Evaluation of the target genes of arsenic trioxide in pancreatic cancer by bioinformatics analysis

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Abstract. The aim of the present study was to evaluate the potential network of arsenic trioxide (ATO) target genes in pancreatic cancer. The DrugBank, STITCH, cBioPortal, Kaplan-Meier plotter and Oncomine websites were used to analyze the association of ATO and its target genes with pancreatic cancer. Initially, 19 ATO target genes were identified, along with their associated protein-protein interaction networks and Kyoto Encyclopedia of Genes and Genomes pathways. ATO was found to be associated with multiple types of cancer, and the most common solid cancer was pancreatic cancer. A total of 6 ATO target genes (namely AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) were found to be associated with pancreatic cancer. Next, the mutation information of the 6 ATO target genes in pancreatic cancer was collected. A total of 20 ATO interacting genes were identified, which were mainly involved in hepatitis B, prostate cancer, pathways in cancer, glioma and chronic myeloid leukemia. Finally, the genes CCND1 and MAPK1 were detected to be prognostic factors in patients with pancreatic cancer. In conclusion, bioinformatics analysis may help elucidate the molecular mechanisms underlying the involvement of ATO in pancreatic cancer, enabling more effective treatment of this disease.

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Abbreviations: ATO, arsenic trioxide; PPI, protein-protein interaction; KEGG, Kyoto Encyclopedia of Genes and Genomes

Introduction

Pancreatic cancer is one of the most aggressive malignancies worldwide, with a mortality rate that is nearly equal to its incidence rate (1). Pancreatic cancer is expected to become the second leading cause of cancer-associated mortality in the US by 2030 (2). Despite advances in diagnostic and therapeutic strategies over the past years, the prognosis of patients with pancreatic cancer remains unsatisfactory, with a 5-year survival rate of <8.5% (3). Pancreatic cancer has become one of the major public health concerns worldwide. In order to improve the treatment of pancreatic cancer, it is necessary to elucidate the pathological mechanism underlying its development, identify a drug-based framework and investigate the functional mechanisms involved.

Arsenic trioxide (ATO) has been reported to be an effective therapeutic agent for acute promyelocytic leukemia (APL) (4). It has been reported that ATO can induce molecular remission, as well as prolong the overall survival of patients with APL (5,6). Combined treatment with retinoic acid (RA) and ATO has been demonstrated to be curative for the majority of patients with APL (7-9). Furthermore, an increasing number of studies have proven the anti-carcinogenic properties of ATO in different tumors, including in gastric cancer (10), lymphoma (11), bladder cancer (12), head and neck cancer (13), and ovarian cancer (14). Although it has been reported that ATO may inhibit the progression of pancreatic cancer (15), the potential targets and molecular mechanisms of action of ATO remain unclear.

In recent years, with the continuous improvement and development of high-throughput sequencing technology, multi-omics research (such as genomics, transcriptomics, proteomics and metabolomics) has gradually improved and has been used to identify disease-associated genes, which may uncover the molecular mechanisms underlying disease development and enable effective treatment. DrugBank is a richly annotated web-based bioinformatics tool that contains multiple drug data with comprehensive drug targets information (16). It provides detailed, step-by-step information on the results of previous studies on drugs, drug targets and drug effects, allowing researchers to search, view and export data, text and image (17). Furthermore, Search Tool for Interactions of Chemicals (STITCH) is an online database of the interaction networks of chemicals and proteins (18).

In the present study, DrugBank and STITCH were used to identify the targets of ATO, in order to construct an ATO-target interaction network. Protein-protein interaction (PPI) network construction and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis demonstrated that ATO is associated with several types of malignancies, including pancreatic cancer. In total, 6 genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) were identified as the target genes of ATO in pancreatic cancer. The interconnection of these 6 ATO target genes in pancreatic cancer was then analyzed using the Search Tool for the Retrieval of Interacting Genes (STRING) database. The cBioPortal website was further used to analyze the genomics data of these 6 target genes, while online Kaplan-Meier (K-M) plotter was used to analyze the prognosis of pancreatic cancer. In addition, the Oncomine website was used to reveal the expression levels of ATO target genes in pancreatic cancer tissues. Taken together, the findings of the bioinformatics analysis performed in the present study may help determine the gene targets of ATO and provide new therapeutic approaches for pancreatic cancer.

Materials and methods

Search for target genes of ATO. DrugBank, version 5.0 (https://www.drugbank.ca), is a richly annotated web-based bioinformatics tool that contains multiple drug data with comprehensive drug target information. In the present study, the DrugBank 5.0 and STITCH (http://stitch.embl.de/) databases were used to identify the ATO-target interactions in order to obtain an ATO-target network. The information on ATO target genes was then used to construct a visualization table and analyzed by STRING for further analysis. The search term 'arsenic trioxide' was used to search the DrugBank 5.0 and STITCH databases, and the targets of ATO in these two websites were identified. A total of 19 targets were recorded and included in subsequent analyses.

KEGG pathway and Gene Ontology analyses, and PPI network construction of ATO targets. The STRING database (https://string-db.org/) gathers and provides known and predicted PPI data for a large number of organisms, including humans (19,20). Cytoscape is a general-purpose software platform used for integrating bimolecular interaction networks (21). CluePedia, a plugin of Cytoscape software, can be used for searching potential genes associated with the reported signaling pathway by calculating linear and non-linear statistical dependencies from experimental data (22). In the present study, the KEGG pathway and Gene Ontology (GO) analyses were conducted using the STRING database. Subsequently, the STRING website and Cytoscape software were utilized to establish a PPI network of the ATO target genes.

Genomics information of ATO targets in pancreatic cancer. The cBioPortal for Cancer Genomics (http://www.cbioportal.org/) is a free platform that is used for finding multidimensional cancer genomics data (23). OncoPrint is an online tool, which can visualize alterations of tumor samples from gene arrays. The alterations of 6 ATO target genes associated with pancreatic cancer (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) were visualized using cBioPortal and

Table I. Target genes (n=19) of arsenic trioxide identified using DrugBank 5.0 and STITCH.

Target gene	Source
IKBKB	Drugbank 5.0
TXNRD1	Drugbank 5.0
JUN	Drugbank 5.0
CCND1	Drugbank 5.0
MAPK3	Drugbank 5.0
MAPK1	Drugbank 5.0
AKT1	Drugbank 5.0
CDKN1A	Drugbank 5.0
PML	Drugbank 5.0 and STITCH
HDAC1	STITCH
RARA	STITCH
ESR1	STITCH
CDKN2A	STITCH
ABCC1	STITCH
SP1	STITCH
DNMT3B	STITCH
DNMT1	STITCH
HSPA4	STITCH
ABCB1	STITCH

OncoPrint (24), and the genomic alteration frequency within the specific cancer study, listed below, was applied as a filter. In the present study, a total of 850 pancreatic cancer samples were analyzed in this section, which included International Cancer Genome Consortium (ICGC; n=99), Queensland Centre for Medical Genomics (QCMG2016; n=456), The Cancer Genome Atlas (TCGA; n=186) and University of Texas Southwestern Medical Center (UTSW; n=109) datasets (25-28).

Overall survival analysis of ATO target genes in patients with pancreatic cancer. The K-M plotter (http://kmplot.com/analysis/) is a free online tool that can be used to assess the association of multiple genes with the survival of patients with cancer using different cancer samples (29). According to mRNA expression data from the aforementioned 6 ATO genes, the patients with pancreatic cancer were divided into the high- and low-expression groups based on the median expression value, and then K-M survival curves were constructed. In the present study, the information of 177 patients with pancreatic cancer was acquired from the K-M website, and the K-M survival curves were used to analyze the association between the expression of ATO target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) and the prognosis of 177 patients with pancreatic cancer.

Determination of the expression of the 3 ATO target genes in pancreatic cancer. Oncomine (https://www.oncomine.org/) is an online cancer microarray website that facilitates the discovery of genome-wide expression analyses (30). In the present study, differential gene expression was detected by Oncomine when comparing cancer tissues with normal

Table II. Kyoto Encyclopedia of Genes and Genomes pathways associated with the arsenic trioxide target genes.

Pathway	Count	False discovery rate	Genes
MicroRNAs in cancer	10	5.09×10^{-15}	ABCB1, ABCC1, CCND1, CDKN1A, CDKN2A, DNMT1, DNMT3B, HDAC1, IKBKB, MAPK1
Pathways in cancer	11	7.73×10^{-14}	AKT1, CCND1, CDKN1A, CDKN2A, HDAC1, IKBKB, JUN, MAPK1, MAPK3, PML, RARA
Chronic myeloid leukemia	8	7.73×10^{-14}	AKT1, CCND1, CDKN1A, CDKN2A, HDAC1, IKBKB, MAPK1, MAPK
Acute myeloid leukemia	7	2.41×10^{-12}	AKT1, CCND1, IKBKB, MAPK1, MAPK3, PML, RARA
Pancreatic cancer	6	6.88×10^{-10}	AKT1, CCND1, CDKN2A, IKBKB, MAPK1, MAPK3
Glioma	6	6.88×10^{-10}	AKT1, CCND1, CDKN1A, CDKN2A, MAPK1, MAPK3
Hepatitis B	7	1.11×10^{-9}	AKT1, CCND1, CDKN1A, IKBKB, JUN, MAPK1, MAPK3
Melanoma	6	1.11×10^{-9}	AKT1, CCND1, CDKN1A, CDKN2A, MAPK1, MAPK3
Prostate cancer	6	3.56×10^{-9}	AKT1, CCND1, CDKN1A, IKBKB, MAPK1, MAPK3
Viral carcinogenesis	7	4.54×10^{-9}	CCND1, CDKN1A, CDKN2A, HDAC1, JUN, MAPK1, MAPK3

pancreatic tissues. The studies by Ishikawa *et al* (31), Iacobuzio-Donahue *et al* (32), Pei *et al* (33), Badea *et al* (34), Logdons *et al* (35) and Segara *et al* (36) were used to reveal the expression of 3 ATO target genes in pancreatic cancer. Differences in transcriptional expression were compared using the Student's t-test. P<0.01 was used to indicate a statistically significant difference and fold change was set to 2.

Results

Evaluation of ATO target genes. ATO is a chemotherapeutic agent of idiopathic function used to treat leukemia that is unresponsive to first-line agents. It is suspected that ATO induces cancer cells to undergo apoptosis (11). In the current study, DrugBank and STITCH tools were used to identify the target genes of ATO. As shown in Table I, a total of 19 target genes were identified, including IKBKB, TXNRD1, JUN, CCND1, MAPK3, MAPK1, AKT1, CDKN1A, HDAC1, PML, RARA, ESR1, CDKN2A, ABCC1, SP1, DNMT3B, DNMT1, HSPA4 and ABCB1.

Gene Ontology (GO) analysis. The online STRING software was used to determine functional enrichments based on 19 ATO target genes. GO analysis revealed a significant difference in biological processes, which included 'response to lipid', 'DNA-templated transcription', 'initiation, regulation of transcription from RNA polymerase II promoter', 'positive regulation of gene expression', and 'transcription initiation from RNA polymerase II promoter,' among others. The molecular function terms identified included 'enzyme binding', 'transcription factor binding', 'sequence-specific DNA binding', 'cyclin-dependent protein serine/threonine kinase regulator activity' and 'transcription corepressor activity', among others. As regards the area of the cell components, the 19 ATO target genes were enriched in 'chromatin', 'nucleoplasm', 'nuclear chromatin', 'chromosome' and 'nuclear lumen'. The top 5 terms for biological processes, molecular function and cellular components were shown in Table SI.

Association between ATO targets and pancreatic cancer. The PPI network (Fig. 1) and KEGG pathway analysis for the 19 ATO target genes (Table II) were obtained from the STRING database. The top 10 signaling pathways associated with the ATO target genes were as follows: MicroRNAs in cancer, pathways in cancer, chronic myeloid leukemia, acute myeloid leukemia, pancreatic cancer, glioma, melanoma, hepatitis B, pancreatic cancer and viral carcinogenesis. The most common solid tumor was pancreatic cancer ($P=6.88 \times 10^{-10}$). A total of 6 genes, namely AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3, were found to be associated with pancreatic cancer. Subsequently, CluePedia software was used to verify and visualize the association of ATO target genes with pancreatic cancer, and the results were consistent with the STRING analysis results (Fig. 2).

Genetic data of ATO target genes in pancreatic cancer. The genetic information of these 6 genes in patients with pancreatic cancer were subsequently evaluated using the cBioPortal. The genomic alterations and clinical expression characteristics of AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3 in the aforementioned datasets ICGC (n=99), QCMG2016 (n=456), TCGA (n=186) and UTSW (n=109) were investigated (25-28). As shown in Fig. 3, the alteration rate of the 6 genes in pancreatic cancer varied between 0 and 63%. AKT1 exhibited an alteration rate between 0 and 18%, CCDN1 had an alteration rate between 0 and 10%, CDKN2A had an alteration between 0 and 42%, IKBKB had an alteration of 0-7%, MAPK1 had an alteration between 0 and 8%, and MAPK3 had an alteration between 0 and 9%. Furthermore, AKT1, IKBKB and MAPK1 exhibited amplification, deep deletion and missense mutations. The alterations of CDKN2A included deep deletion, truncating, missense, inframe mutations and other mutations. The alterations of CCND1 and MAPK3 included amplification.

Interconnection of the 6 ATO target genes in pancreatic cancer. STRING analysis performed in the current study revealed that
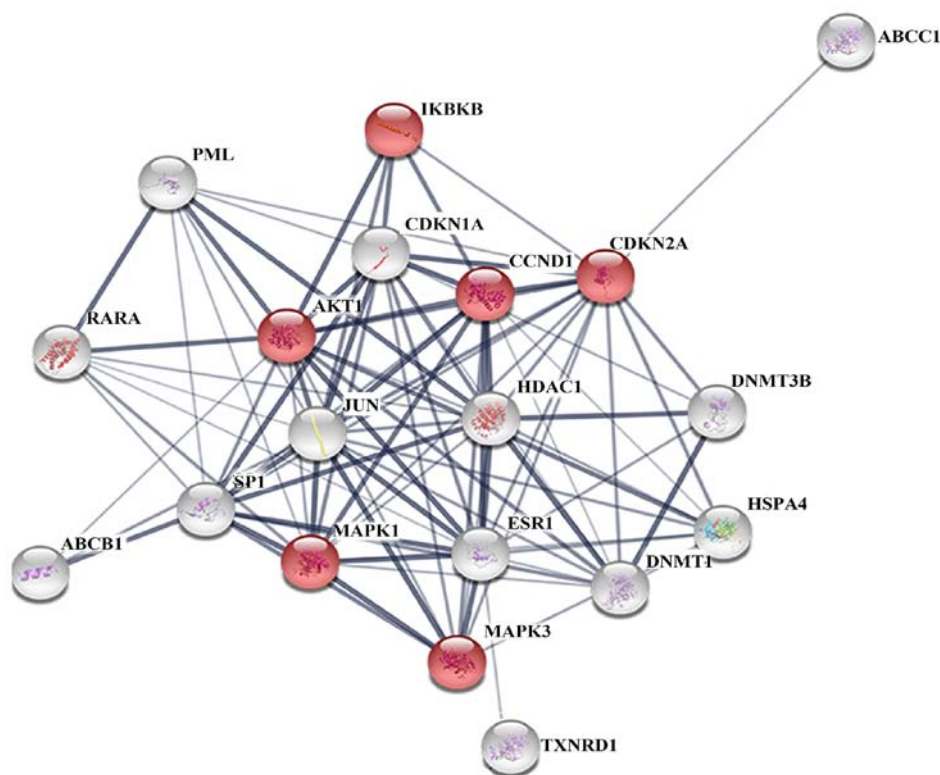
Figure 1. Protein-protein interaction network of arsenic trioxide target genes, including IKBKB, TXNRD1, JUN, CCND1, MAPK3, MAPK1, AKT1, CDKN1A, HDAC1, PML, RARA, ESR1, CDKN2A, ABCC1, SP1, DNMT3B, DNMT1, HSPA4 and ABCB1. Red color indicates association with pancreatic cancer.

the 6 ATO target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) were involved in chronic myeloid leukemia, pancreatic cancer, non-small cell lung cancer, acute myeloid leukemia, melanoma, glioma, prostate cancer, endocrine resistance, FoxO signaling and hepatitis B (Table SII). A PPI network was constructed to analyze the genes interconnected with AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3. A total of 20 ATO interacting genes (FOXO1, CDK6, CDK4, RICTOR, IKBKG, FOXO3, PTEN, NFKB1, PIK3CB, JUN, TP53, PIK3CA, PIK3CG, CDKN1A, CDKN1B, CDK2, PIK3CD, MTOR, NFKBIA and RB1) were identified and were mainly involved in hepatitis B, prostate cancer, pathways in cancer, glioma and chronic myeloid leukemia (Fig. 4 and Table III). The results may indicate a new therapeutic strategy for pancreatic cancer.

Survival prediction of the 6 ATO target genes in patients with pancreatic cancer. After the 6 ATO target genes associated with pancreatic cancer were identified, the K-M plotter was used to analyze the association of these genes with the overall survival of 177 patients with pancreatic cancer. As shown in Fig. 5, a low AKT1 level indicated poorer prognosis in patients with pancreatic cancer [hazard ratio (HR)=0.60; P=0.04]. Furthermore, a high level of CCND1 was correlated with poor prognosis of patients with pancreatic cancer (HR=2.71; P=2x10^{-4}). MAPK1 may also serve as a prognostic factor for patients with pancreatic cancer (HR=1.74; P<0.01), with high expression levels indicating poor prognosis. However, CKDN2A (P=0.17), IKBKB (P=0.33) and MAPK3 (P=0.24) were not found to be prognostic factors for patients with pancreatic cancer.

Differential expression of the 3 ATO target genes in pancreatic cancer. As aforementioned, AKT1, CCND1 and MAPK1 were demonstrated to be associated with the prognosis of pancreatic cancer. Differential expression analysis of these three ATO target genes was then conducted using the Oncomine website. As shown in Fig. 6, AKT1 was observed to be overexpressed in pancreatic cancer compared with normal pancreatic tissue in the studies of Ishikawa *et al* (31), Iacobuzio-Donahue *et al* (32) and Pei *et al* (33) (P<0.01, P<0.01 and <0.01, respectively). Badea *et al* (34), Logdons *et al* (35) and Pei *et al* (33) also reported that CCND1 was more highly expressed in pancreatic cancer as compared with the normal pancreas (P=4.04x10^{-6}, P<0.01 and P=5.51x10^{-4}, respectively). Furthermore, MAPK1 was reported to be overexpressed in pancreatic cancer by Pei *et al* (33) and Segara *et al* (36) (P=0.01 and P<0.01, respectively).

Discussion

Pancreatic cancer is one of the most aggressive malignancies and the fourth cause of cancer-associated mortalities worldwide. This cancer is frequently diagnosed at an advanced stage, and most tumors are unresectable at clinical presentation (37), which leads to a poor prognosis and high mortality rates among patients with pancreatic cancer. Despite the advances in diagnostic and treatment methods, there have been no significant improvements in the prognosis of patients with pancreatic cancer in the past years. Therefore, more effective treatment methods for pancreatic cancer are urgently required.

The antitumor properties of ATO have been identified in a number of tumors (10-14). ATO has also been shown to inhibit the viability of pancreatic cancer stem cells *in vitro*

Figure 2. A visual display of Kyoto Encyclopedia of Genes and Genomes pathways in 6 arsenic trioxide target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) associated with pancreatic cancer.
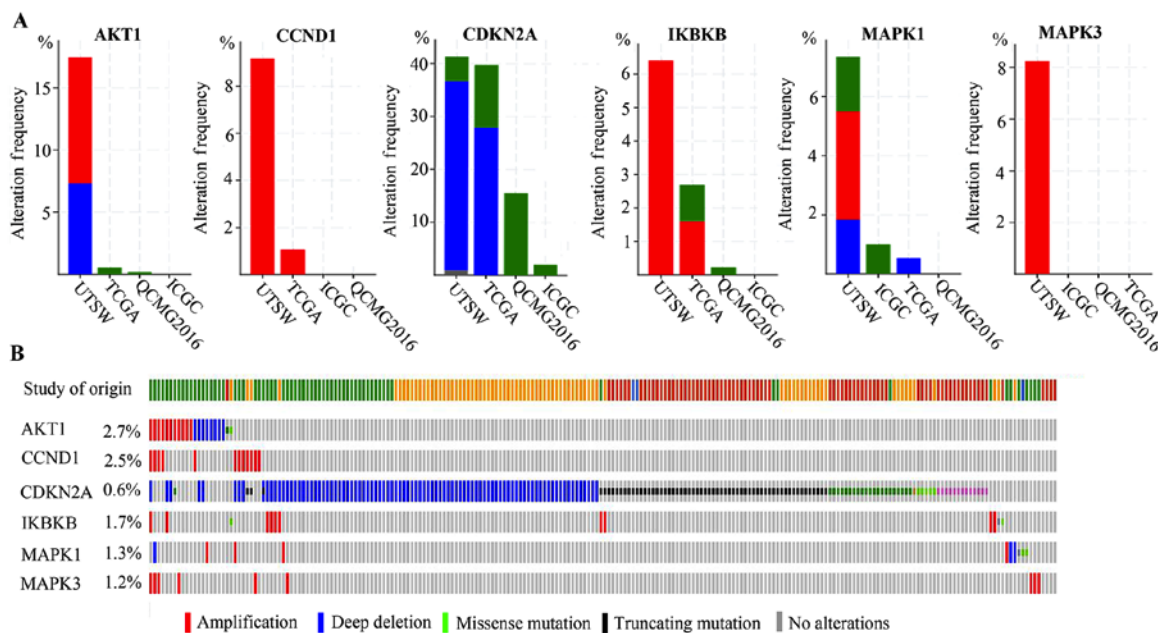

Figure 3. Genetic alterations of arsenic trioxide target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) in four pancreatic cancer studies, embedded in the cBioPortal for Cancer Genomics. ICGC, QCMG2016, TCGA and UTSW represent the different origin of the studies. (A) Overview of changes on genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) in genomics datasets available in four studies. (B) OncoPrint, providing a visual summary of alteration across a set of pancreatic cancer samples based on a query of the 6 genes. There were a total of 850 samples in the four studies included in the analysis.

and *in vivo* (38). In addition, Gao *et al* (15) reported that ATO exerted anticancer effects on pancreatic cancer. The combination of ATO with hypoxia-inducible factor-1 inhibitor was also found to be effective (39). However, the potential targets and molecular mechanisms of action of ATO in pancreatic cancer remain elusive.

Table III. Kyoto Encyclopedia of Genes and Genomes pathways in the protein-protein interaction network of the arsenic trioxide target genes interacted 20 genes.

| Pathway	Count	False discovery rate	Gene name
Hepatitis B	13	4.42×10^{-23}	CDK4, CDK6, CDKN1A, CDKN1B, JUN, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, RB1, TP53
Prostate cancer	12	4.42×10^{-23}	CDKN1A, CDKN1B, FOXO1, MTOR, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, RB1, TP53
Pathways in cancer	15	4.43×10^{-23}	CDK4, CDK6, CDKN1A, CDKN1B, FOXO1, JUN, MTOR, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, RB1, TP53
Glioma	11	1.43×10^{-22}	CDK4, CDK6, CDKN1A, MTOR, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, RB1, TP53
Chronic myeloid leukemia	11	4.99×10^{-22}	CDK4, CDK6, CDKN1A, CDKN1B, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, RB1, TP53
Small cell lung cancer	11	4.21×10^{-21}	CDK4, CDK6, CDKN1B, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, RB1, TP53
Viral carcinogenesis	12	1.16×10^{-19}	CDK4, CDK6, CDKN1A, CDKN1B, JUN, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, RB1, TP53
Melanoma	10	1.48×10^{-19}	CDK4, CDK6, CDKN1A, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, RB1, TP53
PI3K-AKT signaling pathway	13	1.27×10^{-18}	CDK4, CDK6, CDKN1A, CDKN1B, FOXO3, MTOR, NFKB1, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PTEN, TP53
Non-small cell lung cancer	9	4.22×10^{-18}	CDK4, CDK6, FOXO3, PIK3CA, PIK3CB, PIK3CD, PIK3CG, RB1, TP53
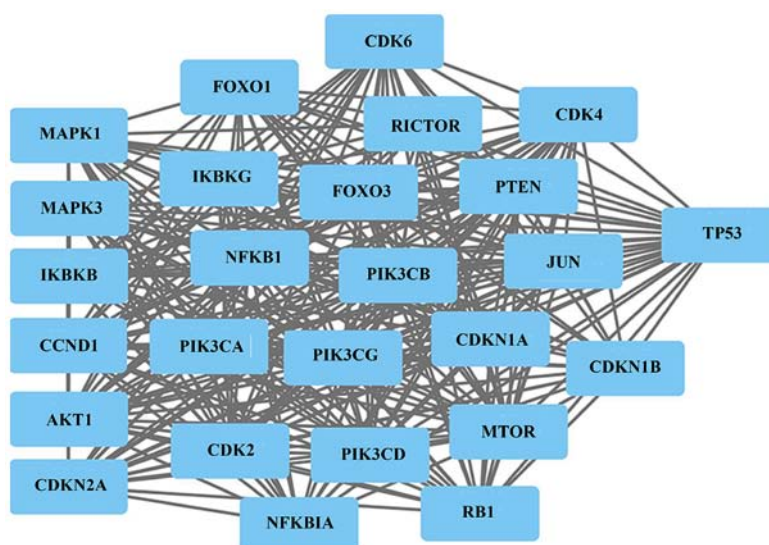
Figure 4. Visualization of the gene network connected to AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3.

In the present study, the molecular targets and associated genes of ATO were investigated by bioinformatics analysis. First, the 19 target genes of ATO were identified by DrugBank 5.0 and STITCH, which included IKBKB, TXNRD1, JUN, CCND1, MAPK3, MAPK1, AKT1, CDKN1A, HDAC1, PML, RARA, ESR1, CDKN2A, ABCC1, SP1, DNMT3B, DNMT1, HSPA4 and ABCB1. Next, the STRING website was used to construct the PPI network and conduct KEGG pathway analysis for the ATO target genes. A total of 6 target genes were demonstrated to be associated with pancreatic cancer, including AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3. Subsequently, the cBioPortal database was used to detect the alterations of these 6 genes, and the results were as follows: AKT1, IKBKB and MAPK1 were found to display amplification, deep deletion and
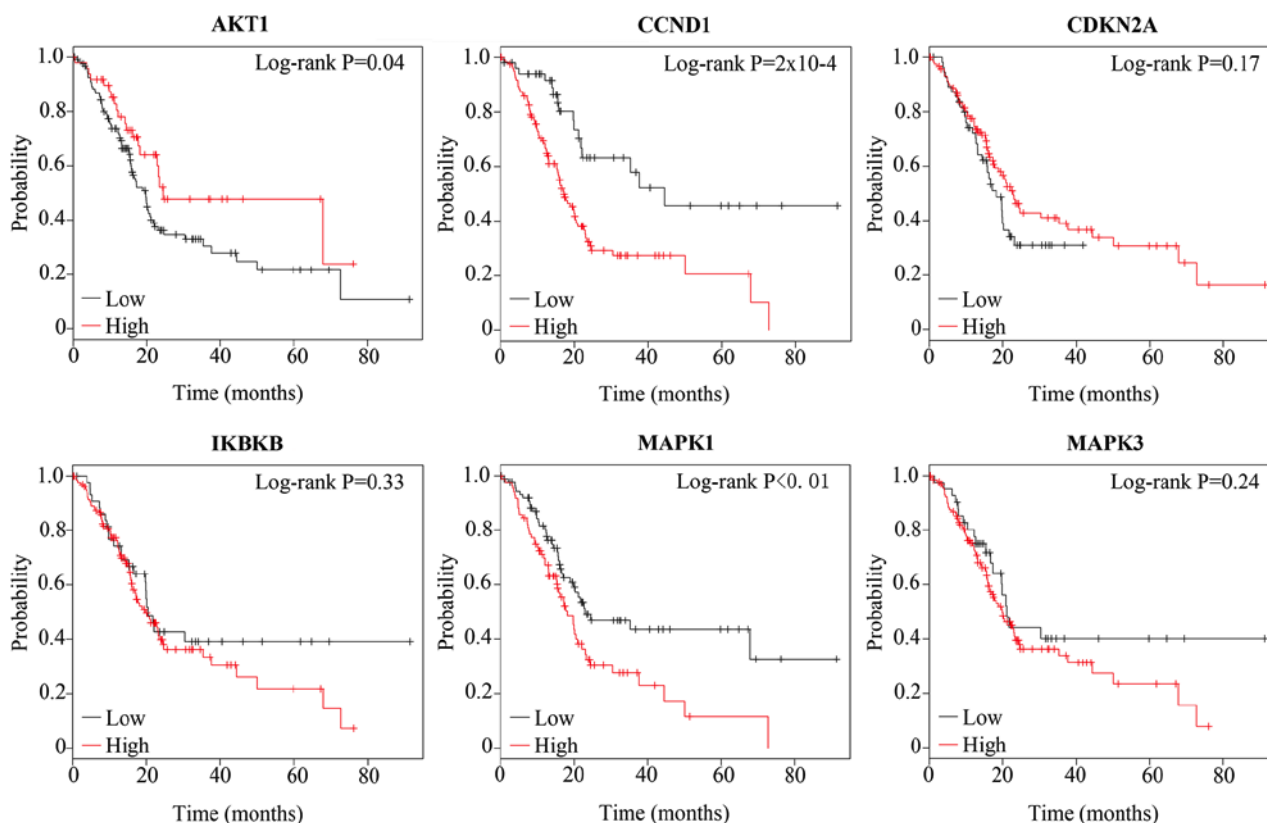
Figure 5. Prognostic analysis of arsenic trioxide target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) in pancreatic cancer patients using the Kaplan-Meier plotter website. A total of 177 samples were used for each prognostic analysis.

missense mutations; CDKN2A exhibited deep deletion, truncating, missense, inframe and other mutations; and CCND1 and MAPK3 exhibited amplification. Furthermore, 20 genes that are interconnected with the 6 ATO target genes in pancreatic cancer were identified. These genes were mainly involved in hepatitis B, pancreatic cancer, pathways in cancer, glioma and chronic myeloid leukemia. Finally, the K-M plotter was used to analyze the association of the 6 target genes with the overall survival of patients with pancreatic cancer and Oncomine was used to analyze differential expression of these genes in pancreatic cancer. The results demonstrated that CCND1 and MAPK1 were overexpressed in pancreatic cancer and may be of prognostic value for patients with pancreatic cancer.

By conducting bioinformatics analysis, 6 ATO target genes were identified in the current study. Among these 6 genes, AKT1 is a member of the PI3K/AKT pathway and serves an important role in multiple types of cancer, including pancreatic cancer (40). CCND1, also referred to as cyclin D1, forms a complex with CDK4, thus phosphorylating and inhibiting RB1, and regulating the cell cycle during G1/S transition. The activation of the CCND1/CDK4 complex also promotes pancreatic cancer cell growth (41). Furthermore, it is well-established that the increased risk of pancreatic cancer is partly due to germline mutation carrier of CDKN2A (42). A previous study demonstrated that nuclear factor (NF)-κB promoted the proliferation and growth, and inhibited the apoptosis of pancreatic cancer cells (43). Inhibition of NF-κB also blocked metastasis in pancreatic cancer-derived xenograft tumors (44). In another study, the MAPK/ERK signaling

pathway was revealed to be correlated with cancer cell growth, proliferation and apoptosis, including pancreatic cancer (45). Hu et al (46) used integrative analysis and identified MAPK3 as a significant hub gene in pancreatic cancer. In the present study, AKT1, CCND1 and MAPK1 were found to be overexpressed in pancreatic cancer, while high CCND1 and MAPK1 levels indicated poor prognosis.

STRING analysis performed in the current study revealed that the 6 ATO target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) were involved in chronic myeloid leukemia, pancreatic cancer, non-small cell lung cancer, acute myeloid leukemia, melanoma, glioma, prostate cancer, endocine resistance FoxO signaling and hepatitis B. The PPI network was also used to analyze the genes interconnected with the 6 ATO target genes, and the 20 interconnected genes were observed to be involved in hepatitis B, prostate cancer, pathways in cancer, glioma and chronic myeloid leukemia. These results may help develop new therapeutic strategies for cancer.

However, there were certain limitations to the present study. Firstly, this research was based on bioinformatics analysis, and experimental results are required to support the conclusions. Secondly, since the NF-κB pathway serves an important role in multiple cancer development, a significant association of IKBKB with poor prognosis of patients with pancreatic cancer was not observed by Kaplan-Meier analysis. Furthermore, the key genes implicated in pancreatic cancer should also be analyzed to confirm the reliability of the results. The present study showed that 6 ATO target genes (AKT1, CCND1, CDKN2A, IKBKB, MAPK1 and MAPK3) were associated
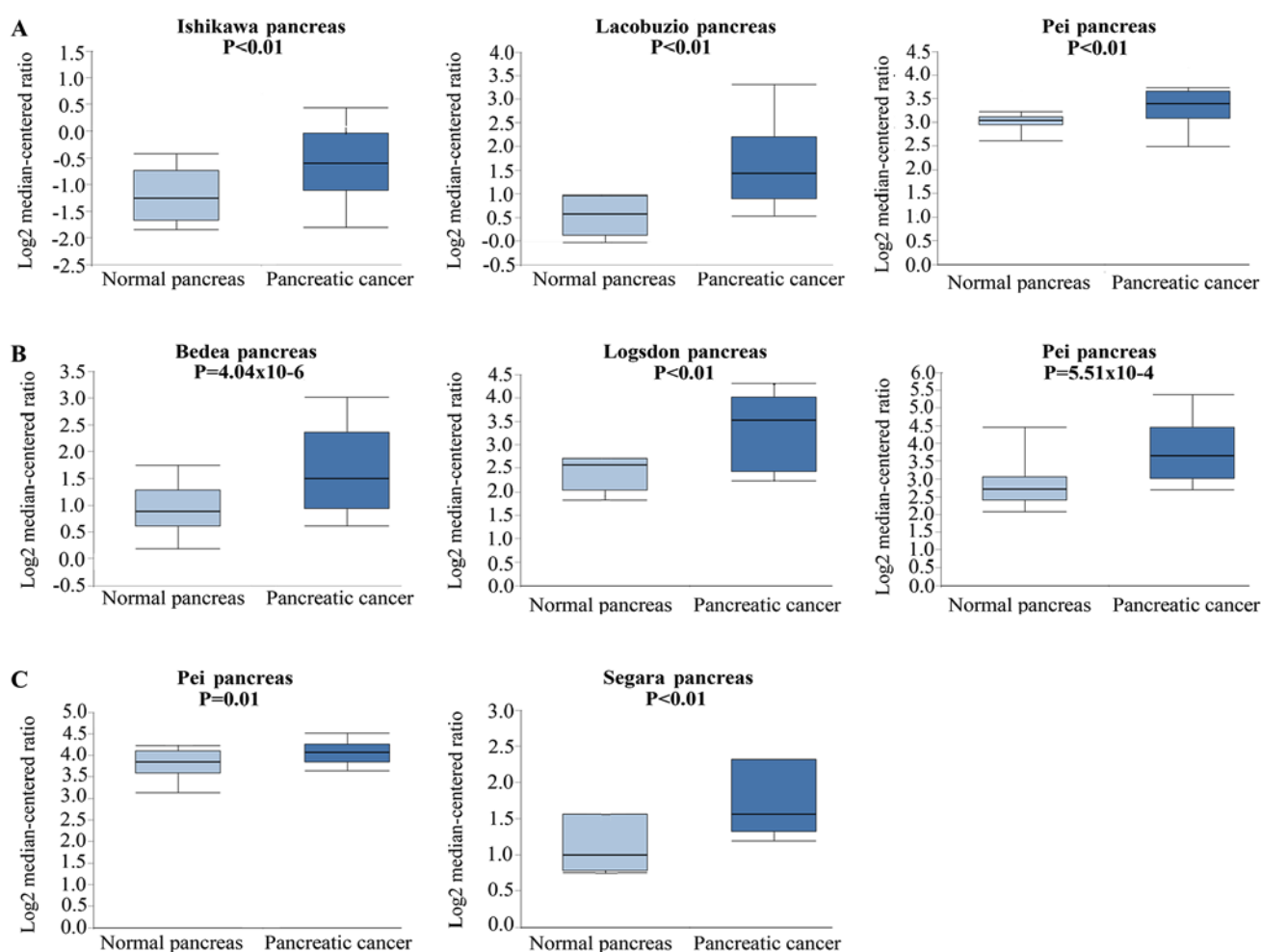
Figure 6. Analysis of the expression of AKT1, CCND1 and MAPK1 in pancreatic cancer and normal pancreatic tissues, performed with the Oncomine website. The expression of (A) AKT1, (B) CCND1 and (C) MAPK1 in different pancreatic cancer studies is shown.

with pancreatic cancer, and that high CCND1 and MAPK1 levels indicated poor prognosis. However, since tissue samples were not collected, these 6 proteins could not be verified in pancreatic cancer samples. Next, immunohistochemistry will be used to validate the expression of these proteins in pancreatic cancer and evaluate their association with the prognosis of patients with pancreatic cancer.

In conclusion, the bioinformatics analysis was used to elucidate the molecular mechanism of action of ATO in pancreatic cancer. The results not only suggest that ATO may be an effective drug for pancreatic cancer, but also provide a novel approach for identifying potential treatments for other diseases by bioinformatics analysis.

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Not applicable.

Availability of data and materials

The datasets generated and analyzed during the present study are available in the public databases.

Authors' contributions

QZ and SXH designed the study. CYZ acquired and analyzed the data, drafted the manuscript and revised it. LYG was involved in data analysis and revised the manuscript. RL, NNW, YYF, YPD, HZ, YQZ and YYZ performed the data analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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