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ORIGINAL ARTICLE

Identification of Key Potential Targets and Pathway for Arsenic Trioxide by Systemic Bioinformatics Analysis in Pancreatic Cancer

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Abstract

Arsenic trioxide is an approved chemotheraputic agent for the treatment of acute promyelocytic leukemia (APL). Recently, numerous studies suggested that arsenic trioxide acts as anti-cancer roles in various human malignancies. However, the molecular mechanisms are not fully elucidated. In this study, we explored the critical targets of arsenic trioxide and their interaction network systematically by searching the publicly available published database like DrugBank (DB) and STRING. Seven direct protein targets (DPTs) and 111 DPT-associated genes were identified. The enrichment analysis of arsenic trioxide associated genes/proteins revealed 10 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Among these pathways, phosphatidylinositol-4,5-bisphosphate-3-kinase -Akt (PI3K-Akt) single pathway and pancreatic cancer pathway are highly correlated with arsenic trioxide and have 5 overlapped targets. Then we investigated the gene alternation of selected critical genes in pancreatic cancer studies using cBio portal. These results indicated that arsenic trioxide could act anti-tumor function through PI3K-Akt single pathway and identified critical genes might be therapeutic targets for pancreatic cancer.

Keywords Arsenic trioxide · Genes/proteins interaction · Bioinformatics analysis · Pancreatic cancer

Introduction

Arsenic trioxide is one kind of odorless toxicant with the appearance as white frost powder [1]. Since researchers found that arsenic trioxide can inhibit the growth and induce the apoptosis of the leukemia cell lines in 1990s [2], people's interest in arsenic trioxide had increased greatly. Nowadays, arsenic trioxide had been approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute promyelocytic leukemia (APL). What's more, some studies found that arsenic trioxide has anti-cancer properties in various solid tumors, such as breast cancer, prostate cancer or pancreatic cancer [3–7].

Pancreatic cancer is one of the most prevalent malignant tumor in the world [8]. Recently, researchers found arsenic trioxide plays a negative role in pancreatic tumorigenesis [7, 9]. The understanding of the reliable mechanisms of arsenic trioxide in pancreatic cancer is still poor. Therefore, identifying the critical molecules and signaling pathways in incalculable target molecules background of arsenic trioxide may help exploring the broader clinical prospects of arsenic trioxide for cancer.

The emerging of bioinformatics medicine tools, such as DrugBank (DB), offers a tool to analyze systematically complexity of a particular disease or drug, helping to identify the target molecules and pathways [10]. Advances in this tool are essential for identifying new therapeutic target and uncovering the biological pathways of massive data obtained from various human cancer studies [11]. STRING is a database of knew and predicted protein-protein interactions and allows researchers to mine the physical and functional associations among multifarious proteins [12]. Both of these databases can provide us more insightful and systemic biological information of drug action in human cancers.

In this study, we queried DB using arsenic trioxide as input and got its detail pharmacological information. Then we built a network of hundreds interacting proteins

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Table 1 Characterization of arsenic trioxide using DB

DB_ID	Name	Group	Category	Indication
DB01169	Arsenic trioxide	Approved, Investigational	Antineoplastic Agents Antineoplastic and Immunomodulating Agents Cytochrome P-450 CYP3A Inhibitors Growth Inhibitors Highest Risk QTc-Prolonging Agents Hyperglycemia-Associated Agents Hypotensive Agents Myelosuppressive Agents	For induction of remission and consolidation in patients with acute promyelocytic leukemia (APL), and whose APL is characterized by the presence of the t(15;17)* translocation or PML/RAR-alpha gene expression

*One kind of reciprocal translocation for APL

Table 2 Identification of direct targets of arsenic trioxide using DB

Searched_Drug(1/1)			Target(7)		
#	DB_ID	Name	Target_Symbol	UniProtKB_AC	Entrez_ID
1	DB01169	Arsenic trioxide	IKBKB	Q14920	3551
2	DB01169	Arsenic trioxide	TXNRD1	Q16881	7296
3	DB01169	Arsenic trioxide	JUN	P05412	3725
4	DB01169	Arsenic trioxide	CCND1	P24385	595
5	DB01169	Arsenic trioxide	MAPK3	P27361	5595
6	DB01169	Arsenic trioxide	MAPK1	P28482	5594
7	DB01169	Arsenic trioxide	AKT1	P31749	207

though STRING. The expression levels of critical targets were explored in human pancreatic tumor tissues and adjacent tissues. KEGG pathway analyzed top 10 genes rich pathways and showed that BCL2 associated agonist of cell death (BAD), conserved helix-loop-helix ubiquitous kinase (CHUK), mitogen-activated protein kinase kinase1 (MAP2K1), nuclear factor kappa B subunit1 (NFKB1), RELA proto-oncogene (RELA), ubiquitin C (UBC) and phosphatidylinositol-4,5-bisphosphate-3-kinase -Akt (PI3K-Akt) pathway were strongly correlated with pancreatic cancer pathway. Thus we proposed arsenic trioxide might have a positive effect to inhibit the tumorigenesis of pancreatic cancer by targeting these critical proteins and PI3K-Akt pathway.

Materials and Methods

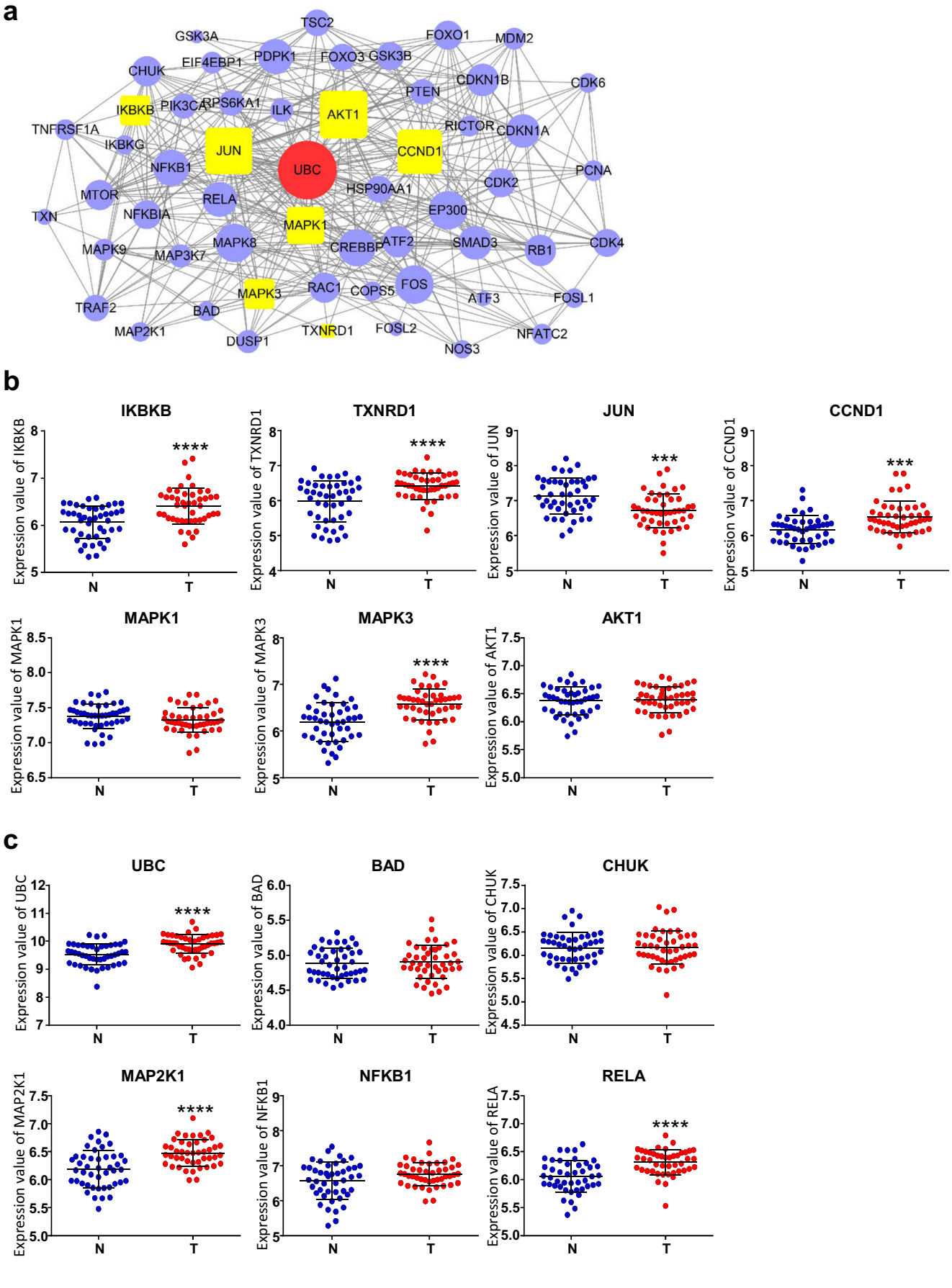
Drug-Target Search

DrugBank (http://www.drugbank.ca) is a comprehensive online database providing extensive biochemical and pharmacological information about drugs. We searched DB for the primary pharmacological information of arsenic trioxide and its targets. Then constructing a visualization chart with the available data. The biological information and primary targets of arsenic trioxide were analyzed using a web-based integrated genes mining database, STRING, to get a system-wide understanding of arsenic trioxide targets.

Network Generation/Visualization and Gene Set Enrichment Analysis

The pharmacological function, drug protein and second level protein-protein interactions data were first generated for arsenic trioxide in DB and STRING. The data were integrated into an arsenic trioxide-mediated network and visualized using Cytoscape (version 3.4.0). Biochemical pathways and functions associated with the arsenic trioxide gene sets were specifically queried and investigated by the KEGG pathway

Fig. 1 The interactome of arsenic trioxide targets and their expression levels in in human pancreatic tumor tissues (T) and paired adjacent tissues (N) (n = 41 independent samples) from GSE28735 data. **a** DB based arsenic trioxide drug-target protein interaction network. Primary direct protein targets (DPTs): IKBKB, TXNRD1, JUN, CCND1, MAPK3, MAPK1 and AKT1 (color in yellow) and secondary DPT-interacting protein (color in blue). UBC gene (color in red) is in the core position of the entire network. **b** Seven DPTs of arsenic trioxide (IKBKB, TXNRD1, JUN, CCND1, MAPK3, MAPK1 and AKT1) expression levels in human pancreatic tumor tissues and paired adjacent tissues. **c** Six critical genes associated with arsenic trioxide (UBC, BAD, CHUK, MAP2K1, NFKB1 and RELA) expression levels in human pancreatic tumor tissues and paired adjacent tissues. ***$P < 0.001$, ****$P < 0.0001$ by unpaired t-test with Welch's correction. Data are shown as mean with standard deviation (SD)


a
TSC2
GSK3A
FOXO1
MDM2
PDPK1
FOXO3
GSK3B
CHUK
EIF4EBP1
CDKN1B
CDK6
PTEN
IKBKB
PIK3CA
RPS6KA1
ILK
AKT1
TNFRSF1A
RICTOR
CDKN1A
IKBKG
JUN
CCND1
NFKB1
UBC
PCNA
HSP90AA1
CDK2
MTOR
RELA
EP300
TXN
NFKBIA
MAPK1
MAPK9
MAPK8
CREBBP
ATF2
SMAD3
RB1
CDK4
MAP3K7
MAPK3
RAC1
COPS5
FOS
ATF3
FOSL1
TRAF2
BAD
MAP2K1
TXNRD1
FOSL2
NFATC2
DUSP1
NOS3
b
IKBKB
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CCND1
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Expression value of IKBKB
Expression value of TXNRD1
Expression value of JUN
Expression value of CCND1
Expression value of MAPK1
Expression value of MAPK3
Expression value of AKT1
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c
UBC
BAD
CHUK
MAP2K1
NFKB1
RELA
Expression value of UBC
Expression value of BAD
Expression value of CHUK
Expression value of MAP2K1
Expression value of NFKB1
Expression value of RELA

enrichment analysis tool in STRING. The significant validated gene sets were then organized based on the KEGG biochemical pathways in a KEGG table. Top 10 pathways with False Discovery Rate (FDR) less than 0.01 were selected.

Exploring Cancer Genomic Data Linked to Arsenic Trioxide by cBio Cancer Genomic Portal

The cBio Cancer Genomics Portal (http://cbioportal.org) is an open-access database for exploring multidimensional cancer genomics data sets by encapsulating molecular profiling data obtained from various cancer tissues and cell lines studies. We investigated cBio Portal about the arsenic trioxide associated genes overlapped in PI3k-Akt and pancreatic cancer pathways. Through using of the portal explore function, arsenic trioxide associated genes in all samples of pancreatic cancer studies are classified as altered or not altered.

Statistical Analysis

GraphPad Prism 6.0 was utilized to graph the results. Data were analyzed using SPSS 17.0 software and analyzed differences between groups by unpaired Student's *t* test. Data are shown as mean with standard deviation (SD). A p value less than 0.05 was considered statistically significant.

Results

Seeking Direct Protein Targets (DPTs) of Arsenic Trioxide Using DB and Visualization of Arsenic Trioxide-Linkage Networks by Cytoscape(Version 3.4.0)

For biological organisms, drugs interact with biomolecules directly or indirectly to result in a physiologic effect. Any one kind of drug will interact with many kinds of biomolecules. Their relationships can be present as networks with nodes representing biological units. We first queried DB using arsenic trioxide as input. This resulted in output DB_01169 categorizing arsenic trioxide as antineoplastic agents, antineoplastic and immunomodulating agents, cytochrome P450 family 3 subfamily A (CYP3A) inhibitors, growth inhibitors, highest risk QTc-Prolonging agents, hyperglycemia-associated agents, hypotensive agents and myelosuppressive agents. Moreover, using the group status of arsenic trioxide as an approved and investigational drug, query of DB indicated that it is a drug used for the induction of remission and consolidation in patients with APL, and whose APL is characterized by the presence of the t(15;17)* translocation or PML/RAR-alpha gene expression (Table 1). From DB, we also found that arsenic trioxide has 7 primary direct protein targets (DPTs), as shown in Table 2. Expanding our search and analysis utilizing STRING v10 database [12], we identified a total number of 111 target-protein interactions designated DPT-associated genes as being related to arsenic trioxide and its 7 primary targets. The 7 primary DPTs and their secondary DPT-associated proteins were shown in Fig. 1a. It should be noted that UBC (EntrezGene ID: 7316) is in the core position of the entire network. Moreover, UBC encodes a protein as a polyubiquitin precursor which is associated with protein degradation, DNA repair, cell cycle regulation, endocytosis, and regulation of other cell signaling pathways [13–16]. These founds indicated that arsenic trioxide may have effects on inhibiting the basic characteristics of cancer cells.

Analysis of Functional Properties of Arsenic Trioxide-Mediated Changes in Genes Sets Using STRING

To assess functional features of arsenic trioxide-mediated gene sets, we performed the KEGG pathway enrichment by STRING. The top 10 KEGG pathways linked to arsenic trioxide DPTs and their DPT-associated genes include hepatitis B (28 genes), prostate cancer (25 genes), pathways in cancer (32 genes), PI3K-Akt signaling pathway (28 genes), Osteoclast differentiation (22 genes), Chronic myeloid leukemia (19 genes), Pancreatic cancer (18 genes), HTLV-I infection (24 genes), TNF signaling pathway (19 genes) and Viral carcinogenesis (21 genes) (Table 3). All enriched pathways identified using this method represent biological areas that show a statistically significant association with arsenic trioxide genes sets thus warranting further investigation. Broad grouping of the functional analysis suggest that arsenic trioxide-associated genes are mainly cancer-related or linked to pathways involved in viral infection and so on, including (I) induction of cancer cell apoptosis by PI3K-Akt signaling pathway, (II) control of HBV or HTLV-I via hepatitis B pathway and HTLV-I infection pathway, (III) regulation the differentiation of osteoprogenitor cell by osteoclast differentiation pathway, (IV) control of the development of acute promyelocytic leukemia (APL) by chronic myeloid leukemia pathway.

Given that many studies had indicated that pancreatic cancer is connected to the PI3K-Akt signaling pathway [17, 18], emphasis was directed to the PI3K-Akt signaling pathway and pancreatic cancer pathway. Further analyses revealed that 5 genes either in the PI3K-Akt signaling pathway or in the pancreatic cancer pathway showed a connection to arsenic trioxide-associated genes, BAD, CHUK, MAP2K1, NFKB1 and RELA (EntrezGene ID: 572, 1147, 5604, 4790, 5970). Thus, based on the functional analysis combined with arsenic trioxide target search, it may be suggested that a functional association exists between PI3K-Akt signaling pathway and arsenic trioxide thereby linking DPTs of arsenic trioxide.

Table 3 List of enriched arsenic trioxide associated gene sets identified using KEGG pathway analysis

Pathway Name	#Gen	Entrez Gene(corresponding gene set)	FDR
Hepatitis B	28	207,1386,572,595,1019,1021,1026,1027,1147,1387,2033,14,281,3551,8517,3725,5604,5594,5602,5595,5599,18,019,4790,4792, 5111,5290,5728,5925,5970	4.07E-44
Prostate cancer	25	207,572,595,1026,1027,1147,1387,2033,2308,2932,3320,3551,8517,5604,5594,5595,4193,2475,4790,4792,5170,5290,5728,5925, 5970	7.58E-44
Pathways in cancer	32	207,572,595,1019,1021,1026,1027,1147,1387,2033,14,281,2308,2932,3320,3551,8517,3725,5604,5594,5602,5595,5599,14,193,2475,4790, 4792,5290,5728,5879,5925,5970, 7186	2.29E-41
PI3K-Akt signaling pathway	28	207,1306,572,595,1019,1021,1026,1027,1147,1978,2309,2932,3320,3551,8517,5604,5594,5595,4193,2475,4790,4846,5170,5290,5728,5879,5970,7249	2.44E-33
Osteoclast differentiation	22	207,1147,14,281,8061,2355,3551,8517,3725,5604,6885,5594,5602,5595,5599,18,019,4790,4792,5290,5879,5970, 7132,7186	3.21E-33
Chronic myeloid leukemia	19	207,572,595,1019,1021,1026,1027,1147, 3551,8517,5604,5594,5595,4193,4790,4792,5290,5925,5970,	1.96E-32
Pancreatic cancer	18	207,572,595,1019,1021,1147,3551,8517,5604,5594,5602,5595,5599,4790,5290,5879,5925,5970,	2.53E-31
HTLV-I infection	24	207,1386,467,595,1019,1026,1147,1387,2033,14,281,8061,2932,3551,8517,3725,5599,18,019,4790,4792,5111,5290,5925,5970,7132	7.57E-30
TNF signaling pathway	19	207,1386,1147,14,281,3551,8517,3725,5604,6885,5594,5602,5595,5599,4790,4792,5290,5970,7132,7186	1.19E-28
Viral carcinogenesis	21	1386,572,595,1019,1021,1026,1027,1387,2033,8517,3725,5594,5595,4193,4790,4792,5290,5879,5925,5970, 7186	1.08E-27

*FDR False Discovery Rate

Seven DPTs and Six Critical Genes of Arsenic Trioxide (IKBKB, TXNRD1, JUN, CCND1, MAPK3, MAPK1, AKT1, UBC, BAD, CHUK, MAP2K1, NFKB1 and RELA) Expression Levels in Human Pancreatic Tumor Tissues

To compare the expression change of DPTs and selected critical genes of arsenic trioxide during pancreatic tumor progression, we investigated their expression in human pancreatic tumor tissues and adjacent tissues. Publicly available databases in Gene Expression Omnibus (GEO) reveled mRNA levels of 7 DPTs (Fig. 1b) and 6 critical genes associated with arsenic trioxide (Fig. 1c) in 41 pairs of human pancreatic tumor tissues and adjacent tissues. We found the expression levels of several critical targets show significant difference in tumor tissues and adjacent tissues, such as IKBKB, TXNRD1, JUN, CCND1, MAPK3, UBC, MAP2K1and RELA. These arsenic trioxide targets have significantly higher expression levels in human pancreatic tumor tissues than adjacent tissues, and JUN shows contrary condition. Collectively, these data demonstrate that these selected genes may be associated with pancreatic tumor development and may be potential therapeutic targets of arsenic trioxide.

Finding Genetic Alterations Connected with Arsenic Trioxide-Associated Genes, UBC, BAD, CHUK, MAP2K1, NFKB1 and RELA, in Pancreatic Cancer by cBio Portal

From DB, we know that arsenic trioxide cloud be the choice for the treatment of APL (Table 1); the functional enrichment uncover the link between arsenic trioxide-associated targets and cancer-related pathways (Table 3). To further explore the validity of this link, cBio portal was used to explore the genetic alteration of genes associated with arsenic trioxide in pancreatic cancer. Since UBC is in core position of network linked to arsenic trioxide-associated genes, and 5 overlapping genes (BAD, CHUK, MAP2K1, NFKB1 and RELA) were also found to be associated with PI3K-Akt signaling pathway and pancreatic cancer by KEGG analysis, we utilized the 5 indicated overlapping genes and UBC to cross check their genomic alternations and clinical profiles in pancreatic cancer. A query of 6 selected genes was performed among 7 pancreatic cancer studies analyzed [19–25], alterations ranging from 1% to 27.5% were found for the genes submitted (Fig. 2a). A summary of the multiple gene alterations observed across each set of tumor samples from UTSW studies [23] showing the most pronounced genomic changes is presented using OncoPrint. The results show that 30 cases (28%) have an alteration in at least one of the six genes queried; the frequency of alteration in each of the selected genes is shown Fig. 2b. For UBC and CHUK, alterations are classified as amplification and deletion. Most gene changes associated with BAD are

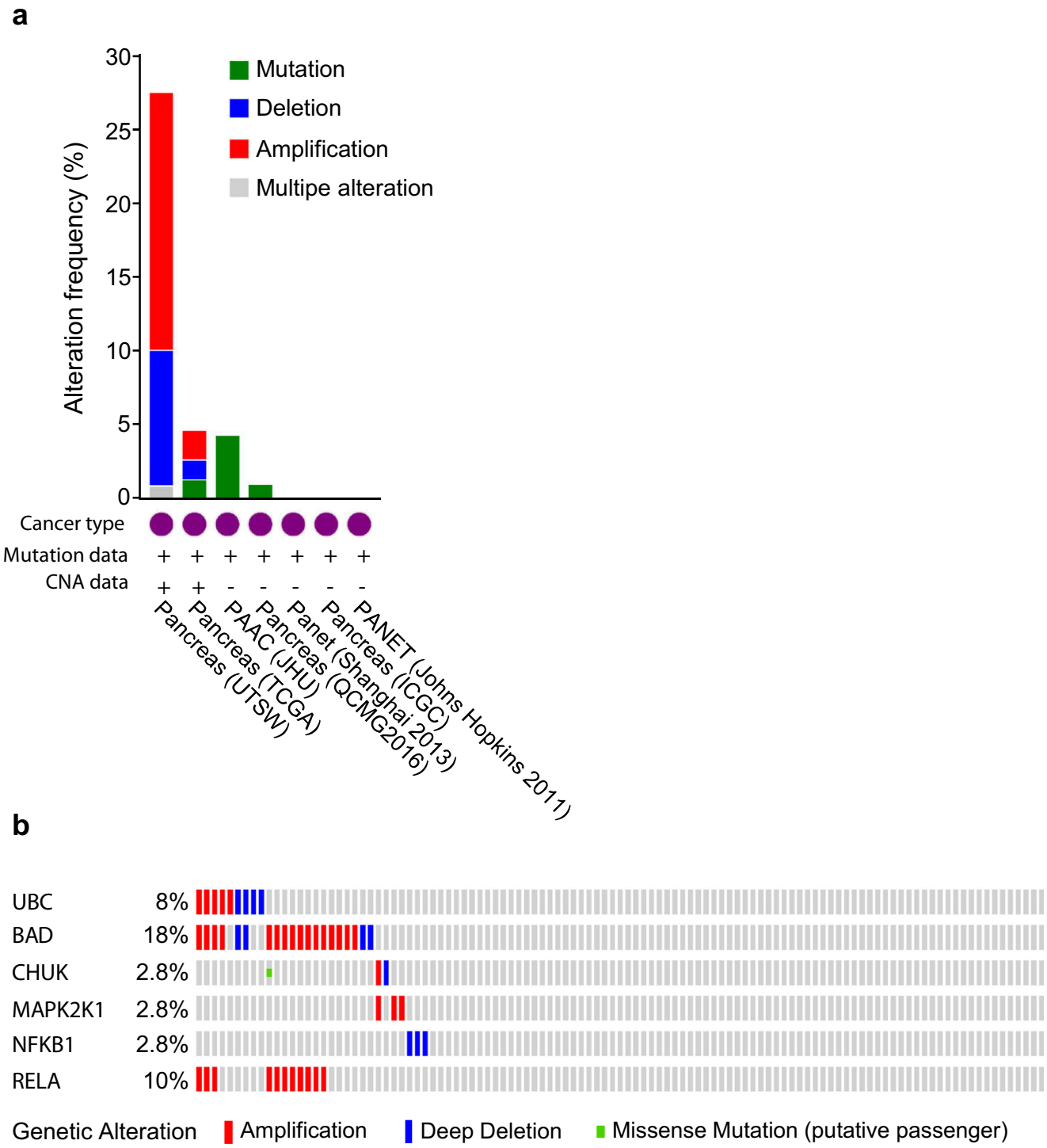


Fig. 2 Cross-cancer alteration summary for BAD, CHUK, MAP2K1, NFKB1, RELA, UBC (7 studies/6 genes). **a** Overview of changes on UBC, BAD, CHUK, MAP2K1, NFKB1 and RELA genes in genomic data sets available in 7 different pancreatic cancer studies. **b** OncoPrint: A visual summary of alteration across a set of pancreatic samples (data taken from the UTSW studies, Nat Commun 2015) [23] based on a query of the 6 selected genes). Genomic alteration including mutations and CNAs (copy number alterations, exemplified by gene amplification and homozygous deletions) are summarized and color coded presented by % changes in particular affected genes in individual tumor samples. Each row represents a gene, and each column represents a tumor sample. Red bars designate gene amplification, blue bars represent homozygous deletions, and green squares indicate nonsynonymous mutations

amplification with a few cases of deep deletion. For RELA and MAP2K1, all gene changes are amplification. And for the other 1 selected genes, NFKB1, gene changes are all classified as deletion.

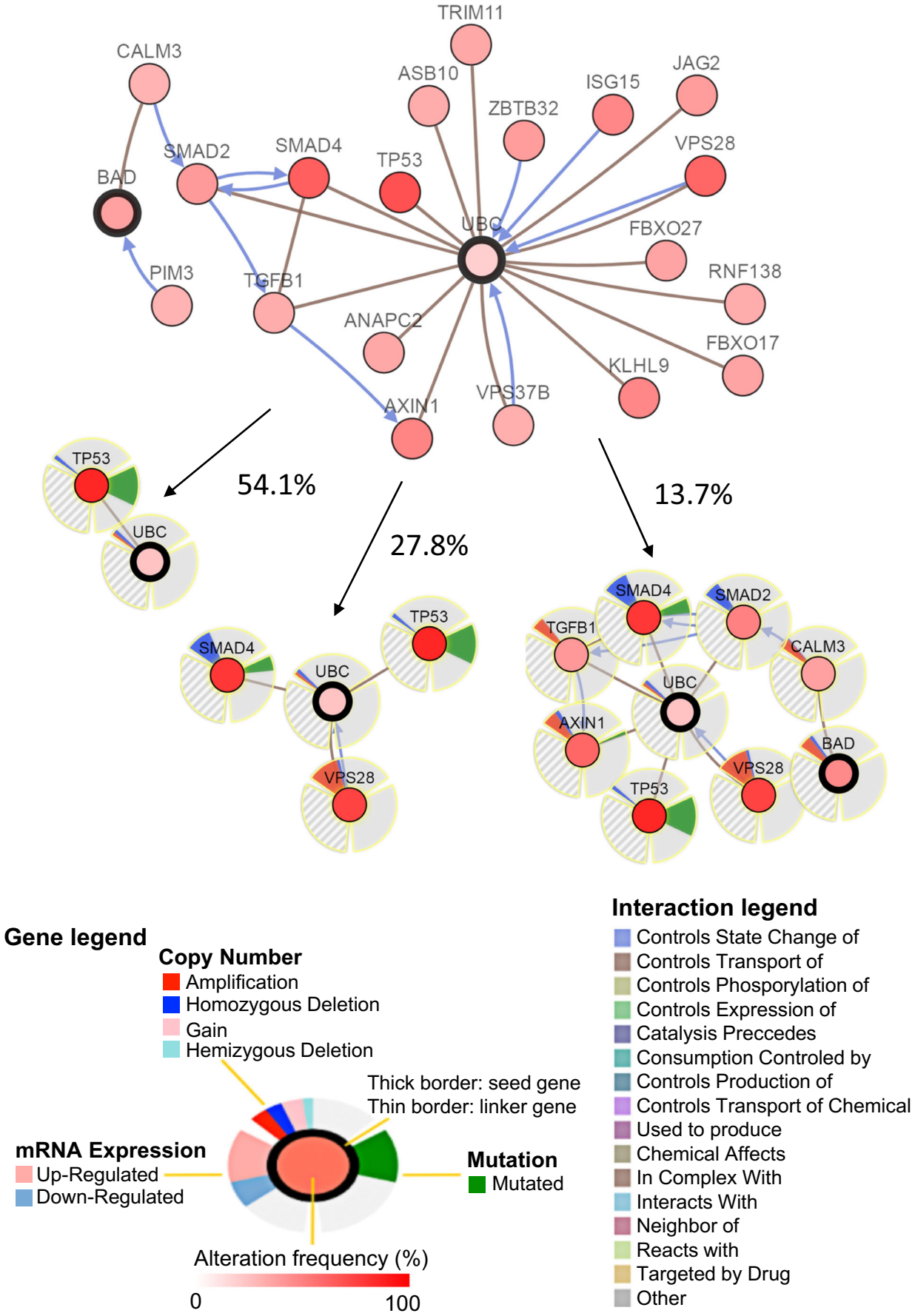
cBio portal also provides interactive analysis and construct networks to view genes that are altered in cancer. In our studies, we first show the network to contain all neighbors of 2 selected genes—UBC and BAD (Fig. 3). For the other 4 selected genes, they were abandoned due to the lower genetic alteration rates and the proved roles of RELA. Next, to decrease the complexity of network analysis, the genomic alteration frequency within the selected cancer study was applied as a filter such that only the neighbors with the highest alteration frequency in addition to our query genes are shown. At the very beginning, UBC and tumor protein p53 (TP53) were identified when neighbors' >54.1% alteration was applied as the filter. Comparatively, 2 genes including vacuolar protein sorting 28 (VPS28) as well as SET and MYND domain containing 4 (SMYD4) were evident using a filter as 27.8% alteration. A 9 gene cluster with SET and MYND domain containing 2 (SMYD2), transforming growth factor beta 1 (TGF-β1), calmodulin 3 (CALM3), BAD and AXIN1 were found using a filter as 13.7% alteration. As we all known, TP53 and SMYD4 were identified as a tumor suppressor gene and associated with a variety of human cancers [26–28]. TGF-β1 regulated cell proliferation, differentiation and can modulate expression and activation of other growth factors including interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) [29–31]. Mutations in AXIN1 were associated with hepatocellular carcinoma and ovarian endometriod adenocarcinomas [32, 33]. The full and pruned networks generated show the potential of complexity as well as the variability of difference in interactions between arsenic trioxide-associated genes most relevant to the genes altered in pancreatic cancer tumor samples from the UTSW studies [23].

Discussion

It has been shown that arsenic trioxide is an effective drug for APL since the landmark finding of the down-regulation of BCL-2 gene expression by arsenic trioxide [34]. Widespread of biological and cellular molecules linked with arsenic trioxide have been identified [35, 36]. Moreover, arsenic trioxide has already been found to develop anti-tumor activity in various human malignant tumors [4, 5, 7, 9]. Still, how arsenic trioxide promotes its wide range of beneficial effects in solid tumors remains incomprehensive understand. Another obstruction in the anti-tumorous studies of arsenic trioxide is that it is difficult to explore the effective target molecules. During the past 30 years, validated therapeutic targets of arsenic trioxide identified by various studies are less than 20, and most of these studies explained the biological mechanism of arsenic trioxide directly from the level of post-transcription and protein expression regulation. Tao et.al. explored the arsenic trioxide targets using a human proteome microarray and identified 360 proteins which specifically bind arsenic. Among these enriched proteins, a key target, hexokinase-2 (HK2), is overexpressed in various cancers and significantly inhibited by arsenic trioxide, indicating a valuable antitumor therapeutic molecule [37]. Tao's study help people get a clearer understanding of the biological mechanism of arsenic trioxide.

In this study, we bridged arsenic trioxide to its DPTs and elucidate a precise molecular mechanisms of arsenic trioxide for the treatment of pancreatic cancer, with several kinds of web-based tools like DB (for exploring the arsenic trioxide target proteins) and cBio portal (for mining alterations of arsenic trioxide target genes in pancreatic cancer), which help researchers get a clear insight to the biological function of arsenic trioxide. We identified 7 primary DPTs and 111 secondary DPT-associated genes/proteins as well as 10 enriched KEGG pathways linked to arsenic trioxide-associated proteins. Based on the known function characteristics of 111 secondary DPT-associated genes/proteins and our current knowledge of KEGG pathways, 32 genes may be considered as validated targets of arsenic trioxide with mechanistic connectivity to cancer. Since previous experiments have indicated the potential correlation between PI3K-Akt signaling pathway and pancreatic cancer, we searched the overlapping genes in these two pathways of KEGG and got 5 genes (BAD, CHUK, MAP2K1, NFKB1 and RELA). The expression levels and alterations of 5 overlapping genes and UBC, which has the strongest relation with the DPT-associated genes/proteins, were further evaluated in pancreatic cancer. In our analysis, BAD has the highest genetic alteration rates among these selected genes in pancreatic cancer. Many studies have also proved that BAD is associated with tumorigenesis. Cekanova et al. found BAD is down-regulated in breast cancer and inhibiting expression of BAD artificially could increase cancer invasion and Akt/p-Akt single levels [38]. Meanwhile, phosphorylation of BAD is essential for the survival of cancer stem cells (CSC) [39].

In summary, we provided reliable bioinformatics and computational evidence that support the role of arsenic trioxide as a potential anti-tumor agent for pancreatic cancer cells. Meanwhile, we proposed that through PI3K-Akt single pathway, arsenic trioxide might regulate its upstream or downstream genes such as BAD, CHUK, MAP2K1, NFKB1, RELA and UBC, leading to the inhibition of cell proliferation in pancreatic


TRIM11
CALM3
ASB10
ISG15
JAG2
ZBTB32
SMAD2
SMAD4
TP53
VPS28
BAD
UBC
FBXO27
PIM3
TGFB1
RNF138
ANAPC2
FBXO17
KLHL9
VPS37B
AXIN1
54.1%
27.8%
13.7%
Gene legend
Copy Number
Amplification
Homozygous Deletion
Gain
Hemizygous Deletion
Thick border: seed gene
Thin border: linker gene
mRNA Expression
Up-Regulated
Down-Regulated
Mutation
Mutated
Alteration frequency (%)
0
100
Interaction legend
Controls State Change of
Controls Transport of
Controls Phosporylation of
Controls Expression of
Catalysis Preccedes
Consumption Controled by
Controls Production of
Controls Transport of Chemical
Used to produce
Chemical Affects
In Complex With
Interacts With
Neighbor of
Reacts with
Targeted by Drug
Other

◀ **Fig. 3** Neighboring genes connected to arsenic trioxide-associated genes as filtered by alterations (%). A visual display of the genes network connected to 6 selected genes in pancreatic cancer (based on the UTSW study, Nat Communication 2015) [23]. The data mined from the cBio cancer genomics portal. 2 selected genes—UBC and BAD—are used as seed genes to automatically harvest all other genes identified as altered in pancreatic cancer. Multidimensional genomic details are shown for seed genes UBC and BAD. Gene legend and interaction legend are also gave in the figure

cancer. Both of arsenic trioxide and its 6 critical arsenic trioxide target genes could be promising therapeutic molecules for pancreatic cancer. Due to the toxic nature of arsenic, it is necessities to further investigate the effects of arsenic trioxide metabolites to make sure the anti-tumor effects of arsenic trioxide are reliable and safe. Whether the PI3k-Akt pathway and selected critical genes shown to exist between arsenic trioxide and pancreatic cancer in our work can be extended to other solid tumors remains to be investigated. And we are taking experiments in pancreatic cancer and other solid tumor cells to testify our proposal.

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Compliance with Ethical Standards All authors have approved the final manuscript.

Conflicts of Interest The authors declare no conflicts of interest.

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