Gene modules and non-coding RNAs involved in pancreatic tumorigenesis through acinar ductal metaplasia

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Research article

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Abstract

Background

Acinar ductal metaplasia (ADM) can progress through pancreatic ductal carcinoma in situ (PanIN) to pancreatic ductal adenocarcinoma (PDAC). However, the genetic alterations and its transcriptional regulators during the process of ADM-driven PDAC tumorigenesis are largely unknown. Therefore, we applied a multidimensional integration strategy to unveil the gene modules and non-coding RNAs that drives the ADM-PanIN-PDAC process.

Methods

GSE40895 and the microarray datasets were integrated to unmask the regulators link ADM, PanIN and PDAC. Based on the differential expressed genes and protein–protein interaction (PPI) networks for each stage, Overlap and crosstalk gene modules in ADM-PanIN-PDAC were identified using STRING and Cytoscape. Function of these modules were elucidated by gene ontology analysis. Expression level of hub genes and survival analysis were investigated in human PDAC via GEPIA. MiRDB database was applied to predict potential non-coding RNAs (ncRNAs) capable of regulating overlap and crosstalk genes.

Results

We found several bridging ADM gene modules (e.g. SMARCA1 and H2AFZ), PanIN gene modules (e.g. HDAC11 and SMARCA2) and PDAC gene modules (e.g. OLFR239 and CLIP3). They were enriched in in nucleosome assembly, chromatin organization and G-protein coupled receptor signaling pathway by GO analysis. MicroRNAs (e.g. mmu-miR-335-5p and mmu-miR-669n) and IncRNAs (e.g. H19 and Gm14207) took part in this ample crosstalk by regulating the gene expression.

Conclusions

SMARCA1, SMARCA2 and CLIP3 were identified as novel crosstalk genes and significant prognostic biomarkers, providing new insights into ADM-driven PDAC carcinogenesis. Transcriptional regulatory non-coding RNAs targeting crosstalk and overlap genes appear promising for early PDAC intervention.

Background

Pancreatic ductal adenocarcinoma (PDAC) is the fourth leading cause of cancer death and still on track to be the second lethal disease within a decade[1, 2]. It is an aggressive cancer with poor outcome due to late diagnosis and refractory to most treatments[3]. The traditional PDAC progression model indicated that pancreatitis associated ADM with accumulation of genetic alterations could develop pancreatic
intraepithelial neoplasia which is a well-known precursor lesion of PDAC. Pancreatitis has been documented as a robust predisposing factor for pancreatic cancer[4, 5]. Acinar-ductal metaplasia (ADM) often results from pancreatitis[6] and is also frequently associated with PanIN[7], making it a linkage between inflammation and malignancy. It is characterized by the loss of morphology and genetic signatures of acinar cells and gain of characteristics of pancreatic ducts[8, 9]. Lineage tracing experiments demonstrated that PanIN lesions arise from ADM and could eventually progress to PDAC[10]. ADM, PanIN and PDAC may have genetic alterations and signaling pathway aberrations in common[11]. Thus, we believe that ADM may represent a very early change in pancreatic tumorigenesis. Characterization of the genetic and epigenetic alterations during ADM-PanIN-PDAC progression may yield insights into the discovery of new diagnostic biomarkers and novel therapeutic targets.

The activation of oncogenes (KRAS, BRAF, AKT2, GATA6 and MYC), inactivation of tumor suppressor genes (CDKN2A, TP53, SMAD4/DPC4 and BRCA2) and mutations in genome maintenance and repair genes (MLL, ATM and ARID1A) have all been implicated in PDAC carcinogenesis[12, 13]. The famous KRAS mutation in PDAC triggers its downstream signaling cascade, such as the mitogen-activated protein kinase (MAPK), phosphoinositol-3 kinase (PI3K), and transforming growth factor-β (TGF-β) signaling pathways, to regulate cell differentiation, proliferation and survival[14]. Importantly, epigenetic process that comprise DNA-methylation, histone-based changes by post-transcriptional modification and remodeling of nucleosome as well as noncoding RNAs can regulate above gene expression without changing DNA sequence, and eventually contributes to PDAC pathogenesis[15]. It has been reported that mutated histone modification enzymes[16] and SWI-SNF complex[17] are one of the key PDAC epigenetic drivers. Several enzymes in charge of histone modification including acetylation and methylation, such as histone acetyltransferase 1(HAT1), and H3K4me3, are crucially linked to PDAC prognosis and cancer immune surveillance[18, 19]. As a part of the SWI/SNF complex, ARID1A is frequently mutated in PDAC and affects PDAC development[20]. Growing numbers of studies have presented that noncoding RNAs (ncRNAs) are also highly related with PDAC carcinogenesis and prognosis. Of these, microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are relatively well-studied ncRNA in carcinogenesis, including oncogenic candidate miR-21, miR-217, which could regulate PDAC invasion and metastasis by targeting key KRAS signaling pathways[21]. Overexpressed lncRNA (H19) in PDAC was reported to promote tumor invasion by sponging a miRNA, let-7[22].

Although genetic and epigenetic changes of PDAC have been explored, the crosstalk within genetic alterations involved in the three-stage progression model of ADM-PanIN-PDAC and its network interaction with epigenetic alterations (miRNAs and lncRNAs) remain ill-defined. Here we identified potential driver genes promoting the development of ADM-PanIN-PDAC, determined the miRNAs and lncRNAs regulating the expression of genes involved in the progression of ADM-PanIN-PDAC. These genetic alterations and its transcriptional regulators during the process of ADM could deepen our understanding of the molecular mechanisms of PDAC carcinogenesis and open a new opportunity for cancer prevention and early detection.
Materials And Methods

Selection of sample and differentially expressed genes.

we downloaded GSE40895 from Gene Expression Omnibus containing whole genome information on ADM, PanIN and PDAC through National Center of Biotechnology Information. Mice injected with caerulein for three days was considered as ADM group [23]. Mice injected with PBS following the same protocol was set as control group. Pdx1-Cre;Kras+/+ mice was chosen as control group for PanIN group and PDAC group. Pdx1-Cre; LSL-KrasG12D/+ model was used to establish PanIN and PDAC. Gene expression was standardized by Limma package for R [24]. P value less than 0.05 was considered as statistically differentially expressed genes. Heatmap of DEGs was also drawn in R.

Establishing PPI network and gene modules

To understand the interactions among ADM, PanIN and PDAC, protein-protein interaction (PPI) was obtained from STRING database and its network was analyzed by Limma package for R. Based on the PPI network, we used MCODE plugin in Cytoscape (http://apps.cytoscape.org/apps/mcode) to select gene module from ADM, PanIN and PDAC respectively.

Overlap gene modules among ADM, PanIN and PDAC

Overlap gene module between samples of ADM and PanIN was selected by hypergeometric test with following formula[25]:

\[
P = 1 - \sum_{i=0}^{m} \left( \frac{n}{i} \right) \left( \frac{N-n}{M-i} \right) \left( \frac{N}{M} \right)
\]

M, n, N and m represents the number of genes in ADM module, PanIN module, STRING database and overlap modules in total respectively. Overlap gene module between samples of PDAC and PanIN was also selected by the formula mentioned above. In this case M and n means the number of genes in PanIN and PDAC, other values remain the same as above. P value less than 0.05 was considered statistically significant. Same test was run again on these two overlap gene modules. We finally obtained significant overlap gene module of ADM-PanIN-PDAC. Cytoscape was used to visualize interaction network of overlap gene modules.

Crosstalk gene modules among ADM, PanIN and PDAC

Whether the crosstalk of two gene modules is statistically significant depends on the number of interaction between two certain PPI networks and random computation[25]. One pair of sub-network modules of ADM and PanIN (PanIN and PDAC) had m times of participation interaction in actual conditions. The original PPI network was randomized 1000 times by maintaining the degree of distribution of the unchanged nodes. The two sub-network modules with the same size as the original
network modules were randomly screened. We computed the interaction times in random sub-network modules in the same pair of ADM and PanIN (PanIN and PDAC) modules. The p value for the significance of interaction between a single pair of sub-network modules was calculated as the randomized simulation computation of interaction times larger than the actual participation interaction times divided by 1000 times. Interactive sub-network modules with a p value less than 0.05 were considered significant interactive sub-networks. Crosstalk of ADM-PanIN-PDAC was selected based on the method above.

**Gene ontology analysis of overlap and crosstalk gene modules**

The function of significant overlap and crosstalk gene modules was investigated by GO analysis through DAVID database (https://david.ncifcrf.gov). Fisher exact test was applied and P value less than 0.05 was defined as statistically significant.

**MicroRNA and IncRNA network regulating the overlap and crosstalk gene modules**

MiRDB database was used to predict those microRNAs capable of regulating significant overlap and crosstalk gene modules with bioinformatic tool MirTarget. All the mice IncRNA information were obtained from deepbase (http://biocenter.sysu.edu.cn/deepBase/browser.php). Co expression of IncRNA and potential target genes were acquired based on Pearson correlation by R. Only those with both P value less than 0.05 and correlation value more than 0.7 were considered as predicted IncRNA.

**Differentially expressed and prognostic overlap or crosstalk genes in human PDAC**

To explore the expression level of overlap and crosstalk genes in human PDAC samples, we used GEPIA tool[26] to perform differential expression analysis in 171 normal pancreata and 179 PDAC tissue produced by The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEX) projects. Genes with absolute log₂ Fold Change (|log₂FC|) > 1 and P < 0.05 are considered differentially expressed. Overall survival analysis was also performed by GEPIA tool. It classified the high-expression and low-expression cohorts according to the median for log-rank test (Mantel-Cox test). Hazard ratios (HR) and confidence intervals (CI) were given. Genes with P < 0.05 were considered as significant potential prognostic biomarkers for PDAC. Results with statistical significance were reported.

**Results**

**DEGs and PPI network in ADM-PanIN-PDAC**

In the GSE40895 dataset, a total of 1658 DEGs in ADM (972 upregulated, 686 downregulated), 557 DEGs in PanIN (254 upregulated, 303 downregulated) and 705 DEGs in PDAC (355 upregulated, 350
downregulated) were identified among samples compared with matched non-precursor lesions or non-tumor tissue samples respectively. The heatmap of the DEGs expression was also created in ADM, PanIN and PDAC groups correspondingly (Fig. 1a). To investigate the regulatory correlations of the DEGs in ADM, PanIN and PDAC, PPI network of the DEGs was mined. 935 DEGs from a total of 1658 DEGs in ADM (Fig. 1b) were filtered into the DEG PPI network complex, including 6278 edges and 935 nodes. The degree value of the genes was indicated by the size of the nodes. The top 10 largest nodes in ADM included Ehmt1, Hdac3, Cecr2, Cdk6, Ranbp2, Bptf, Actg1, Acta1, Ncbp1 and Cul3. We then clarified 639 PPI pairs among 261 filtered DEGs in PanIN and found 10 nodes with the higher degree (Rhob, Hist1h3g, Hist1h4j, Hist4h4, Hdac11 and Cdk17, Fig. 1c). Among all the 705 DEGs in PDAC, 320 DEGs were filtered into the PPI network with 320 nodes and 777 edges. Rhoq, Actr8, Frk, Zap70, Mras, Akt3, Lyn, Rab25, Pik3c3 and Jup were the top 10 largest nodes in the PPI network of PDAC (Fig. 1d).

**Significant overlap gene modules in ADM-PanIN-PDAC**

Totally, twenty-six, seven and nineteen gene modules were selected from PPI networks of ADM, PanIN and PDAC respectively based on MCODE plugin of Cytoscape software. Using the hypergeometric tests among the genes above, we found one pair of modules containing significant 4 overlap genes between ADM module-4 and PanIN module-1 (p = 0.012, Fig. 2). DEGs in ADM module-4 classified by GO analysis were enriched in nucleosome assembly, positive epigenetic regulations and initiation of DNA templated transcription. Interestingly, DEGs in PanIN module-1 were enriched in similar functions including epigenetic regulation of gene expression, DNA-templated transcription and DNA methylation. 75% of all the genes annotated in both ADM and PanIN modules were members of the histone family, indicating strongly its potential roles in promoting ADM to PanIN. Coincidently, all the 4 overlap genes (Hist1h2an, Hist1h4c, Hist1h4m and Hist4h4) belong to core histone family, H2A and H4, suggesting the critical roles they may play in promoting ADM to PanIN. To further understand the major functions of the overlap genes, we performed a GO analysis based on the DAVID database (Table 1). Unfortunately, no significant overlap genes were found between PanIN and PDAC modules. It indicated that overlap genes were highly involved in the initiation stage of PDAC (ADM and PanIN), rather than PanIN-PDAC stage. However, whether overlap genes exist between PanIN-PDAC based on other database and what are the specific genes remain to be explored in future. Therefore, we believe the mechanism for regulating ADM-PanIN-PDAC progression may be mostly relied on crosstalk genes, especially for the PanIN-PDAC stage.
Crosstalk gene modules in ADM-PanIN-PDAC.

Crosstalk modules between AMD and PanIN

Table 1
The function of the significant overlap modules.

| Module  | Genes                                      | GO term                                      | P value  |
|---------|--------------------------------------------|----------------------------------------------|----------|
| ADM-4   | Hist1h4h, Hist1h4m, Hist2h4, Hist1h4i, Smyd5, Atrx, Actr10, Hist1h2a, Hist1h2b, Hist1h2bn, Ttf2, Hist1h4c, Hist1h2an, Hist1h4f | GO:0006334 ~ nucleosome assembly             | 9.43E-18 |
|         |                                            | GO:0045815 ~ positive regulation of gene expression, epigenetic | 6.79E-14 |
|         |                                            | GO:0006352 ~ DNA-templated transcription, initiation | 1.42E-13 |
| PanIN-1 | Hist1h2an, Hist1h4c, Hist4h4, Hist1h4m, Hist1h2ag, Hist1h2ae, Hist1h4j, Hist3h2a, Hist2h2ac, Top1mt, Hist1h2af, Rbm43, Ercc6 | GO:0032776 ~ DNA methylation on cytosine | 8.23E-07 |
|         |                                            | GO:0045815 ~ positive regulation of gene expression, epigenetic | 9.05E-07 |
|         |                                            | GO:0006352 ~ DNA-templated transcription, initiation | 1.29E-06 |

Crosstalk modules between PanIN and PDAC

Seven crosstalk modules between PanIN and PDAC were uncovered, shown in Table 2. PanIN module-4 has crosstalk with three different PDAC modules, indicating the close interaction between these two stages (Fig. 3d-3f). OR family also link PanIN module-6 and PDAC module-1(Fig. 3g). ORs have been shown to be involved in cell differentiation and carcinogenesis[27]. However, its role in pancreas is unclear. PanIN module-3 interacted with both PDAC module-10 and 13. Interaction between PanIN
module-1 and PDAC module-9 was also uncovered (Fig. 3h-3j). These crosstalk modules may provide new insights into how PanIN gradually progressed to PDAC.

Table 2
The crosstalk gene modules between PanIN and PDAC samples

| PDAC modules | crosstalk edges | PanIN modules | P value |
|--------------|-----------------|---------------|---------|
| PDAC-13-module | 14              | PanIN-3-module | 0.000   |
| PDAC-9-module | 15              | PanIN-4-module | 0.006   |
| PDAC-19-module | 4               | PanIN-4-module | 0.012   |
| PDAC-10-module | 29              | PanIN-3-module | 0.000   |
| PDAC-1-module | 12              | PanIN-6-module | 0.002   |
| PDAC-9-module | 42              | PanIN-1-module | 0.036   |
| PDAC-10-module | 3               | PanIN-4-module | 0.040   |

Crosstalk modules in ADM-PanIN-ADM

We finally combined all the 10 crosstalk modules above to select crosstalk modules among three different modules (ADM, PanIN and PDAC). Two crosstalk sub-network of ADM-PanIN-PDAC were discovered (Fig. 3k&3l). Interestingly, most genes involved in the crosstalk of ADM-PanIN-PDAC are from Histone family. It’s conceivable to hypothesize that mutation and modification of histone may promote ADM progress to PDAC through multiple ways including nucleosome assembly, microtubule-based process and chromatin modification predicted by GO analysis (Table 3). The top 10 genes regulating ADM-PanIN-PDAC with highest degree were Chd1, Bptf, Smarca1, Cecr2,H2afz annotated in ADM module-1, Smarca2 in PanIN module-4, and Frk, Clip3, Kcnmb2, Ccng1 in PDAC module-9 (Fig. 3k). Another crosstalk network focuses on OR superfamily (Fig. 3l). GO analysis shows that these genes mainly function through G-protein coupled receptor (GPCR) signaling pathway. So far, the association of ORs and GPCR was underappreciated. Some reported that certain ORs inhibited the proliferation of lung and prostate cancer cell line[28, 29].
| Module   | Genes                                                                 | GO term                                                                 | P value       |
|----------|----------------------------------------------------------------------|-------------------------------------------------------------------------|---------------|
| ADM-1    | Hdac3, Hist1h2b, Hist1h2bl, Hist1h2bm, Hist2h2ab, Hist1h2bf, Hist3h2a, Hist2h3b, Smarca1, Cecr2, Top2b, Acta1, Actg1, Cenpa, Arid4a, Chd8, Asf1a, Bptf, Ehmt1, Chd1, H2afz | GO:0006334 ~ nucleosome assembly                                        | 6.23E-08      |
|          |                                                                       | GO:0016569 ~ covalent chromatin modification                            | 6.52E-06      |
|          |                                                                       | GO:0045892 ~ negative regulation of transcription, DNA-templated       | 0.022         |
|          |                                                                       | GO:0006351 ~ transcription, DNA-templated                               | 0.041         |
| ADM-4    | Hist1h4h, Hist1h4m, Hist2h4, Hist1h4i, Smyd5, Actr10, Hist1h2a, Hist1h2b, Hist1h2bn, Ttf2, hist1h4c, Hist1h2an, Hist1h4f | GO:0006334 ~ nucleosome assembly                                        | 9.43E-18      |
|          |                                                                       | GO:0045815 ~ positive regulation of gene expression, epigenetic        | 6.79E-14      |
|          |                                                                       | GO:0006352 ~ DNA-templated transcription, initiation                    | 1.42E-13      |
| ADM-5    | Olfr172, Olfr993, Olfr294, Olfr99, Olfr202, Olfr1076, Olfr516, Olfr1104, Olfr1393, Olfr1453 | GO:0007186 ~ G-protein coupled receptor signaling pathway               | 5.81E-10      |
| PanIN-4  | Hist1h3g, Hdac11, Smarca2, 4933411g06rik                               | GO:0006325 ~ chromatin organization                                     | 0.007         |
|          |                                                                       | GO:0006334 ~ nucleosome assembly                                        | 0.017         |
| PanIN-6  | Olfr394, Olfr648, Olfr517                                            | GO:0007186 ~ G-protein coupled receptor signaling pathway               | 0.009         |
| PDAC-1   | Olfr24, Olfr658, Olfr414, Olfr705, Olfr330, Olfr1349, Olfr635, Olfr1459, Olfr239, Olfr24 | GO:0007186 ~ G-protein coupled receptor signaling pathway               | 6.19E-09      |
|          |                                                                       | GO:0007165 ~ signal transduction                                        | 0.014         |
| Module | Genes | GO term | P value |
|--------|--------|---------|---------|
| PDAC-9 | Gm6026, Smarcd1, Hdac6, Kcnu1, Ubtfl1, Kcnmb2, Tunmb2, Tub4a, Tub1, Ppp2r5e, Tubb3, Clip3, Zap70, Frk, Ccng1 | GO:0007017 ~ microtubule-based process | 0.026 |

Importantly, we mapped all the significant overlap and crosstalk genes into human homologies to investigate their expression level in PDAC and potential relationships with prognosis using GEPIA tool. We found that SAMRCA1, SMARCA2, CLIP3, BPTF and H2AFZ were significantly overexpressed in PDAC compared with normal pancreas tissue (Fig. 4a). KCNMB2 and H2AFP (human homology of mouse HIST1H2AN), SMARCA1, CLIP3 and SMARCA2 were significant prognostic factors for PDAC (Fig. 4b). Information on expression and prognosis of other overlap and crosstalk genes were provided in additional file (Fig. S1).

**Non-coding RNAs regulating ADM-PanIN-PDAC**

We finally predicted the lncRNAs and microRNAs regulating the overlap and crosstalk genes during ADM-PanIN-PDAC progression by miRDB database. There are 44 lncRNAs and 56 microRNAs in total found to regulate the overlap genes (Fig. 5). As the node degree higher, the relationship between the non-coding RNAs and their related genes become more significant. The top five most regulated microRNAs were mmu-miR-335-5p, mmu-miR-669n, mmu-miR-7646-5p, mmu-miR-1191b-3p, mmu-miR-1224-5p. These miRNAs targeted two overlap genes: Hist1h4m and Hist4h4. The top 10 most related lncRNAs were C530005A16Rik, 1810062O18Rik, 2010204K13Rik, 2810002D19Rik, 4732463B04Rik, H19, Pvt1, Gm14207, Gas5 and Mir17hg. They mainly targeted at overlap gene Hist1h2an.

572 microRNAs and 55 lncRNA were found significantly regulating the crosstalk genes. The top 5 microRNAs with greatest node degree were mmu-miR-325-3p, mmu-miR-590-3p, mmu-miR-743a-3p, mmu-miR-743b-3p, Gm14207, H19, 2610203C20Rik, C130021I20Rik, 1700086L19Rik, 2810002D19Rik, BC006965, D630029K05Rik, Meg and Pvt1 were the top 10 lncRNAs with greatest node degree (Fig. 6). Amongst 2810002D19Rik, H19 and Gm14207 were predicted to regulate both crosstalk and overlap genes.

**Discussion**

This study is conducted to unveil the genetic alterations and its regulators that drive ADM toward the direction of PanIN and subsequently PDAC. We have identified 45 genes in ADM stage, 7 genes in PanIN and 28 genes in PDAC interacted with each other. Overlap and crosstalk genes in ADM-PanIN-PDAC contain several bridging ADM gene modules (e.g. Hist2h2ab and smarca1), PanIN gene modules (e.g. Hdac11 and smarca2) and PDAC gene modules (e.g. Olfr239 and Hdac6). GO analysis showed that these genes mainly played roles in nucleosome assembly, chromatin organization and G-protein coupled
receptor signaling pathway. The expression of cancer-related genes was affected by epigenetic dysregulation via DNA methylation, histone modification and regulated by small non-coding regulatory microRNAs (e.g. mmu-miR-335-5p) and IncRNAs (e.g. H19).

Overlap genes and most crosstalk genes belong to histone family. Histone is highly conserved protein with extensive cellular functions. It constitutes two functional part: core histones (H2A, H2B, H3 and H4) and linker histones (H1 and H5)[30]. In our study, most overlap genes are core histones, including HIST1H2AN, also known as H2AC22 (homology of human H2AC11), three members of Histone H4 (Hist1h4c, Hist1h4m and Hist4h4). Crosstalk genes including H2AFZ (synonym of H2A.Z) were annotated in ADM-PanIN-PDAC. Histones are found to be associated with the cancer-predisposing inflammation or even trans-differentiation[31]. Histone H3 has the potential to be a biomarker for evaluating the severity of acute pancreatitis due to caerulein triggered extensive pancreatic acinar cell death in animal model[32]. Histone H4 was found to bind with smooth muscle cells and triggered arterial tissue inflammation[33]. Histone variant H2A.J was accumulated with aging in specific tissue and may contribute to chronic inflammation, aging-associated disease and cancers[34]. Roles of H2AFZ have been well established in several types of cancer, but poorly explored in PDAC. It is upregulated in breast, liver, bladder and lung cancer and has oncogenic properties in prostate cancer[35].

Apart from the differential expression level of histone variants, modification of histones could also exert effects on carcinogenesis[36]. We found several histone deacetylase (HDAC) including HDAC3 in ADM module-1, HDAC11 in PanIN module-4 and HDAC6 in PDAC module-9 were important to network of ADM-PanIN-PDAC. High expression of HDAC3 in the precursor lesions of prostate cancer were presented, indicating its critical role in the initiation stage of tumorigenesis[37]. Aberrant expression of HDAC6 also plays critical roles in cell differentiation, apoptosis and cell cycle control[38]. Hdac11 has been shown as a novel target in antitumor therapy[39]. Loss of histone trimethyl transferase, H3K36, facilitated ADM formation through epigenetic dysregulation and led to extracellular matrix (ECM) production in PDAC[40].

Great numbers of genes predicted in ADM-PanIN-PDAC regulation are also identified and they have interactions with histones in deferent extent. Several genes annotated have been previously validated in PDAC. Absence of ATRX in adult mice with oncogenic KRAS mutation, a subgroup of SWI/SNF complex (Switch/Sucrose Non-Fermentable chromatin remodeling), resulted in increased ADM and even more progressive PanIN lesions[41]. Deletion of ARID1A in pancreas, a SWI/SNF component, exaggerated ADM formation, diminished regeneration after injury and lead to intraductal papillary mucinous neoplasm and PanIN when cooperated with mutant KRAS[20]. We believe another family member, ARID4A, predicted in ADM module, might play a role in PDAC initiation as well. Crosstalk gene, SMARCA1, was related with inflammation related disease and cancer cell proliferation, migration, growth, death and DNA damage[42, 43]. The first study investigating its role in tumor was done in 2018, revealing its repression in soft tissue sarcoma. Another two member in SMARCA class have been successfully linked to PDAC. SMARCA2, annotated in PanIN module, was correlated with poor survival of pancreatic cancer patients and associated with cancer growth or chemoresistance[44]. SMARCA4-deficient mice in cooperation with
oncogenic Kras promoted PDAC precursor lesions[45]. Given that SMARCA1 may act upstream of p53 which is a very common mutant gene in PDAC, by regulating the expression of p53 gene through Wnt pathway, and its putative prognostic biomarker for PDAC, researches targeting its potential roles in PDAC initiation is merited.

Another crosstalk gene CHD1, a chromatin remodeling factor which specifically binds to methylated histone H3 lysine 4 residue (H3K4me3), is involved in nuclear shuttling in pancreatic cancer cell[46]. Similarly, BPTF (bromodomain PHD transcription factor) could also bind with H3K4me3 to stabilize NURF (nucleosome remodeling factor) complex on chromatin, resulting in transcriptional regulation[47]. It was recently reported that BPTF was expressed at intermediate levels in PDAC-derived cell lines and responsible for cancer cell proliferation and PDAC initiation and maintenance by interacting with c-MYC[48]. FRK played a role in pancreatic cancer cells migration and proliferation, and was suggested to be critical therapeutic targets of pancreatic cancer[49]. CLIP3 was shown as anti-inflammatory regulator involved in TNF-α signaling[50] and also attributed to injury recovery[51], while it was a novel target in cancer predicted in the crosstalk gene network. CECR2 functions with SMARCA1 in CERF complex (CECR2-containing remodeling factor) to regulate cell differentiation and development[52]. Interestingly, SMARCA1, SMARCA2 and CLIP3 were not only overexpressed in human PDAC, but also significant prognostic factors for overall survival prediction. It highlights necessities to explore their roles in ADM-PanIN-PDAC and independently confirmed our findings.

We, for the first time showed that Olfactory receptors (OR/OLFR) superfamily genes were relatively independent modules involved in PDAC formation. Emerging data has been shown that ORs were related with cell invasiveness[53] and could work as putative drivers of cancer. Olfactory receptors (OR/OLFR) superfamily genes belongs to G protein-coupled receptors (GPCR) which is involved in inflammatory response and cancer development via NF-kB signaling[54]. Our findings on the relation of 22 ORs with ADM-PanIN-PDAC concededly support the notion that olfactory transduction pathway is associated with elevated pancreas cancer risk[55]. Another OR member, prostate-specific G-protein-coupled receptor (PSGR/OR51E2), was upregulated in prostate cancer and could allegedly induce prostatitis at early age of mouse and promote prostatic intraepithelial neoplasia[56]. MiRNA-374a and miRNA-410, putative regulators of cancer-related genes, were inversely correlated with PSGR overexpression[57]. Lately, overexpression of Olfr544, Olfr543 and Olfr1349 at mRNA level were found to play a role in regulating glucagon secretion in pancreatic cells[58]. ORs are linked to H2AFZ and histone superfamily through 4 IncRNAs (Gm9866, 4833422C13Rik, BC016548 and 2810407A14Rik). Exploring the relationship between the spectrum of OR and cancer is invaluable for kindling new therapeutic target.

It is well known that long noncoding RNAs (lncRNAs) and small noncoding RNAs (miRNA) facilitate tumor initiation and progression through regulating tumor suppressor genes or oncogenes. Our analysis revealed a complex network among miRNAs, lncRNAs and their targeted genes during PDAC tumorigenesis. Consistently, one of our strongest candidates, Gas5, was recently shown to regulate pancreatic cancer metastasis via PTEN[22]. MiR-143, reported to be suppressed in colorectal neoplasia[59], was predicted to regulate ADM-PanIN-PDAC via targeting ACTR10. MiR-193b, validated as
a tumor suppressor in various cancer types, was found to regulate CLIP3 and interact with oncogenic lncRNA (MIR31HG) in our network[60]. Another tumor suppressor Meg3, predicted to interact with Hist1h2bn in our study, was found to be involved in pancreatic cancer[61]. H19, identified as oncogenic lncRNA, played a role in pancreatic cancer invasion and metastasis[59]. In line with previous findings, we found H19 as the top lncRNA in crosstalk with ADM, PanIN and PDAC. miR-335-5p, miR-7646-5p and miR-669n target both Hist4h4 and Hist1h4m. For now, only one study pointed out that MiR-335-5p may attenuate pancreatic cancer development through modulating the downstream oncogene[62]. Biological functions of these lncRNA/miRNAs in PDAC identified in our network for the first time remain to be clarified. Some other tumor suppressors were also annotated in our network.

**Conclusion**

In summary, we attempted to reveal the mechanisms that regulates the progression of ADM-PanIN-PDAC at both genetic and epigenetic (differentially expressed genes, miRNA and lncRNA) levels. Amongst, SMARCA1, SMARCA2 and CLIP3 were not only significant crosstalk genes, but also deferential expressed genes and potential prognostic factors for human PDAC. These newly identified genes and their regulators opens a new window of opportunity for early detection and prevention of PDAC.

**Declarations**

**Competing interests:**

The authors declare no competing interests.

**Contributions:**

B.G. and ZH.G. contributed to study design and data analysis. HR.Z contributed to study design, data interpretation and wrote the manuscript. WH.Z and BY.S. analyzed the data and revised the manuscript. All the authors reviewed the manuscript.

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Figures
Figure 1

Visualization of differentially expressed genes and its PPI network in ADM, PanIN and PDAC. a The heatmap depicts all the differentially expressed genes in ADM, PanIN and PDAC respectively. b-d PPI network of the differentially expressed genes in ADM (b), PanIN (c) and PDAC (d) with top 10 mRNAs in degree illustrated.
Figure 2

The overlap subnetwork of ADM-4 and PanIN-1 modules. Green nodes, purple nodes and red nodes represent the genes in PanIN-1, ADM-4 and the overlap genes among modules, respectively. Black lines represent gene-gene interaction.
Figure 3

The crosstalk genes in ADM-PanIN-PDAC. a The crosstalk subnetwork of ADM-1 and PanIN-4. b The crosstalk subnetwork of ADM-4 and PanIN-4. c The crosstalk subnetwork of ADM-5 and PanIN-6. d The crosstalk subnetwork of PanIN-4 and PDAC-19. e The crosstalk subnetwork of PanIN-4 and PDAC-10. f The crosstalk subnetwork of PanIN-4 and PDAC-9. g The crosstalk subnetwork of PanIN-6 and PDAC-1. h The crosstalk subnetwork of PanIN-3 and PDAC-13. i The crosstalk subnetwork of PanIN-1 and PDAC-9. j The crosstalk subnetwork of PanIN-3 and PDAC-10. k and l The combined crosstalk subnetwork of ADM-PanIN-PDAC. Green and purple nodes represent the DEGs in ADM and PanIN modules, respectively. Red edge represents gene crosstalk. Black edge represents gene interaction in the same module.
Figure 4

Expression (a) and Kaplan-Meier survival (b) analysis of significant overlap and top 10 crosstalk genes from mouse models between human PDAC samples (n=179, red box) and normal pancreas tissue (n=171, blue box).
Figure 5

The microRNA and lncRNA regulatory network of the overlap genes in ADM and PanIN. Green nodes and purple nodes represent the DEGs in ADM and PanIN, respectively. Red nodes represent the overlap genes. Yellow square node and blue rhombus node represent microRNA and lncRNA targeting the overlap genes, respectively.
Figure 6

The significant crosstalk genes in ADM-PanIN-PDAC progression. Green nodes, purple nodes and yellow nodes represent the DEGs in ADM, PanIN and PDAC respectively. Red lines link the crosstalk genes. Grey nodes represent microRNA and lncRNA.

Supplementary Files

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