Biochemical Genetics (2021) 59:1326–1358
https://doi.org/10.1007/s10528-021-10062-x

ORIGINAL ARTICLE

An Integrated Data Analysis of mRNA, miRNA and Signaling Pathways in Pancreatic Cancer

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Received: 4 November 2020 / Accepted: 16 March 2021 / Published online: 3 April 2021
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Abstract

Although many genes and miRNAs have been reported for various cancers, pancreatic cancer's specific genes or miRNAs have not been studied precisely yet. Therefore, we have analyzed the gene and miRNA expression profile of pancreatic cancer data in the gene expression omnibus (GEO) database. The microarray-derived miRNAs and mRNAs were annotated by gene ontology (GO) and signaling pathway analysis. We also recognized mRNAs that were targeted by miRNA through the mirDIP database. An integrated analysis of the microarray revealed that only 6 out of 43 common miRNAs had significant differences in their expression profiles between the tumor and normal groups (P value < 0.05 and |log Fold Changes (logFC)|> 1). The hsa-miR-210 had upregulation, whereas hsa-miR-375, hsa-miR-216a, hsa-miR-217, hsa-miR-216b and hsa-miR-634 had downregulation in pancreatic cancer (PC). The analysis results also revealed 109 common mRNAs by microarray and mirDIP 4.1 databases. Pathway analysis showed that amoebiasis, axon guidance, PI3K-Akt signaling pathway, absorption and focal adhesion, adherens junction, platelet activation, protein digestion, human papillomavirus infection, extracellular matrix (ECM) receptor interaction, and riboflavin metabolism played important roles in pancreatic cancer. GO analysis revealed the significant enrichment in the three terms of biological process, cellular component, and molecular function, which were identified as the most important processes associated strongly with pancreatic cancer. In conclusion, *DTL, CDH11, COL5A1, ITGA2, KIF14, SMC4, VCAN*, hsa-mir-210, hsa-mir-217, hsa-mir-216a, hsa-mir-216b, hsa-mir-375 and hsa-mir-634 can be reported as the novel diagnostic or even therapeutic markers for the future studies. Also, the hsa-mir-107 and hsa-mir-125a-5p with *COL5A1, CDH11* and *TGFBR1* genes can be introduced as major miRNA and genes on the miRNA-drug-mRNA network. The new regulatory network created in our study could give a deeper knowledge of the pancreatic cancer.

Keywords Pancreatic neoplasms · Differentially expressed genes · Bioinformatics analysis · miRNAs · GEO

Extended author information available on the last page of the article

Introduction

Pancreatic cancer (PC) is the 8th leading cause of death from cancer worldwide and the 4th most common cancer in the USA, with a mortality rate of about 30,000 deaths each year (Vincent et al. 2011; Pourshams et al. 2018; Han et al. 2015). Unfortunately, no definitive therapy has been found, and most of the patients die because of this disease (Pourshams et al. 2018). Modern tumor diagnosis and therapy is now looked at the molecular level ranging of the biomarkers (AbdelGhafar et al. 2019; El-Guindy et al. 2019; Tobin et al. 2015, Habib et al. 2020). To the best of our knowledge *K-ras* gene with over 85% of prevalence is one of the genes most involved in pancreatic cancers (Li et al. 2004; Uehara et al. 1999, Rungjarernarrejitt et al. 2018). P16, a tumor suppressor gene, as well as p53, are deactivated in about 95% of pancreatic cancers (Schutte et al. 1997). Imaging and marker analyses don't really discriminate between pancreatic adenocarcinoma and non-neoplastic pancreatic diseases in patients which pancreatic cancer is suspected. For these purposes, to promote early screening and identification, much work has been made to recognize reliable markers of pancreatic cancer (Goggins 2007). While some conventional markers such as cancer antigen (CA) 15-3 and carcinoembryonic antigen (CEA) are used for early screening and diagnosis of pancreatic cancer, its sensitivity and specificity are low (Ghafar et al. 2020). Other genes include *HER2, MYB, AKT2, BRCA2, FHIT, CDKN2A, PALB2, STK11,* and *PRSS1*, which are associated with the activation or inactivation of proto-oncogenes and other related genes, such as tumor suppressor genes. Although the new diagnosis and therapeutic approaches have grown over recent years (Rezaie et al. 2020a; Baudino 2015); the underlying causes of this cancer have not yet been fully identified (Han et al. 2015; Li et al. 2004; Hidalgo 2010). The microRNAs (miRNAs) are essential regulators of gene expression in cancer cells. The miRNAs are short, non-coding, and single-stranded RNA molecules (17–25-nucleotide), that can control gene expression, by joining to 3-untranslated region (3-UTR) genes or mRNA degradation (Andorfer et al. 2011; Schetter et al. 2008). The microRNAs participate in the regulation of cellular pathways such as apoptosis, differentiation, proliferation, metastasis, and senescence (Wang et al. 2015; Khafaei et al. 2019). Thus, they can be applied as potential therapeutic or diagnostic biomarkers in cancer (Andorfer et al. 2011; Schetter et al. 2008; Mendell and Olson 2012; Shah et al. 2016). They have been extremely involved in the pathogenesis of human cancer and some investigations showed that the miRNAs specifically act in various cancers. For example in breast cancer, miR-200 showed upregulation as an oncogene (Korpal et al. 2011), while in the lung, kidney, and ovarian cancers downregulation of miR-200 significantly correlated with decreased angiogenesis and poor survival (Pecot et al. 2013). In pancreatic cancer the hsa-miR-217, hsa-miR-96, miR-216a, and miR-148a/b by targeting KRAS and other genes, are downregulated, and also the miR-221, miR-210, miR-155, and miR-21 are upregulated (Xue et al. 2013). Nevertheless, in some cancers, microRNAs have dual functions. For example, the miR-221, which has been shown to be upregulated in liver and colon cancers, acts as an oncogenic factor by inhibiting tumor suppressors *PTEN* and *RECK*, whereas it acts as a tumor suppressor by derepression of

oncogenes such as *c-KIT* and *ETV1* (Berindan-Neagoe et al. 2014). Although many miRNA and genes have been reported for various cancers (Berindan-Neagoe et al. 2014; Sohrabi et al. 2020) such as miR-200c for ovarian cancer, hsa-miR-142-5p and hsa-miR-375 for gastric cancer, miR-133 for breast cancer, and miR-21 for colon cancer, and lung cancer, to best of our knowledge, for pancreatic cancer diagnosis, suitable markers with adequate accuracy are needed (Ghafar et al. 2020; Berindan-Neagoe et al. 2014). Molecular markers are increasingly being suggested for the screening and diagnosis of PC, but they are not feasible for routine clinical use (Fry et al. 2008; Hasan et al. 2019).

Bioinformatics and system biology tools are remarkably used in the different fields of medical biology (Gasparini-Junior et al. 2019; Lu et al. 2018; Mohammadi et al. 2020; Rezaie et al. 2020b, 2018; Keshtvarz et al. 2017). Analyzing and understanding the genes-miRNAs network for cancer enables us to find genes and miRNAs that have significant expression level differences over cancer states. In addition, we can find genes significantly affected by miRNAs, identify different target genes for miRNAs, identify the mechanism of the disease, and finally introduce potential new and reliable biomarkers.

Aimed at gene expression analysis, the microarray provides a high-throughput platform that in recent years, has been extensively conducted as a powerful tool for assessing general genetic alteration during carcinogenesis (Kim 2004; Zhang et al. 2017). The microarray technology, which can calculate the expression changes of the different genes in the healthy and tumor groups, enables the researcher to study the expression of several thousands of genes simultaneously (Zhang et al. 2017). For example, in Yi lu study the *ITGA2, MMP7, ITGB4, ITGA4, ITC3, VCAN,* and *PLAU* genes have been identified after the bioinformatics analysis of the microarray data from patients with pancreatic ductal adenocarcinoma (Berindan-Neagoe et al. 2014). Several studies also revealed that metabolic pathways and signaling interactions were associated with the shortening of life expectancy in this disease (Lu et al. 2018; Li et al. 2018). The *MMP7* and *ITGA2* genes have also been correlated with the prognosis and diagnosis of pancreatic cancer (Zhang et al. 2017; Li et al. 2018; Long et al. 2016). It is necessary to explore new molecular biomarkers facilitating detection or increasing the screening and treatment rate of pancreatic cancer. As a result, in the present work, we tried to study the genes-miRNAs-drugs network and understand their signaling pathways in pancreatic cancer to introduce the new diagnosis and therapeutic targets.

Methods

Pancreatic Cancer Biomarkers

We applied the medical subject headings (Rezaie et al. 2020a) based keywords (pancreatic cancer AND (biomarker* OR current marker*) AND discovery AND human) in Google Scholar, Pubmed from 2015 to 2020, and selected the most common biomarkers of pancreatic cancer.

Microarray Data

We searched expression profiles of miRNAs and mRNAs in the GEO database (https://www.ncbi.nlm.nih.gov/geo/) using the following keywords: pancreatic neoplasms AND Homo sapiens. The inclusion criteria were as follows: (1) samples diagnosed with pancreatic cancer (PC) and normal tissue samples, (2) profiling of gene expression for mRNA and miRNA, and (3) enough data to plan the study.

Data Processing

GEO2R online webserver was used to identify differentially expressed genes and miRNAs between PC and normal tissue samples. As the criteria, a P value < 0.05 and a $|\log FC| > 1$ were set. To increase the specificity, further analyses with common miRNAs in both datasets (P value < 0.05) were designed and submitted to the MirDIP database to obtain the miRNA's target genes. Finally, we identified common genes between targets of miRNAs and differential expression genes (DEGs) using the Venn diagram.

Functional and Pathway Enrichment Analysis

Kyoto encyclopedia of genes and genomes (KEGG) and GO analysis, including biological process (BP), molecular function (Sandhu et al. 2016), and cellular component (Tahira et al. 2011), were used for functional study of single genes or large-scale genome. Both analyses were done in the EnrichR database (Chen et al. 2013; Kuleshov et al. 2016). The cut-off criterion was set to P value < 0.01.

Protein–Protein Interaction (PPI) Network Construction and Analysis of Modules

The DEGs were mapped to STRING (recovery tool for interacting genes) database (http://string-db.org/) to evaluate the protein–protein interaction integration and then visualized with Cytoscape. The molecular complex detection (MCODE) plug-in (http://apps.cytoscape.org/apps/mcode) was used to screen PPI network hub gene modules with cut-off degree = 10, haircut = on, node score cut-off = 0.2, k-core = 2, and max. Depth = 100. Clusters with more than 5 scores were selected for further analysis (Fig. 1).

Survival Analysis

Survival analysis was performed using five studies with terms of Pancreatic Adenocarcinoma (TCGA, PanCancer Atlas), Pancreatic Adenocarcinoma (TCGA, Provisional), Pancreatic Cancer (UTSW, Nat Commun 2015), Pancreatic Adenocarcinoma (QCMG, Nature 2016) and Pancreatic Adenocarcinoma (ICGC, Nature 2012) from the cBioPortal database (Gao et al. 2013), (survival analysis refers to the overall survival Kaplan–Meier estimate). The datasets used in this study were composed of 1034 pancreatic cancer/adenocarcinoma samples/patients. Based on a relationship

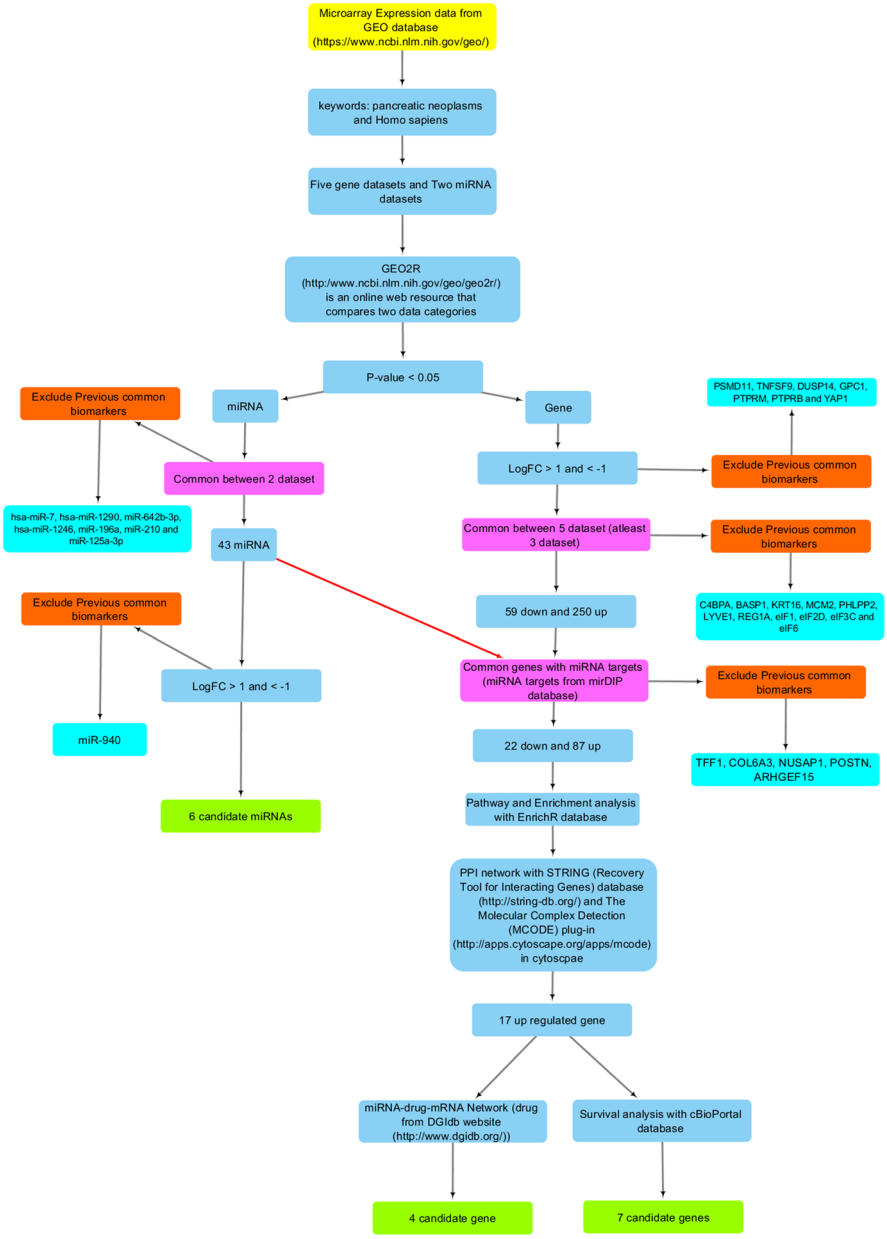

Fig. 1 Flow chart of data analysis. Firstly, we identified differentially expressed mRNAs and miRNAs in pancreatic cancer through integrating expression microarray data then we constructed network of miRNA–mRNA based on Microarray data. Also, we enrichment genes and analyzed protein–protein network and finally survival of genes were investigated

network built by MCODE (clusters 1 and 2 with score > 5), gene names were submitted in cBioPortal, and survival analysis was accomplished, of which genes with Log rank test of $P < 0.05$ were presented.

Construction of Regulatory miRNA-Drug-mRNA Network

Herein, we identified the mRNAs targeted by miRNA through mirDIP 4.1 (Tokar et al. 2017; Shirdel et al. 2011). Then, we identified the mRNAs that correlated with miRNA expression in pancreatic cancer through a Venn diagram. The target genes of the common miRNA from GSE71533 and GSE2479 were predicted with mirDIP, an online MicroRNA target-predicting database, that comprise of 28 database (BCmicrO,BiTargeting, CoMeTa, Cupid, DIANA,ElMMo3,GenMir++, microrna.org, mirbase, mirCoX, miRcode, miRDB, miRTar2GO, MAMI, MBStar, MirAncesTar, MirMAP, MirSNP, MirTar, Mirza-G, MultiMiTar, PACCMIT, PicTar, PITA, RepTar, RNA22, RNAhybrid, TargetRank, TargetScan and TargetSpy). The network was constructed between 43 selected miRNAs and 17 selected genes, including cluster one and two MCODE analysis (score > 5) in cytoscape version 3.6.0. Genes correlated with different miRNAs also entered into the DGIdb website (http://www.dgidb.org/) to find target gene drugs. A general network of genes, miRNAs, and their drugs was constructed with cytoscape software.

Results

Previous Biomarkers for Pancreatic Cancer

Some genes and miRNAs, which have been mentioned in previous studies as pancreatic cancer biomarkers, were identified. These genes and miRNAs are summarized in Table 1.

Many of these genes and miRNAs were excluded from our study due to insignificant P-Value and/or sharing between datasets (Table 2; Fig. 1). So far, many genes or miRNAs in pancreatic cancer had relatively good conditions for biomarkers, but often for various reasons, their importance has been diminished. Some of them have same expression profile in different cancers, others are not detectable in the early stages of cancer or at different stages. Others need to be studied with a larger sample size, some of which have only been tested in a pancreatic cancer subtype or under the influence of a particular drug, and some of them are not able to distinguish cancer from inflammatory conditions. These factors reduce their specificity and sensitivity.

Differential Expression Profiles of miRNAs and Genes

In this study after analysis of the 341 cases and 108 controls (Table 3), we tried to identify the miRNA and genes associated with pancreatic cancer and their interactions. Eventually, we could introduce the new potential biomarkers for this cancer.

Table 1 Advantages and disadvantages of previous biomarkers for pancreatic cancer

Biomarker	Year	Advantages	Disadvantages	References
CEACAM1	2007	- CEACAM1's sensitivity (85%) and the specificity is (98%) good	1. The expression of CEACAM1 has been demonstrated to be lower in tumor compared with normal tissue in cancers of the breast, colon, prostate, and endometrium 2. In contrast, CEACAM1 expression is increased in lung cancer and melanoma 3. CEACAM1 cannot differentiate pancreatic cancer from chronic pancreatitis	Simeone et al. (2007)
CA19-9	2010	- The most frequently used biomarker for Pancreatic ductal adenocarcinoma (PDAC)	1. Its sensitivity and specificity are unsatisfactory, especially for the diagnosis of early-stage PDAC and for discrimination of PDAC from benign pancreatic disease 2. It still could be false negative in Lewis negative phenotype and false positive in other forms of digestive tract cancer and some non-cancerous conditions	Dong et al. (2018), Luo et al. (2017) and Rückert et al. (2010)
COL6A3	2011	1. COL6A3 protein levels were significantly upregulated in 77% of the paired PDA-adjacent tissue examined 2. COL6A3 was mainly present in the desmoplastic stroma of Pancreatic ductal adenocarcinoma (PDA), with high deposition around the malignant ducts and in between the sites of stromal fatty infiltration	1. Need future studies to explore the oncogenic and diagnostic potential of COL6A3 isoforms as PDA-specific	Arafat et al. (2011)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
miR-3679-5p and miR-940	2015	- These miRNAs possess good discriminatory power to detect resectable pancreatic cancer	1. The sensitivities and specificities ranged from 60 to 80%	Xie et al. (2015)
REG1A, LYVE1, TFF1	2015	1. Three-biomarker urine panel that discriminates early-stage PDAC patients from healthy subjects with high accuracy 2. When combined, REG1A, TFF1 and LYVE1 form a powerful urinary panel that can detect patients with stages I–II PDAC, with over 90% accuracy	1. REG1 (non-specified) expression has been reported previously in about 25% of PDACs ($n=20$) while in other study observed strong expression of REG1A in 73% of the cases examined here 2. REG1A and REG1B proteins are almost 90% identical, and are difficult to distinguish 3. TFF1 also play similar pivotal roles in cancer cells, and are thus involved in the development and progression of various cancer types 4. Transcripts of all three members of the family, and in particular TFF3, have been observed in the urinary tract of healthy subjects, but only TFF2 peptide was excreted in the urine 5. LYVE1 role in PDAC still needs to be established 6. LYVE1 expression was scarce due to the under-representation of extratumoral tissues within our case series	Makawita et al. (2013) and Radon et al. (2015)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
C4BPA	2016	-Serum C4BPA level is a potential serum biomarker to distinguish PDAC from chronic pancreatitis and major gastroenterological cancers	1. Further analysis needed in large cohort studies will warrant C4BPA as a promising biomarker of PDAC in clinical use 2. The respective sensitivities were 67.3% for serum C4BPA (the specificity was 95.4%)	Sogawa et al. (2016)
KRT16	2017	-A higher expression of KRT16 was observed in tumor than its adjacent normal pancreatic tissue	1. Overexpression of KRT16 mRNA has been identified as a prognostic markers in triple negative breast cancer	Mao et al. (2017)
miR-196a and miR-210	2017	1. miR-196a overexpression was significantly associated with poorer survival rate 2. Significantly, miR-210 displayed a positive value in terms of prognosis and miR-196a was negative for prognosis	1. miR-210 was an independent negative prognostic factor for breast cancer and neck cancer patients 2. In-depth studies are needed to illuminate the molecular mechanisms and the therapeutic target(s) of miRNAs in PDAC patients	Yu et al. (2017)
Periostin (POSTN) and CA242	2018	-The potential diagnostic biomarkers complementing CA19.9 in detecting pancreatic cancer	1. Few studies have focused on the clinical significance of serum POSTN in patients with PDAC 2. No obvious changes were observed for those patients with metastasis 3. Prognostic value for multiple tumors, such as hepatocellular carcinoma, esophageal squamous cell carcinoma, non-small cell lung cancer and breast cancer	Dong et al. (2018)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
Brain acid soluble protein 1 (BASP1,CAP-23, NAP22)	2019	-The independent prognostic importance of BASP1 was validated in a large series of pancreatic cancer patients, together with its interaction partner WT1	1. Possessing largely unknown biological and clinical functions and was selected for further analysis 2. BASP1 was found to be a potential tumor suppressor and implicated in many cancers 3. The fresh frozen samples used in the discovery phase were limited in number 4. The tissue microarray samples were accrued over a long time period with potential changes in histopathological characterization, treatment and follow-up	Zhou et al. (2019)
Glypican-1 (GPC1)	2019	-Combined detection of exosomal GPC1, exosomal CD82, and serum CA19-9 shows great promise as a standard method for PC detection	1. Rates of positive exosomal GPC1 protein expression varied greatly according to different batches of samples 2. More rigorous studies with PC patients at different clinical stages and larger population cohorts should be conducted to determine whether the detection panel can be used for early-stage PC screening	Xiao et al. (2020)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
YAP1	2020	1. YAP1 is an independent prognostic marker associated with recurrence and unfavorable survival in pancreatic cancer 2. Inhibition of YAP1/TEAD interaction interferes with the expression of AREG, CTGF, CYR61, and MSLN suggesting that YAP1 transcriptional activity may affect the development and persistence of a fibrotic tumor microenvironment	1. YAP1 protein expression did not reach statistical significance in their Kaplan–Meier analysis, likely due to the small cohort size, to clarify the prognostic role of YAP1 protein expression in pancreatic cancer 2. Additional studies based on larger cohorts are needed	Zhou et al. (2020)
PHLPP2	2020	-Illustrated a novel and precise mechanism of action of epigenetic alterations that underly the inhibition of VC in pancreatic cancer	1. Just focus on epigenetic target for the treatment of vitamin C in pancreatic cancer	Chen et al. (2020)
TNFSF9	2020	-TNFSF9 is associated with prognosis and CD8+T cell infiltration levels in patients with pancreatic cancer	1. The expression of TNFSF9 is also associated with a variety of human tumors, including melanoma, liver cancer, colorectal cancer, and lung cancer 2. TNFSF9 could not affect total immune cell infiltration but it could regulate immune cell subtypes	Wu et al. (2020)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
eIF family	2020	-eIF1, eIF2D, eIF3C and eIF6 are downregulated in PDAC, and are predictors for overall survival in PDAC patients	1. Just focusing on PDAC and some of eIF family 2. A broad range of cancer types, including pancreatic cancer, have been candidates for targeting the PI3K/AKT/mTOR pathway due to its common deregulation via amplification, mutation or loss of key regulators 3. eIFs are overexpressed in various malignancies, such as squamous cell carcinoma of the head and neck, lung, thyroid, breast and colorectal cancer 4. Need Future experiments for focus on tumor cell type-specific expressions of eIFs under consideration of tumor heterogeneity	Golob-Schwarzl et al. (2020)
ARHGEF15	2020	-Upregulation of ARHGEF15 in pancreatic cancer increased activation of the Rho-family proteins, especially RhoA, Cdc42 and Rac, resulting in enhanced motility of the pancreatic cancer cells	1. Just focusing on PDAC and several previous studies have demonstrated that overexpression of the Rho-family proteins together with enhanced Rho signaling was involved in the proliferation of cancer cells in many malignant tumors	Fukushima et al. (2016)
miR-125a-3p, miR-5100 and miR-642b-3p	2020	- These miRNAs were the most promising model in the diagnosis of PC patients from healthy controls with Sensitivity 0.98 and Specificity 0.97	1. Multiple studies have reported the effect and differential expression of these miRNAs in various cancers especially gastro Intestinal cancers	Shams et al. (2020)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
hsa-miR-7	2020	1. miR-7 expression was dramatically decreased in the plasma of patients with gemcitabine-resistant pancreatic cancer and in vitro upregulation of miR-7 significantly enhanced the sensitivity of pancreatic cancer cells to gemcitabine 2. These data suggested that miR-7 might potentiate the tumoricidal effect of gemcitabine via targeting autophagy to impair glycolysis	1. The significance of miR-7 in cancer is well documented to directly inhibit a number of oncogenic targets in multiple types of tumors, including hepatocellular carcinoma, gastric cancer, and colorectal cancer	Ye et al. (2020)
hsa-miR-1290 and hsa-miR-1246	2020	-The combined detection of CA19-9, together with miR-1290 or miR-1246, could improve the diagnostic accuracy of Pancreatic Cancer	1. The diagnostic efficiency of circulating miR-1290 and miR-1246 were tested in various cancers, including non-small cell lung cancer, prostate cancer and PC 2. There are some disadvantages for exo-miRNA research approaches due to the lack of normalization on the isolation of exosomes and absolute quantification 3. Prospective studies with larger sample size are required to explore their prognostic value for PC and expression levels of two miRNAs were not validated in PC tissues samples	Wei et al. (2020)

Table 1 (continued)

Biomarker	Year	Advantages	Disadvantages	References
PARP inhibitor	2020	-PARPis can sensitize cancer cells to DNA-damaging chemotherapies	1. Resistance to PARP inhibitors has partially has prevented their use in clinical applications 2. The most prominent target gene is BRCA, in which mutations were first identified in breast cancer and ovarian cancer	Zhu et al. (2020)
PSMD11, PTPRM and PTPRB	2020	-Protein tyrosine phosphatases, PTPRM and PTPRB, were decreased in plasma of patients with poor pancreatic ductal adenocarcinoma (PDAC) prognosis, while proteasomal subunit PSMD11 was increased in microparticles of patients with poor prognosis	1. Further studies needed for elucidating the role of these proteins in PDAC progression 2. Future research in a larger patient cohort and validation by an independent method will be required to confirm these novel findings	Sahni et al. (2020)
MCM2 and NUSAP1	2020	-MCM2 and NUSAP1 can be used as potential biomarkers for the diagnosis and prognosis of Pancreatic cancer (PC)	1. A certain degree of heterogeneity was present in the datasets selected for this study, and only four normal samples were included in TCGA 2. A larger sample size, a higher-quality dataset and biology experiments are still required to verify the reliability of the results	Deng et al. (2020)
DUSP14	2020	-DUSP14 is a novel molecular target that can be used for the treatment of pancreatic cancer	1. DUSPs act pivotally in the pathological process of multiple diseases, as well as in some kinds of cancers 2. Further study needed to reveal the potential mechanism in it	Wei et al. (2020)

Table 2 Reasons for rejecting often previous biomarkers

Genes and miRNAs previously identified as biomarkers	Available data	Reason	References
REG1A	GSE16515 down-107610 down	Lack of common in at least 3 dataset	Makawita et al. (2013)
LYVE1	GSE16515 down-46234 down	Lack of common in at least 3 dataset	Radon et al. (2015)
eIF1, eIF2D, eIF3C and eIF6	GSE 15471-16515	Lack of common in at least 3 dataset	Golob-Schwarzl et al. (2020) and Goonesekere et al. (2018)
TFF1 and COL6A3	GSE 15471 up- 16515 up- 46234 up	Lack of sharing with targets of genes affected by miRNAs	Radon et al. (2015) and Svoronos et al. (2020)
GPC1, PTPRM, PTPRB and YAP1	GSE 15471- 16515	Lack of significant logFC	Xiao et al. (2020), Zhou et al. (2020), Mantini et al. (2020) and Sahni et al. (2020)
PSMD11	GSE15471- 16515-107610	Lack of significant logFC	Sahni et al. (2020)
PHLPP2	GSE46234 up	Lack of common in at least 3 dataset	Chen et al. (2020)
TNFSF9	GSE16515	Lack of significant logFC	Xiao et al. (2020), Wu et al. (2020), Goonesekere et al. (2018) and Liu et al. (2020)
MCM2	GSE16515up-107610up	Lack of common in at least 3 dataset	Deng et al. (2020)
NUSAP1	GSE15471 up- 16515 up- 107610 up	Lack of sharing with targets of genes affected by miRNAs	
DUSP14	GSE107610- 15,471	Lack of significant logFC	Wei et al. (2020)
POSTN and ARHGEF15	GSE15471 up-16515 up- 46234 up	Lack of sharing with targets of genes affected by miRNAs	Fukushima et al. (2016)
KRT16	GSE16515 up	Lack of common in at least 3 dataset	Mao et al. (2017)
BASP1	GSE15471 up -16515 up	Lack of common in at least 3 dataset	Zhou et al. (2019) and Rajamani and Bhasin (2016)
C4BPA	GSE15471 up- 46234 up	Lack of common in at least 3 dataset	Sogawa et al. (2016)
hsa-miR-1246	GSE 24279	Lack of common in 2 dataset	Wei et al. (2020)
hsa-miR-7, hsa-miR-1290, miR-642b-3p, hsa-miR-1246, miR-196a, miR-210 and miR-125a-3p	GSE 71533	Lack of common in 2 dataset	Yu et al. (2017), Shams et al. (2020), Ye et al. (2020) and Wei et al.(2020)
miR-940	GSE 24279-71533	Lack of significant FC	Xie et al. (2015) and Shams et al. (2020)

Table 3 Five gene expression profiles and two miRNA expression profiles and their features

GEO dataset	Platform	Controls	Tissue	Years	References
miRNA					
GSE24279	GPL10944	22	136	2012	Bauer et al. (2012)
GSE71533	GPL18058	16	72	2017	Sandhu et al. (2016)
Genes					
GSE15471	GPL570	39	39	2009	Idichi et al. (2017) and Badea et al. (2008)
GSE16515	GPL570	16	36	2009	Ellsworth et al. (2013) and Pei et al. (2009)
GSE30134	GPL3985	9	15	2011	Tahira et al. (2011)
GSE46234	GPL570	4	4	2017	Barrett et al. 2012)
GSE107610	GPL15207	2	39	2018	Seino et al. (2018)

Efforts to understand the relationships between miRNAs and genes in different diseases already have been performed by the analysis of microarray data. After a search in the GEO database with the related keywords, five datasets (GSE15471, GSE16515, GSE30134, GSE46234, and GSE107610) were collected for gene expression and two datasets (GSE71533 and GSE24279) for miRNA expression analysis (Table 3).

Genes and miRNAs showing significant increase (P value < 0.05 and logFC > 1) and decrease (P value < 0.05 and logFC < -1) were identified as DEGs and differential expression miRNAs (DEMs) (Fig. 1). Finally, as shown in Figs. 2 and 3, we reached the 309 DEGs (59 down and 250 upregulated distributed in 3 databases) and 6 DEMs (hsa-miR-210 upregulated and hsa-miR-217, hsa-miR-216a, hsa-miR-216b, hsa-miR-375, and hsa-miR-634 downregulated) (Fig. 3a, b). To increase the specificity and identify more genes, we performed further analysis with common miRNAs (43 numbers with P value < 0.05) in both datasets (Fig. 3c). They were submitted to the MirDIP database and 6006 genes were predicted for these miRNAs. The common genes between 309 (DEGs) and 6006 miRNA target genes were identified, which are shown in the Venn diagram. We ultimately obtained 109 mRNAs, of which 22 and 87 were down and upregulated respectively (Fig. 4). Unlike some previous studies and as it is shown in Fig. 1, there are some important criteria in our study such as presence in at least 3 datasets, over- or under-expression with P value < 0.05 and $|\text{logFC}| > 1$, the similarity with miRNAs targets, MCODE and survival analysis. These criteria have been caused to exclude many previously introduced biomarkers like *CA19-9, TFF1, COL6A3* and *CEACAM1* from our further analysis (Table 2).

Functional and Pathway Enrichment Analyses

To further understand the functions and mechanisms of the identified DEGs, functional and pathway enrichment studies have been performed, including GO and KEGG, with the EnrichR database. The GO term enrichment analysis showed that the upregulated genes were massively enriched in the biological

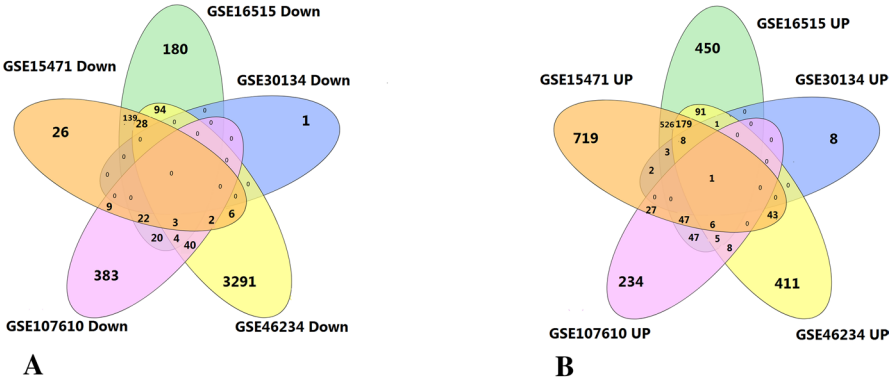

Fig. 2 Venn diagrams represent the commonly down and upregulated genes (309 DEGs), among the five identified databases. **a** Downregulated DEGs in pancreatic cancer among the five datasets were recognized via Venn diagrams, 59 genes were reported to be downregulated at least in three datasets. **b** Upregulated DEGs in pancreatic cancer among the five datasets, 250 genes were reported to be upregulated at least in three datasets

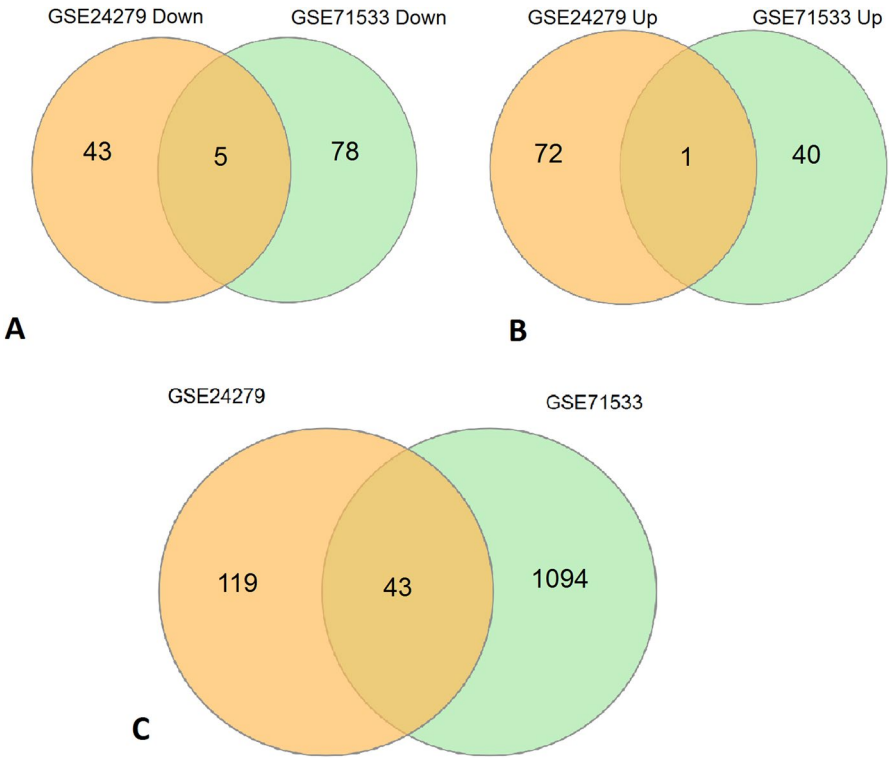

Fig. 3 Venn diagrams represent common miRNAs with different filters identified in the two datasets. **a** DEMs with *P* value less than 0.05 and logFC < − 1 were identified in both datasets. **b** DEM with *P* value less than 0.05 and logFC > 1 were identified in both datasets. **c** Common miRNAs with *P* value less than 0.05 were identified in both datasets that were recognized via Venn diagrams

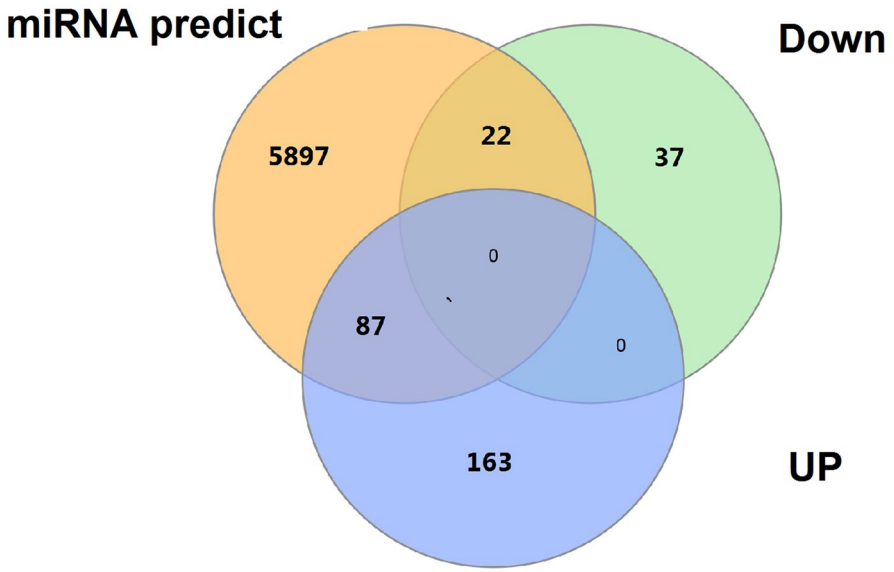

Fig. 4 Venn diagrams shows common genes between 309 (DEGs) and 6006 (miRNA targets) genes were identified. Commonality between the miRNAs predicted targets (6006 genes) and common DEGs in at least 3 databases for down and upregulation genes (59 and 250 genes) which 22 and 87 genes were associated with down and upregulated genes respectively. Finally, enrichment for these genes (22 down and 87 up) was carried out with used EnrichR and their protein networks were constructed String database. Then, these protein networks were analyzed with MCODE in Cytoscape and the important genes were introduced

process-associated group like extracellular matrix organization, collagen fibril organization, skeletal system development, regulation of cell migration, regulation of cell proliferation, regulation of the apoptotic process, cellular response to cytokine stimulus, neutrophil degranulation and regulation of transcription, while the downregulated genes mainly involved in peptide metabolic process, cellular protein localization, cellular response to insulin stimulus and organonitrogen compound catabolic process (Table S1).

Also cell component analysis showed that the upregulated genes were enriched in the endoplasmic reticulum lumen, membrane rafts and tertiary granule, integral component of the plasma membrane, focal adhesion, and lysosome. The downregulation of the genes was mainly found in the integral component of the plasma membrane and endoplasmic reticulum-Golgi intermediate compartment (Table S2). Moreover, in terms of molecular function, the upregulated genes were enriched in platelet-derived growth factor binding, transcriptional activator activity, RNA polymerase II core promoter proximal region sequence-specific binding, collagen binding, kinase binding, peptidase activity, acting on L-amino acid peptides, and transcription regulatory region sequence-specific DNA binding. The downregulated genes were enriched in zinc ion binding, metalloaminopeptidase activity, transition metal ion binding, protein homodimerization activity, and aminopeptidase activity (Table S3).

Furthermore, the KEGG pathway analysis showed upregulated genes involved in ECM-receptor interaction, amoebiasis, Axon guidance, PI3K-Akt signaling pathway, Focal adhesion Protein digestion and absorption, adherens junction, Platelet activation, and human papillomavirus infection. Downregulated genes involved in riboflavin metabolism (Table 4).

Analysis of PPI Network Modules

Up- and downregulated DEGs in pancreatic cancer were mapped via the STRING database with a PPI score > 0.4. Twenty-two nodes and one edge for downregulated genes (Fig. 5a) and 87 nodes and 134 edges for upregulated genes were constructed (Fig. 5b). MCODE analysis cannot be used for downregulated genes due to the lack of network, but such analysis was constructed for three networks (Fig. 6a–c) with different scores, which are detailed in Table 5. Seventeen genes had scores > 5 after the MCODE analysis.

Survival Analysis

After MCODE analysis, seventeen genes have been assessed in cluster 1 and 2 for pancreatic cancer survival (derived from 5 studies by cBioPortal database). As shown in Table 6, among all genes, seven upregulated genes (*CDH11, COL5A1, DTL, ITGA2, KIF14, SMC4,* and *VCAN*) significantly shortened the life expectancy ($P < 0.05$) (Fig. 7).

This significant difference can be due to five datasets related to pancreatic cancer, the sharing of genes in at least three datasets, and having other applied criteria in this study (Fig. 1). We analyzed the survival of five previously identified genes (*TFF1, COL6A3, NUSAP1, POSTN,* and *ARHGEF15*), which were removed in our latest filter. Nevertheless, they did not seem to have significant effects on patients' survival length (log rank test P value > 0.05) (Fig. 8).

miRNA-drug-mRNA Network Construction

Our goal in constructing this network is to identify important genes that are affected by different drugs and miRNAs that may be used as new agents in future studies of pancreatic cancer.

As shown in Fig. 9, initially, interaction analysis showed that multiple drugs were introduced for 12 genes (*RACGAP1, ITGA2, COL5A1, COL3A1, COL1A2, COL1A1, CDH11, CCNA2, VCAN, TGFBR1, SDC1,* and *RRM2*). Then the 23 miRNAs associated with these genes were identified, among those, 12 miRNAs (hsa-mir-107, hsa-mir-532-3p, hsa-mir-320a/b, hsa-mir-320c/d, hsa-mir-302e, hsa-mir-342-3p, hsa-mir-375, hsa-mir-217, hsa-mir-429 and hsa-mir-125a-5p) affects at least two gene.

Table 4 Enrichment up and downregulated genes in Kegg database

	P value	Genes
Kegg-upregulated genes		
ECM-receptor interaction	1.53E-06	COL1A1;COL1A2;ITGA2;SDC1;LAMC2;CD47
Amoebiasis	6.21E-05	COL1A1;COL3A1;COL1A2;LAMC2;VCL
Axon guidance	1.39E-04	EFNA1;SEMA3C;CFL1;CXCR4;EFNA5;MET
PI3K-Akt signaling pathway	1.54E-04	COL1A1;EFNA1;COL1A2;ITGA2;LAMC2;EFNA5;YWHAZ;MET
Focal adhesion	2.33E-04	COL1A1;COL1A2;ITGA2;LAMC2;MET;VCL
Adherens junction	2.74E-04	LEF1;MET;TGFBR1;VCL
Protein digestion and absorption	6.42E-04	COL1A1;COL3A1;COL1A2;COL5A1
AGE-RAGE signaling pathway in diabetic complications	9.53E-04	COL1A1;COL3A1;COL1A2;TGFBR1
Platelet activation	0.00210712	COL1A1;COL3A1;COL1A2;ITGA2
Pathways in cancer	0.00215558	EGLN3;ITGA2;LEF1;CXCR4;LAMC2;PTGS2;MET;TGFBR1
Relaxin signaling pathway	0.00250154	COL1A1;COL3A1;COL1A2;TGFBR1
Human papillomavirus infection	0.00317694	CCNA2;COL1A1;COL1A2;ITGA2;LAMC2;PTGS2
Small cell lung cancer	0.00778396	ITGA2;LAMC2;PTGS2
Kegg-downregulated gene		
Riboflavin metabolism	0.008768	ENPP1

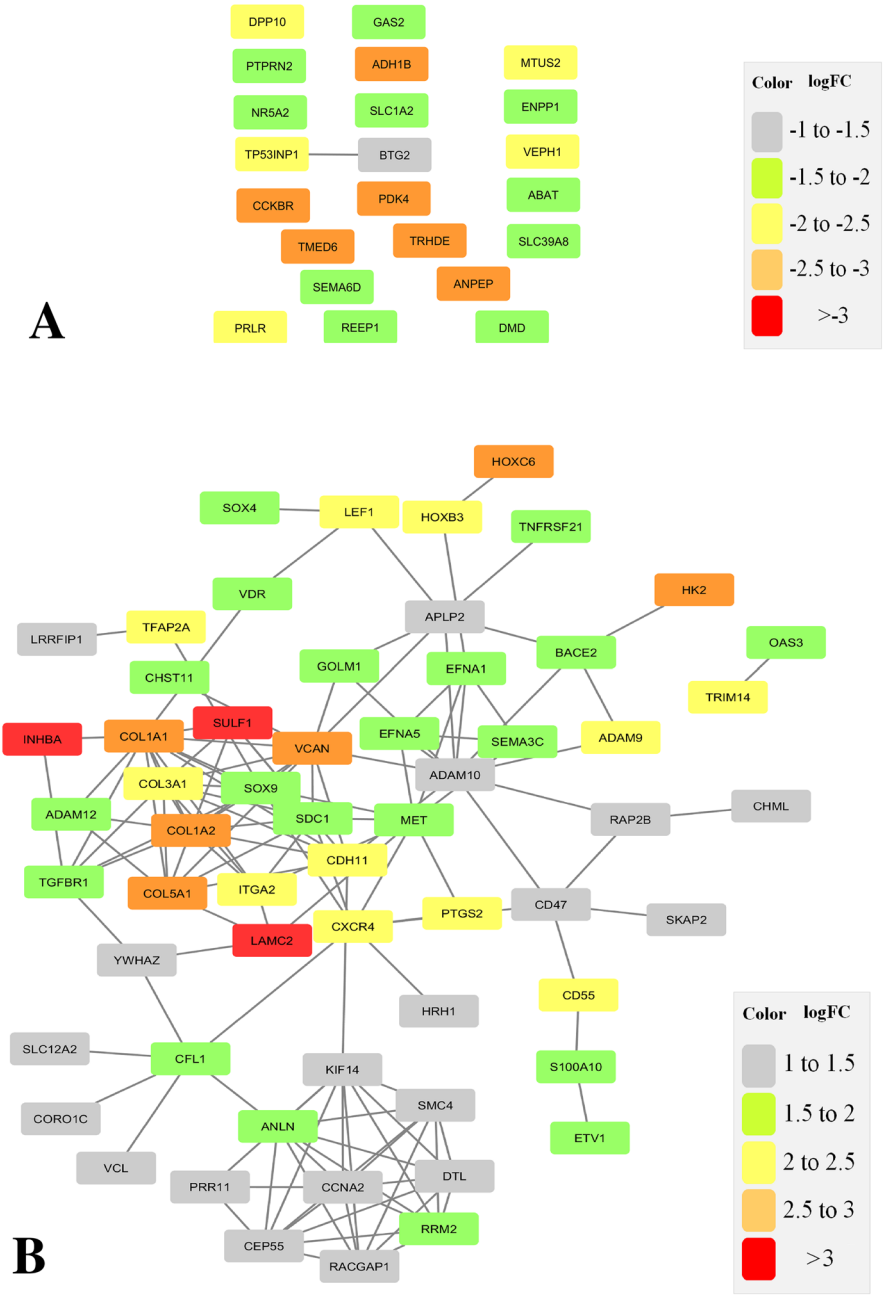

Fig. 5 PPI networks of DEGs identified in pancreatic cancer status versus normal status. **a** Downregulation of DEGs identified in at least three datasets and common with DEMs target gene, were used to construct the PPI network. The lines between nodes represent the interactions between genes. **b** Upregulation of DEGs identified in at least three datasets and common with DEMs target gene. The color of each gene is determined based on the logFC. Guide for logFC are listed at the bottom right of the page

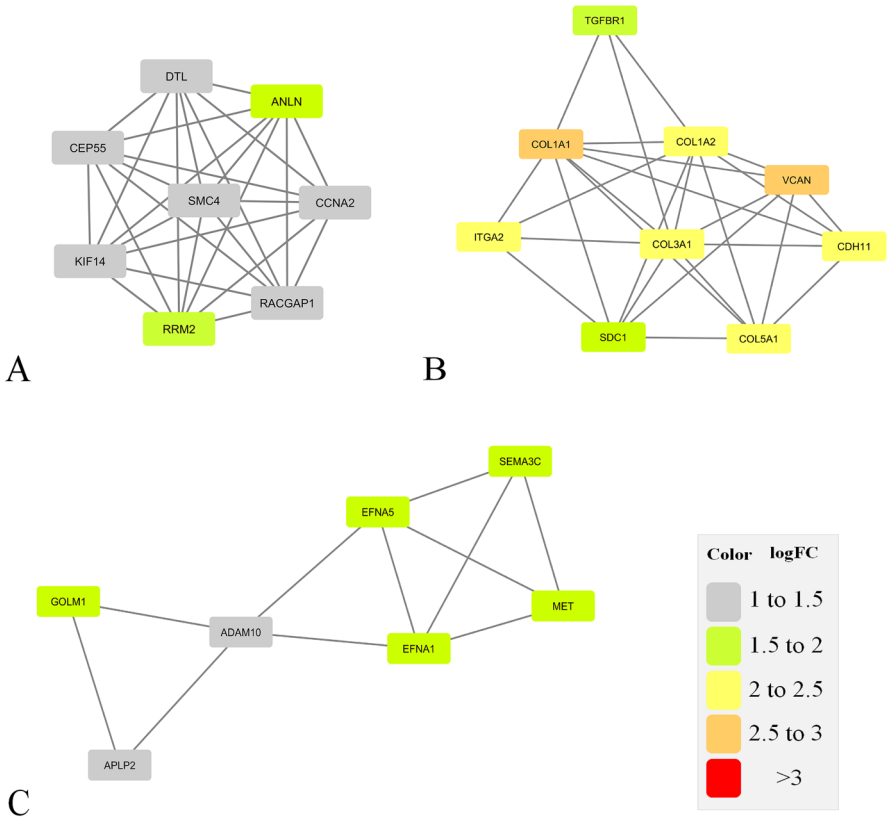

Fig. 6 Three PPI modules were extracted from the PPI network using MCODE in Cytoscape. *PPI* protein–protein interaction, *DEGs* differentially expressed genes, blue nodes indicate upregulated genes. The color of each gene is determined based on the logFC. Guide for logFC are listed at the bottom right of the page

Table 5 Three networks constructed with MCODE analysis for DEG identified in at least three datasets and common with DEMs target gene

Cluster	Score	Nodes	Edges	IDs
1	8	8	28	CEP55, DTL, SMC4, ANLN, KIF14, RACGAP1, CCNA2, RRM2
2	6.75	9	27	CDH11, ITGA2, COL3A1, SDC1, COL1A1, COL1A2, VCAN, TGFBR1, COL5A1
3	3.667	7	11	GOLM1, EFNA5, SEMA3C, ADAM10, EFNA1, APLP2, MET

Based on the figure, we found that Hsa-mir-107 and hsa-mir-125a-5p can regulate 6 genes in this network, that their common genes are *COL5A1, CDH11,* and *TGFBR1*. These two miRNA and three genes can be introduced as major miRNAs and genes of this network.

Table 6 Median months survival in patients with altered 7 genes expression

Gene symbol	Cases with or without alteration(s) in query gene(s)	Number of cases, total	Number of cases, deceased	Median months survival
VCAN	With	10	10	14.13
	Without	359	189	20.35
SMC4	With	10	8	10.12
	Without	359	191	20.19
KIF14	With	8	7	8.02
	Without	361	192	20.19
ITGA2	With	3	2	4.73
	Without	366	197	19.96
DTL	With	8	7	4.73
	Without	361	192	20.19
COL5A1	With	11	9	15.95
	Without	358	190	20.34
CDH11	With	6	6	19.48
	Without	363	193	20.34

Discussion

The microarray data analysis has been used in many studies on the different types of tumors to find the important gene, miRNA, and metabolic pathways (Tu et al. 2019). In general, the role of miRNAs and genes in carcinogenesis and cancer progression is well known, but their expression, function, and association with pancreatic cancer development are not yet fully investigated (Sun et al. 2017). Early detection of small cancers before the onset of metastasis is currently the only tools to significantly improving resection, post-resection prognosis, and ultimately survival. However, not all available diagnostic tools and biomarkers for PDAC are able to detect early or preventive cancer and suffer from low specificity and sensitivity (Sharma et al. 2020).

In this study, we attempted to explore the interactions between genes, miRNAs, and important pathways in pancreatic cancer with the lowest filtration limitation and relatively high sample size through an accepted analysis method such as GEO2R. We identified the *DTL, CDH11, COL5A1, ITGA2, KIF14, SMC4,* and *VCAN* genes and hsa-mir-210, hsa-mir-217, hsa-mir-216a, hsa-mir-216b, hsa-mir-375, and hsa-mir-634 miRNAs associated with pancreatic cancer. Consequently, we could introduce the new potential biomarkers for this cancer**.**

One important gene is *VCAN* (belonging to the sulfate proteoglycans family), which has been expressed in many malignancies, such as pancreas, gastric, and prostate cancers. This gene often associated with poor prognosis (Barry et al. 2013; Jiang et al. 2019). In an integrated bioinformatics analysis for pancreatic ductal adenocarcinoma, some genes like *MMP7, MMP1, COLA1, CDH11, COL3A1, ITGA2*, and *VCAN* were introduced as hub genes. These may

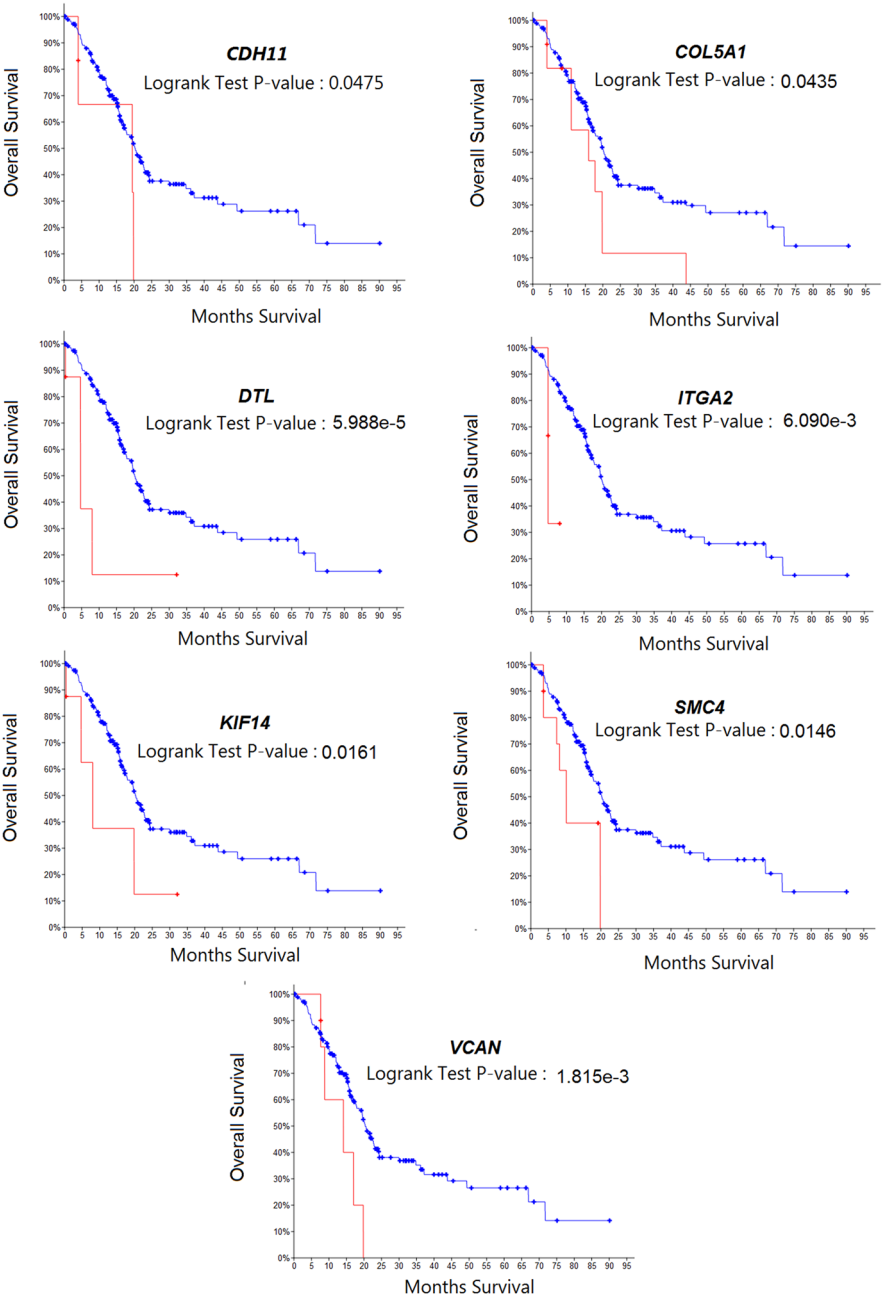

Fig. 7 Overall Survival Kaplan–Meier estimate of 7 genes in 1034 samples from TCGA datasets with term of Pancreatic Adenocarcinoma (TCGA, PanCancer Atlas), Pancreatic Adenocarcinoma (TCGA, Provisional), Pancreatic Cancer (UTSW, Nat Commun 2015), Pancreatic Adenocarcinoma (QCMG, Nature 2016) and Pancreatic Adenocarcinoma (ICGC, Nature 2012). Red line represents cases with alterations. Blue line represents cases without alterations (VCAN, $P = 1.815e^{-3}$), (SMC4, $P = 0.0146$), (KIF14, $P = 0.0161$), (ITGA2, $P = 6.090e^{-3}$), (DTL, $P = 5.988e^{-5}$), (COL5A1, $P = 0.0435$), (CDH11, $P = 0.0475$)

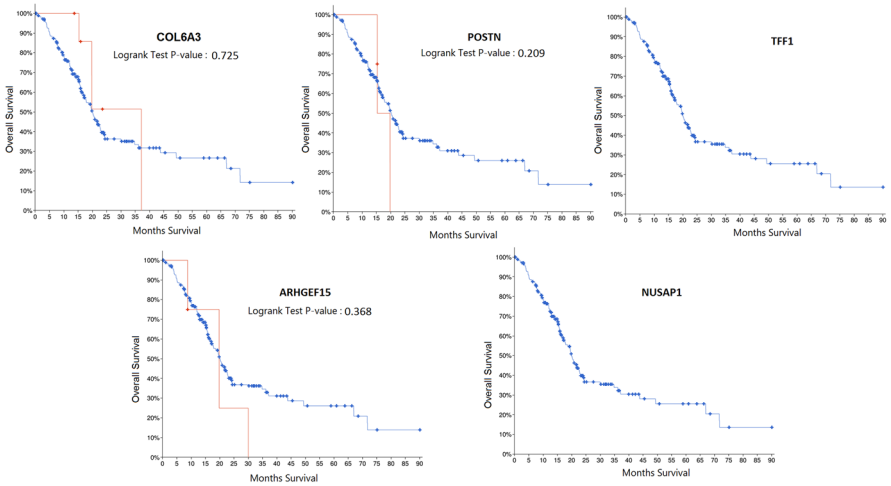

Fig. 8 Overall survival Kaplan–Meier estimate of five genes that were previously identified as pancreatic cancer biomarkers and they removed in our latest filter in 1034 samples from TCGA datasets with term of Pancreatic Adenocarcinoma (TCGA, PanCancer Atlas), Pancreatic Adenocarcinoma (TCGA, Provisional), Pancreatic Cancer (UTSW, Nat Commun 2015), Pancreatic Adenocarcinoma (QCMG, Nature 2016) and Pancreatic Adenocarcinoma (ICGC, Nature 2012). Red line represents cases with alterations. Blue line represents cases without alterations (*COL6A3*, $P=0.725$), (*POSTN*, $P=0.209$), (*ARHGEF15*, $P=0.368$). *TFF1* and *NUSAP1* did not have enough information in this database

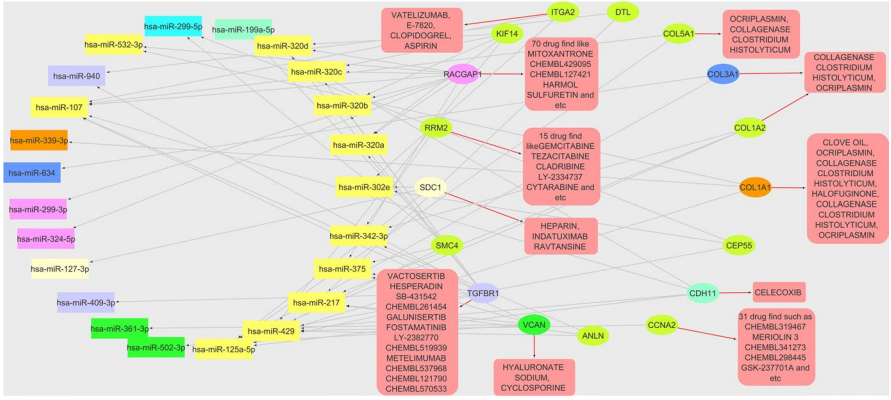

Fig. 9 Interaction network between the 17 gene from MCODE analysis (cluster one and two) and 43 reported miRNAs. Circle represent genes, rectangle represent miRNAs and round rectangle show drugs. Each miRNA and gene is recognized by a specific color and miRNAs with yellow rectangles have targets of more than 2 genes. 23 of 43 miRNA and 147 related drugs were associated with 17 genes, then these drugs were inserted into the network and the final form was constructed

be potential targets for diagnosis, treatment, and prognostic prediction (Lu et al. 2018). Two studies conducted in 2014 and 2019 have shown that *S100A6* was significantly upregulated in pancreatic carcinoma compared to normal tissues. They also showed that *ITGA2* overexpression and hypomethylation of *MET* and *ITGA2*

were significantly associated with overall survival (Liu et al. 2019; Nones et al. 2014).

In compliance with our results, a study conducted by Mingge Shang et al. (2019 has shown an association between increased expression of six genes (*KRT7, KRT19, SEMA3C, ITGA2, MYOF*, and *ANXA1*) and their poor survival. PI3K-Akt, Focal adhesion and ECM-receptor interaction were also recognized as important pathways (Shang et al. 2019). It is noteworthy that these results were based on other databases and smaller samples than our investigation. Ivane Abiatari et al. (2009 showed upregulation of kinesin family member 14 (*KIF14*) and Rho-GDP dissociation inhibitor beta (*ARHGDIbeta*) mRNA levels in patients with pancreatic cancer (Abiatari et al. 2009).

Song Ye in 2014 analyzed the GEO-derived pancreatic cancer microarray data with 60 cancer samples and 21 controls. Through investigating the association between genes and miRNAs, they identified different miRNAs and genes as important elements in this cancer (Ye et al. 2014). In comparison to their study, the present research includes a higher number of samples and a new data analysis method. miRNA-210 had a significant upregulation in both studies, while miR-217 and miR-216a had a significant downregulation.

In agreement with our results, another study in 2014 on pancreatic cancer showed a significant increase in miR-210 and a significant decrease in miR-217, miR-216, and miR-375. Furthermore, our results showed a significant decrease in miR-216a and miR-634, but their expression has not been mentioned in that study (Ye et al. 2014). This difference can be due to the number of samples and the type of data analysis methods.

High expressions of miR-196a and miR-210 were associated with poor survival (*P*-Value = 0.001 and *P* value = 0.003) (Yu et al. 2017); however, miR-196a was excluded from our study due to lack of sharing between two miRNA datasets. miR-216a may potentially serve as a novel tumor marker and prognostic factor for pancreatic cancer and miR-217 functions as a prognosis predictor and inhibits pancreatic cancer cell proliferation, invasion and promotes apoptosis via targeting *E2F3*.

The next miRNA showing a significant downregulation in our study was miR-375. Previously, downregulation of this miRNA was demonstrated by in vitro methods such as real-time PCR in pancreatic, glioma, and gastric cancers. The hsa-miR-375 is associated with inhibition of migration and proliferation of pancreatic and glioma cancer cells via downregulating of *RWDD3* gene (Ji et al. 2020). Our mRNA–miRNA interaction network also demonstrated that the hsa-miR-375 can regulate the *RACGAP1, TGFBR1, SMC4, VCAN* genes. The *RACGAP1* gene is one of the most important predictors of poor prognosis in the pancreas adenocarcinoma (Khalid et al. 2019). *TGFBR1* has been involved in invasion, migration, angiogenesis, and tumorigenesis of pancreatic cancer cells and it is also active in cellular pathways such as TGF-β/SMAD (Gasparini-Junior et al. 2019; Zhou et al. 2018).

Ultimately the last miRNA that was examined in the present study was miR-634, with a significant downregulation. This event has also been reported in different cancers (Gao et al. 2016; Fischer et al. 2001). Previous studies have already shown its anti-tumor role and promotive action in the apoptosis of cancer cells. The mRNA–miRNA interaction network showed that hsa-miR-634 could regulate

COL3A1. Upregulation of the *COL3A1* gene is directly associated with gliomas, renal cell carcinoma (RCC), and bladder malignancies growth, metastasis, progression, and prognosis (Su et al. 2014; Shi and Tian 2019). It may be referred to as a diagnostic or therapeutic biomarker (Gao et al. 2016). In general, the inconsistency between the genes and miRNAs reported in the different system biology studies maybe depend on many factors such as the cancer type, the sample size, filtration approaches, and the procedures of data analysis.

These genes and miRNAs were found to be related to drug response. Inactivating mutations in both *TGFBR1* and *TGFBR2* have been observed in pancreatic carcinoma and constitutively decreased *TGFBR1* expression may have a decreased risk of pancreatic cancer by regulating factors such as TGF-β-mediated growth inhibition (Adrian et al. 2009). In agreement with our results, in human pancreatic cancer (PC) samples and 12 PC cell lines, an increase in *TGFBR1* expression has been observed (Adrian et al. 2009; Fan et al. 2020). Yue Fan and et al. (2020) showed that *TGFBR1, VTCN1*, and *LGALS9* were found to be associated with the worse outcomes of patients with PC. Also, they demonstrated, upregulation of *TGFBR1* was closely pertained to poor overall survival and significantly associated with the prognosis in PC (Fan et al. 2020).

Collagen type V (COL5) presents in most connective tissue matrix and plays a functional role in different cancers such as breast cancer (Barsky et al. 1982), colon cancer (Fischer et al. 2001), and pancreatic ductal adenocarcinoma (Berchtold et al. 2015). Bioinformatic identification showed that *COL5A1* may be a major factor in many types of cancers like breast cancer, gastric cancer, papillary thyroid carcinoma, ovarian cancer, oral squamous cell carcinoma, and lung adenocarcinoma. Also, overexpression of *COL5A1* significantly correlates with the overall survival of patients with clear cell renal cell carcinoma (Feng et al. 2019).

CDH11 signaling may play an essential role in mediating the function of activated stellate cells, defining the fibrotic and inflammatory microenvironment in both pancreatitis and cancer. In agreement with our results, Cadherin-11 (Cad-11, also known as OB cadherin or CDH11) has shown upregulation in pancreatic cancer and involved in pancreatic stellate cells (PSCs) activation and pancreatic cancer metastasis (Birtolo et al. 2017).

The miR-107 is abnormally expressed in several metastatic tumors like colorectal, breast, gastric, liver, lung, bladder, and cervical cancer, and its upregulation contributes to cancer progression and metastasis. Also, upregulation of miR-107 is associated with poor clinicopathological parameters and prognosis in pancreatic ductal adenocarcinoma (PDAC) patients (Xiong et al. 2017). miR-107 had been considered as an oncogene miRNA in gastric and liver cancer (Gong et al. 2019).

miR-125a-5p has been shown to play critical functions in human malignancies. miR-125a-5p acted as a tumor suppressor in various human malignancies, such as hepatocellular carcinoma, breast cancer, lung cancer, gastric cancer, and glioblastoma (Gao et al. 2014). YANG and ZENG by integrating transcriptome analysis showed the upregulation of hsa-mir-125a-5p in miRNA–mRNA crosstalk in pancreatic cancer (Yang and Zeng 2015). Lichao Pan and et al. (2018) showed that the miR-125a by targeting mitofusin 2 (Mfn2), promotes apoptosis, metabolism disorder, and migration impairment in pancreatic cancer cells (Pan et al. 2018).

Conclusion

The important genes and miRNAs introduced in this study, due to the significant change in expression in tumor and normal tissue and the effect on patient survival, can be more specific and sensitive than previous tests for pancreatic cancer and may be used alone or in combination with other tests for diagnosis or prognosis. However, it is necessary for these identified genes and miRNAs to pass the experimental approvals later.

To the best of our knowledge, we attempted to identify DEGs using comprehensive bioinformatics evaluations and come up with potential biological markers to predict disease progression. After analysis, a total of 309 DEGs and 6 DEMs were screened with promising targets for pancreatic cancer treatment, management, and prognosis, among which the *DTL, CDH11, COL5A1, ITGA2, KIF14, SMC4, VCAN*, hsa-mir-210, hsa-mir-217, hsa-mir-216a, hsa-mir-216b, hsa-mir-375 and hsa-mir-634 had pivotal functions. Also, the wide relation of the hsa-mir-107 and hsa-mir-125a-5p and *COL5A1, CDH11* and *TGFBR1* genes to drug response was represented in the miRNA-drug-mRNA network. These outcomes call for more organized researches to model exact aspects of gene networks in pancreatic cancer.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10528-021-10062-x.

Acknowledgements The authors would like to thank office center of Baqiyatallah Research Center for Gastroenterology and Liver Diseases for providing the right conditions to doing this work.

Declarations

Conflict of interest The authors are not declaring any conflict of interest.

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