloaded from the GEO database. GSE35196 includes array data on S100PBP knockdown for 2 control samples and 3 S100PBP siRNA transfection samples. GSE35198 includes array data on S100PBP overexpression for 3 control samples and 3 samples with S100PBP overexpression.

Collection and inclusion criteria of studies

We searched the GEO database using the following keywords: "pancreatic cancer" (study keyword), "S100PBP" (study keyword), "Homo sapiens" (organism), and "series" (entry type). The search returned 3 items. The inclusion criteria for studies were as follows: (I) samples needed to be in 2 groups, including the control group and the experimental group; (II) the sample count needed to be appropriate; (III) S100PBP expression in the experimental group needed to be either knockdown or overexpression; and (IV) sufficient information was needed to perform the analysis. Accordingly, SuperSeries GSE35199, which is composed of GSE35196 and GSE35198, was used for the analysis.

Data processing

A large amount of high-throughput functional genomic data are stored in the GEO database for free research and are normalized using various methods or tools. Limma package was used to identify the different expression of genes by linear modelling. $P<0.05$ and fold change >1.5, or <0.67 were set as the cut-off criteria. R software package, a language tool for statistical calculations and drawing that provides a wide variety of statistical and graphical techniques, was used to obtain the heatmaps of DEGs, and $P<0.05$ was set as the cut-off criterion.

Functional and pathway enrichment analysis

The Database for Annotation, Visualization and Integrated Discovery (DAVID, http://www.david.niaid.nih.gov) is a database that is used for annotation, visualization, and integrated discovery (7). FunRich is a software tool that is mainly used for gene and protein functional enrichment and interaction network analyses. Gene Ontology (GO)

enrichment analysis of identified DEGs was annotated and visualized using DAVID and FunRich, with P<0.05 set as the cut-off criterion. Kyoto Encyclopedia of Genes and Genomes (KEGG, http://www.genome.jp/kegg/pathway.html) is an integrated database resource used for the biologic interpretation of genome sequences and other high-throughput data (8). The KEGG Orthology-Based Annotation System (KOBAS, http://kobas.cbi.pku.edu.cn/annotate.php) is a web server for gene/protein functional annotation and functional gene set enrichment. In the present study, we conducted KOBAS and KEGG pathway enrichment analyses.

PPI network construction and analysis of modules

The Search Tool for the Retrieval of Interacting Genes (STRING, http://string-db.org/) database is an online tool that collects and integrates information on all functional interactions between expressed proteins through consolidating known and predicted protein–protein association data for organisms (9). A minimum required interaction score of >0.15 was set as the cut-off criterion. Cytoscape is a popular bioinformatics package that visualizes the biologic network and integrates data (10). DEGs were mapped to STRING to evaluate the PPI information and were visualized using Cytoscape.

Survival analysis of DEGs

To analyze the prognosis of identified DEGs, the expression datasets were downloaded from The Cancer Genome Atlas (https://tcga-data.nci.nih.gov/tcga). The OS analysis was carried out using R software package, and results were determined by Kaplan-Meier curves, on which following the P value was shown. Gene Expression Profiling Interactive Analysis (GEPIA, http://gepia.cancer-pku.cn/) is a database that can comparatively analyze gene expression in tumor and normal tissues (11). We displayed the expression of key genes of pancreatic cancer tissues and adjacent tissues, using P<0.05 as the critical criterion.

Statistical analysis

Survival analysis of the key genes was performed by the Survival package in the R software. Survival plots were showed by the Kaplan-Meier method, and the significance was estimated by the log-rank test. P value <0.05 was considered as statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All information from GEO is available and free for public, so the agreement of the medical ethics committee board was not necessary.

Results

Identification of DEGs

From GSE35196 and GSE35198, 606 DEGs (316 upregulated and 290 downregulated) and 961 DEGs (451 upregulated and 510 downregulated) were identified, respectively. Then, we took the intersection of the downregulated DEGs from GSE35196 and the upregulated DEGs from GSE35198, and found 11 upregulated genes (*Figure 1A* and *Table 1*). A further 23 downregulated genes were found by taking the intersection of the upregulated DEGs from GSE35196 and the downregulated DEGs from GSE35198 (*Figure 1B*). In total, 34 DEGs (11 upregulated and 23 downregulated genes) were screened out. By using R package, heatmaps of the DEGs were generated (*Figure 1C,D*).

Functional and pathway enrichment analysis

To obtain further insight into the function of the identified DEGs, functional enrichment analysis was performed using DAVID and FunRich. The GO enrichment analysis showed that in the biologic process-associated category, DEGs were significantly enriched in the production of siRNA involved in RNA interference, the production of miRNAs involved in gene silencing by miRNA, and pre-miRNA processing. Cell component analysis showed the DEGs to be enriched in the nucleus, nuclear envelope, and focal adhesion. For molecular function, DEGs were revealed to be enriched in ATPase activity (*Figure 2* and *Table 2*). Furthermore, the KEGG pathway analysis, using KOBAS, showed that the DEGs were significantly enriched in apoptosis, non-homologous end-joining (NHEJ), and miRNAs in cancer, with P<0.05 as the cut-off criterion (*Figure 3A* and *Table 3*).

PPI network construction

In the PPI network of identified DEGs, 21 nodes and 30 edges were mapped, including 7 upregulated genes and 14 downregulated genes. Some of the genes isolated relatively at the edge were removed; therefore, not all of the

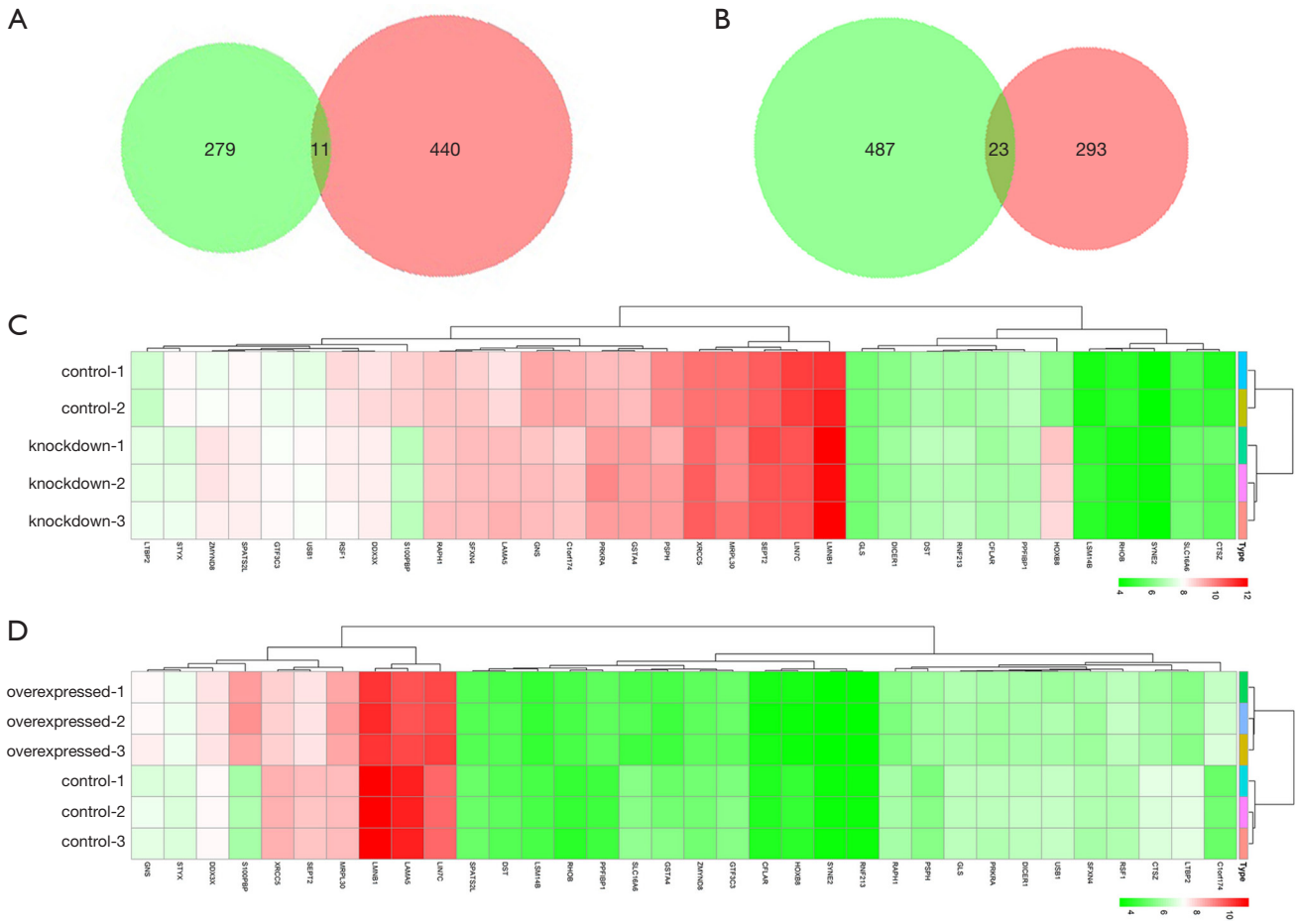

Figure 1 Identification of differentially expressed genes (DEGs). (A) Green represents downregulated genes in GSE35196. Red represents upregulated genes in GSE35198. Eleven DEGs were identified as upregulated genes. (B) Red represents upregulated genes in GSE35196. Green represents downregulated genes in GSE35198. Twenty-three DEGs were identified as downregulated genes. (C,D) Heatmaps of DEGs from two microarray datasets generated using R software (red, upregulation; green, downregulation).

Table 1 Identification of differentially expressed genes and gene names

DEGs	Genes name
Up-regulated	*S100PBP, DDX3X, STYX, PPFIBP1, LIN7C, PSPH, C1orf174, RHOB, GNS, MRPL30, RSF1*
Down-regulated	*HOXB8, RNF213, DST, CFLAR, USB1, SYNE2, LAMA5, GSTA4, SFXN4, LSM14B, SPATS2L, LTBP2, DICER1, GTF3C3, LMNB1, PRKRA, CTSZ, SLC16A6, GLS, SEPT2, RAPH1, XRCC5, ZMYND8*

34 genes are shown in the network. Red nodes represent the upregulated genes and the green nodes represent the downregulated genes (*Figure 3B*).

Overall survival (OS) analysis

All 21 genes in the PPI network, including *LIN7C*, *LSM14B*, *SEPT2*, *RHOB*, *HOXB8*, *SYNE2*, *CFNE2*, *RNF213*, *LMNB1*, *DST*, *GNS*, *CTSZ*, *RSF1*, *PRKRA*, *GTF3C3*, *PSPH*, *DDX3X*, *DICER1*, *GLS*, *LMNB1*, and *STYX*, were analyzed using the survival package in R, and the OS of these genes for patients with pancreatic cancer is shown in *Figure 4*. Of the upregulated genes, *DDX3X*, *STYX*, and *RSF1* were significantly associated with

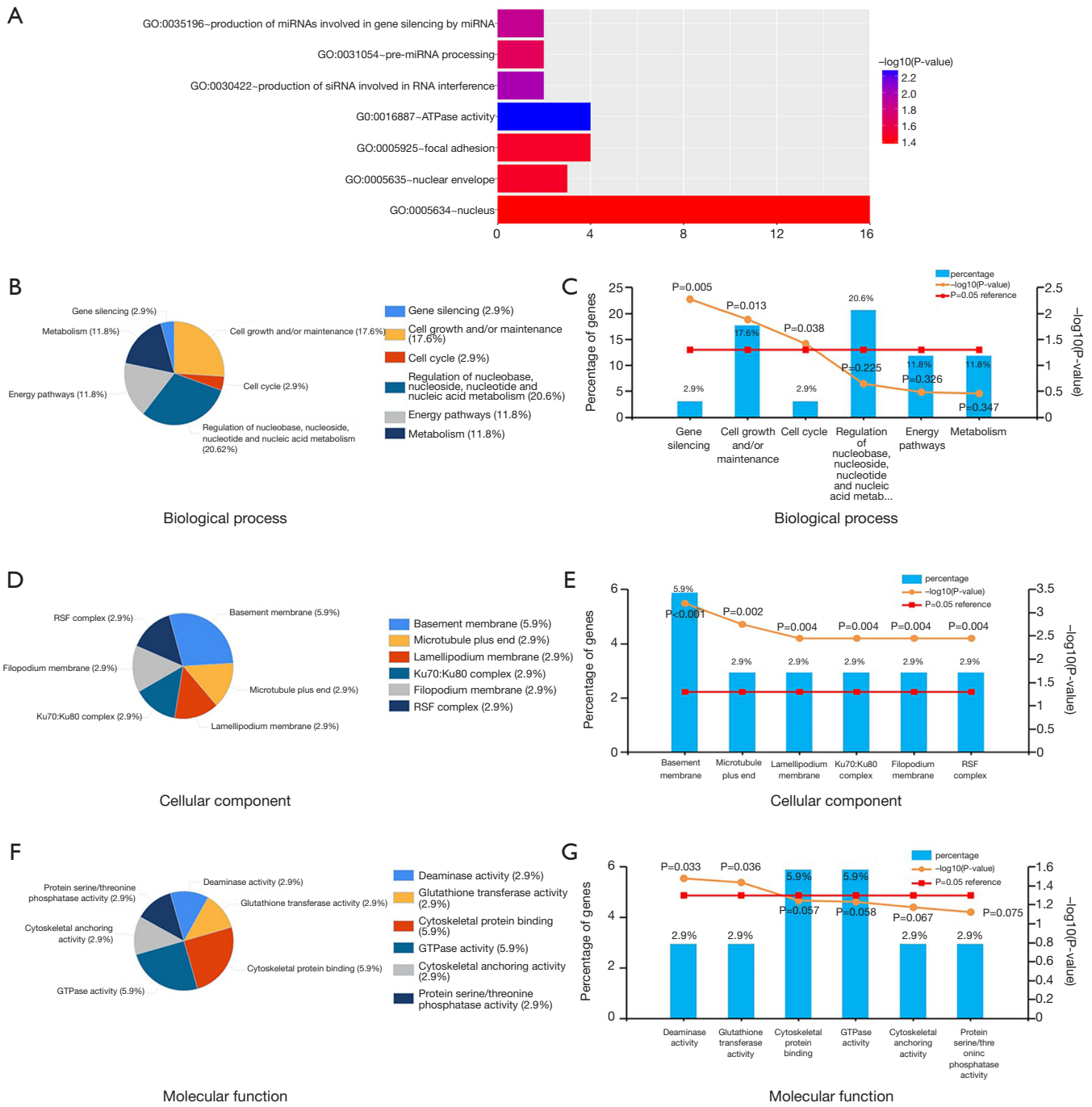

Figure 2 Functional enrichment analysis (GO analysis). (A) GO analysis of identified differentially expressed genes (DEGs) using the Database for Annotation, Visualization and Integrated Discovery. (B,C,D,E,F,G) Functional enrichment analysis of identified DEGs by FunRich, including biologic processes, cell components, and molecular functions.

Table 2 Gene Ontology enrichment analysis of differentially expressed genes

Category	Term	Count	%	P value
GOTERM_MF_DIRECT	GO:0016887~ATPase activity	4	11.76470588	0.005383803
GOTERM_BP_DIRECT	GO:0030422~production of siRNA involved in RNA interference	2	5.882352941	0.013735725
GOTERM_BP_DIRECT	GO:0035196~production of miRNAs involved in gene silencing by miRNA	2	5.882352941	0.022227855
GOTERM_BP_DIRECT	GO:0031054~pre-miRNA processing	2	5.882352941	0.022227855
GOTERM_CC_DIRECT	GO:0005925~focal adhesion	4	11.76470588	0.033246716
GOTERM_CC_DIRECT	GO:0005635~nuclear envelope	3	8.823529412	0.033471497
GOTERM_CC_DIRECT	GO:0005634~nucleus	16	47.05882353	0.040230878

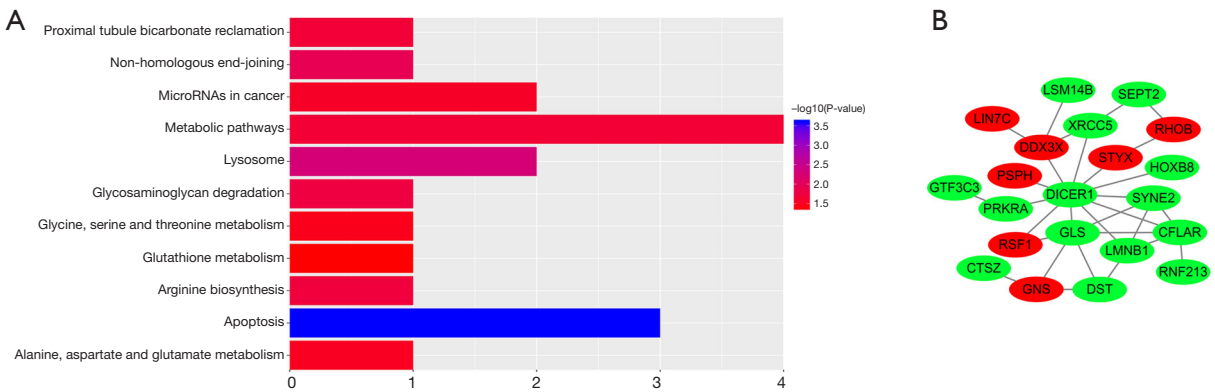

Figure 3 Pathway enrichment analysis and protein–protein interaction (PPI) network. (A) Pathway analysis of identified differentially expressed genes (DEGs) by Kyoto Encyclopedia of Genes and Genomes Orthology-Based Annotation System. (B) PPI network of DEGs using Cytoscape software. Red nodes represent upregulated genes, green nodes represent downregulated genes.

Table 3 Signaling pathway enrichment analysis of differentially expressed genes

Pathway ID	Term	Count	P value
hsa04210	Apoptosis	3	0.000250568
hsa04142	Lysosome	2	0.005141728
hsa03450	Non-homologous end-joining	1	0.011897331
hsa00531	Glycosaminoglycan degradation	1	0.016954027
hsa00220	Arginine biosynthesis	1	0.018634003
hsa04964	Proximal tubule bicarbonate reclamation	1	0.020311193
hsa01100	Metabolic pathways	4	0.021089253
hsa05206	MicroRNAs in cancer	2	0.027283703
hsa00250	Alanine, aspartate and glutamate metabolism	1	0.030316064
hsa00260	Glycine, serine and threonine metabolism	1	0.034455428
hsa00480	Glutathione metabolism	1	0.04432005

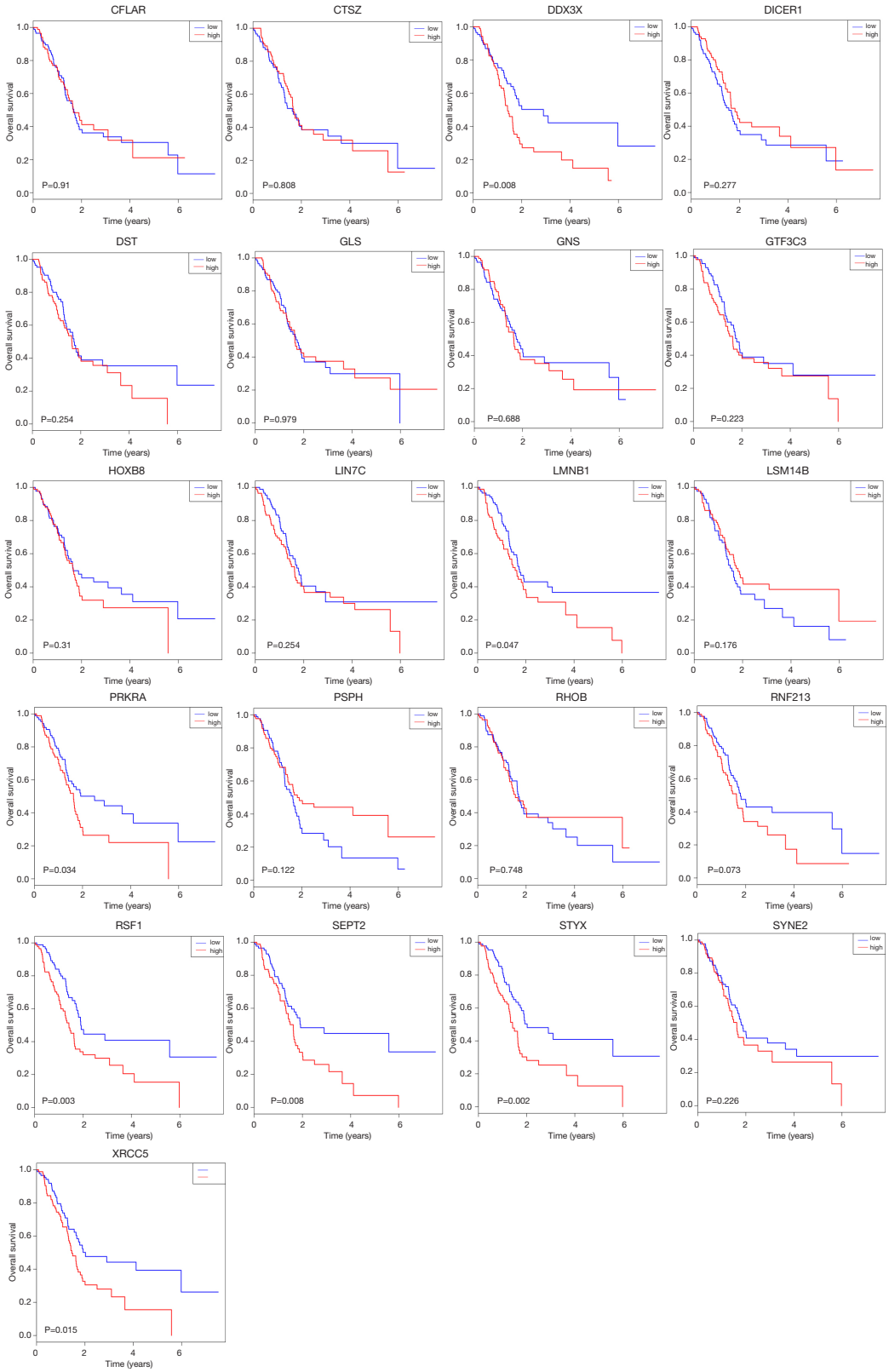

Figure 4 Overall survival analysis of 21 genes in the protein–protein interaction network for pancreatic cancer was analyzed.

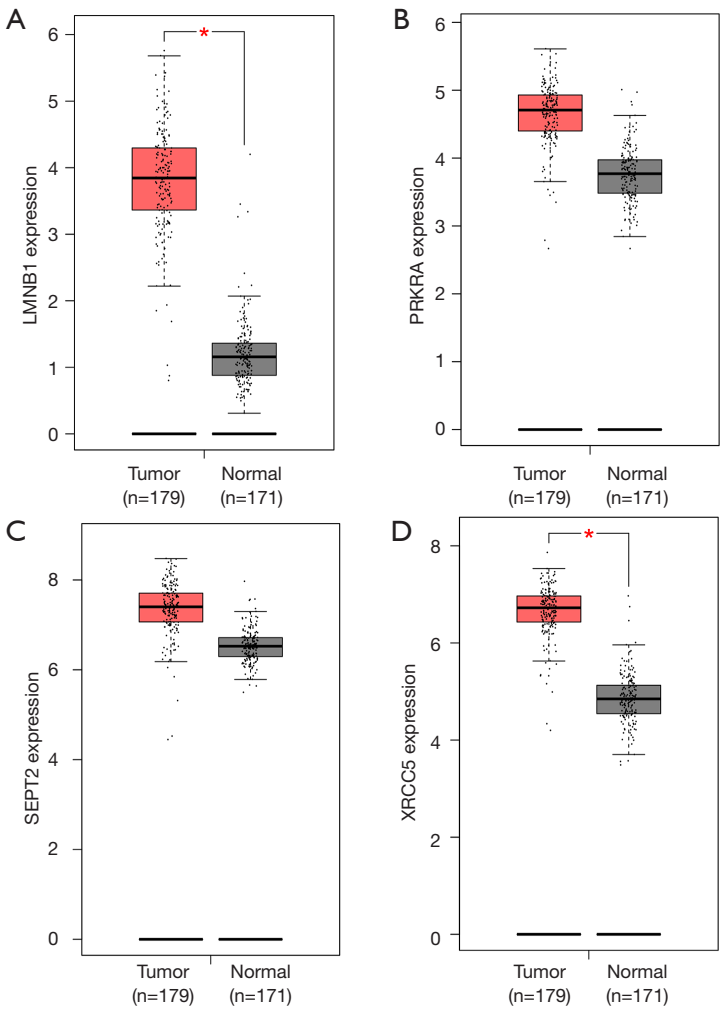

Figure 5 Gene expression of *LMNB1*, *PRKRA*, *SEPT2*, and *XRCC5*.

prognosis. Of the downregulated genes, *LMNB1*, *PRKRA*, *SEPT2*, and *XRCC5* were associated with OS. A low expression of these 4 downregulated genes was associated with better survival, which indicates that S100PBP may downregulate these genes to inhibit the invasion and migration of pancreatic cancer cells. We also analyzed the expression of these 7 genes in pancreatic cancer by using the GEPIA database. The results showed that the expression levels of *LMNB1* and *XRCC5* were higher in pancreatic cancer tissues than in normal tissues (P<0.05) (*Figure 5*).

Discussion

As one of the most highly malignant tumors, pancreatic cancer is the fourth leading cause of cancer death, with a 5-year survival rate of only 7% (12,13). Despite a large number of related studies, due to a lack of understanding of the molecular mechanisms of the carcinogenesis of pancreatic cancer, there is still insufficient information on its early diagnosis and treatment. Therefore, further research into the etiological factors and mechanisms of pancreatic cancer progression should be performed to improve the survival rate of patients. The rapid development of microarray technology has enabled the general genetic alterations of disease progression to be determined, which may make it easier to identify the target genes for the diagnosis, therapy, and prognosis of diseases.

In our previous study to identify the potential function of S100PBP in pancreatic cancer, original pancreatic cancer cells and pancreatic cancer cells with S100PBP knockdown

or overexpression were compared through analysis of the microarray datasets GSE35196 and GSE35198; a total of 34 DEGs were screened out, consisting of 11 upregulated genes and 23 downregulated genes. Through functional and pathway enrichment analyses, these genes were found to be enriched in the production of siRNA involved in RNA interference, the production of miRNAs involved in gene silencing by miRNA, and pre-miRNA processing. An OS analysis of 21 node genes in the PPI network (*LIN7C*, *LSM14B*, *SEPT2*, *XRCC5*, *DDX3X*, *STYX*, *RHOB*, *GTF3C3*, *PSPH*, *DICER1*, *HOXB8*, *PRKRA*, *SYNE2*, *GLS*, *RSF1*, *CFLAR*, *LMNB1*, *CTSZ*, *GNS*, *DST*, and *RNF123*) was also performed. We paid particular attention to *LMNB1*, *PRKRA*, *SEPT2*, and *XRCC5*, as they are highly expressed in pancreatic cancer and are associated with a poor prognosis.

LMNB1 is a component of the nuclear lamina, which encodes 1 of the 2 B-type lamin proteins. Lamins function in nuclear stability, transcription, DNA replication, and genome repair, together with lamin-binding proteins (14). *LMNB1* regulates the proliferation and senescence of human diploid cells via a reactive oxygen species signaling pathway (15). The function of *LMNB1* in cancer development and progression is still unclear. Some researchers have claimed that the overexpression of *LMNB1* has been found in prostate, liver, and pancreatic cancers, whereas downregulation has been observed in gastric, colon, and lung cancers (14,16,17). Li *et al*. found that *LMNB1* positively regulates the proliferation, invasion, and tumorigenicity of pancreatic cancer cells (18). In colon cancer, the overexpression of *LMNB1* induces a small part of apoptosis by mitotic catastrophe, strengthens cell-cell junctions, and limits the migration of cancer cells by regulating β-catenin, lamin A/C, actin, and tubulin (19).

PRKRA is a protein activator of interferon-induced protein kinase PKR. *PRKRA* activates PKR to function as a negative regulator of growth in cellular apoptosis (20). In colon cancer, PKR activated by *PRKRA* plays a tumor suppressor function via the p53 signaling pathway (21). However, PKR also increases cell growth through the p38 mitogen-activated protein kinase and nuclear factor-κB pathways (22,23). *PRKRA* expression is higher in skin cancer and colorectal cancer than in healthy tissue (24,25). Furthermore, the PRKRA-PKR signaling pathway inhibits p53 turnover via a sumoylation-dependent mechanism, with the promotion of p53 phosphorylation and translational activation resulting in cell cycle arrest, which is related to tumor progression (26).

SEPT2 is a septin with GTPase activity and is consistently upregulated in most cancer types, such as brain, breast, cervical, gastric, head, and liver cancers (27). In hepatocellular carcinoma, *SEPT2* accelerates cell growth by upregulating matrix metalloproteinases (MMP)-2 and -9 (28). In biliary tract cancer, *SEPT2* is negatively regulated by miR-140-5p to accelerate cell proliferation and invasion (29). In a previous study, *SEPT2* was found to promote breast cancer cell migration and invasion via activation of the MEK/extracellular signal-regulated kinase pathway (30).

XRCC5, an 80-kD subunit of the Ku heterodimer protein, binds to XRCC6 to form a dimer, which functions together with the IV-XRCC4 complex in the repair of DNA double-strand break by NHEJ. Many reports have found that NHEJ deficiencies increase genomic instability and tumorigenesis (31-36). *XRCC5* expression is significantly higher in lung adenocarcinoma and esophageal squamous cell carcinoma than in corresponding healthy tissues (37,38). In hepatocellular carcinoma, *XRCC5* inhibits tumor growth by inducing S-phase arrest through a p53-dependent pathway (39). However, *XRCC5* can promote colon cancer growth through the XRCC5/p300/cyclooxygenase-2 signaling pathway (40).

In summary, we identified DEGs by performing a comprehensive bioinformatics analysis to identify multiple key genes downstream of S100PBP in pancreatic cancer. *LMNB1*, *PRKRA*, *SEPT2*, and *XRCC5* were screened out and might play an important role in the development of pancreatic cancer. However, the specific functions of these genes and their mechanisms in pancreatic cancer require further analysis, and performing targeted experiments will be the aim of our future investigations. The expression levels of the 4 key genes in pancreatic cancer tissues are all higher than those in normal tissues, which might indicate that the people with higher expression levels of *LMNB1*, *PRKRA*, *SEPT2* or *XRCC5* are more likely to have pancreatic cancer if examined early. Meanwhile, we found the high expression of these 4 genes is related to poor survival, and this suggest that the expression levels of *LMNB1*, *PRKRA*, *SEPT2* or *XRCC5* may have a potential predictive role in the prognosis of pancreatic cancer patients. Our results might be promising for clinical transformation, which could provide new insight into the diagnosis and treatment of pancreatic cancer patients.

Conclusions

LMNB1, *PRKRA*, *SEPT2*, and *XRCC5* might be the

downstream key genes for the S100PBP gene in the promotion of the occurrence and development of pancreatic cancer.

Acknowledgements

Funding: None.

Footnote

Reporting Checklist: The authors have completed the MDAR checklist. Available at http://dx.doi.org/10.21037/tcr-20-2531

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr-20-2531). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All information from GEO is available and free for public, so the agreement of the medical ethics committee board was not necessary.

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Cite this article as: Lu YJ, Yang Y, Hu TH, Duan WM. Identification of key genes and pathways at the downstream of S100PBP in pancreatic cancer cells by integrated bioinformatical analysis. Transl Cancer Res 2021;10(2):806-816. doi: 10.21037/tcr-20-2531

