



Correlation of gene expression profiles to identify pancreatic cancer cell lines that best model primary human tumors

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Background: Cancer cell lines are important research models for studying tumor biology in vivo. The accuracy of such studies is highly dependent on the phenotypic and genetic similarity of cell lines to patient tumors, but this is not always the case, particularly for pancreatic cancer.

Methods: We compared the gene expression profiles of various pancreatic cancer cell lines and primary human pancreatic tumor tissues to determine which pancreatic cancer cell line best models human primary tumor. Profiles of messenger RNA (mRNA) expression of 33 pancreatic cancer cell lines and 892 patient samples of pancreatic adenocarcinoma (PAAD) were obtained from the Gene Expression Omnibus (GEO) database. Microarray data were normalized using the robust multichip average (RMA) algorithm and batch effect removal was performed using ComBat. The pooled data of each PAAD cell line were compared to patient tumors based on the top 2,000 genes with largest interquartile range (IQR), 134 gene-collections of cancer-related pathways, and 504 gene-collections of cancer-related functions using pairwise Pearson's correlation analysis.

Results: PAAD cell lines were poorly correlated with patient tumor tissues based on the top 2,000 genes. Up to 50% of cancer-related pathways were not strongly recommended in PAAD cell lines, and a small proportion of cancer-related functions (12–17%) were poorly correlated with PAAD cell lines. In pan-pathway analysis, the cell lines showing the highest genetic correlation to patient tumors were Panc 03.27 for PAAD cell lines from a primary lesion site and CFPAC-1 for PAAD cell lines from a metastatic lesion site. In pan-function analysis, the cell lines showing the highest genetic correlation to patient tumors were Panc 03.27 for PAAD cell lines from a primary lesion site and Capan-1 for PAAD cell lines from a metastatic lesion site.

Conclusions: The gene expression profiles of PAAD cell lines correlate weakly with those of primary pancreatic tumors. Through comparison of the genetic similarity between PAAD cell lines and human tumor tissue, we have provided a strategy for choosing the appropriate PAAD cell line.

Keywords: Pancreatic cancer; genetic profile; cell line; tumor tissue

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Introduction

Cancer cell lines have had an increasingly important role in the study of cancer biology, and they are an invaluable model system for *in vitro* cancer research (1-5). A vast number of different cancer cell lines have been developed, yet only a few can be used in any given study due to financial and experimental constraints. As little information is available on how well the behavior of a particular cell line matches that of the primary tumor, most investigators choose a cell line based on empirical evidence or simply choose the most commonly used cell line (6-8). Unfortunately, empirical methods may not be adequate. For example, the commonly-used ovarian cell line SKOV3 has less genomic fidelity to patient tumors than the 2 less-described cell lines KURAMOCHI and OVSAHO (9). In two commonly used cell lines BxPC-3 and PANC-1, genes involved in epithelial-mesenchymal transition (EMT) and carbohydrate metabolism are quite different (10,11). Therefore, understanding and quantifying the genetic similarity between cell lines and patient tumors, and choosing the most appropriate cell lines is of critical importance for *in vitro* cancer studies.

Several recent studies have compared the messenger RNA (mRNA) expression profiles of cell lines and primary tumors of various cancers (12-16); the genetic similarity between cell lines and primary tissues was found to be

tumor dependent. Cell lines with moderately similar gene expression to primary tumors were reported to have a median correlation coefficient of 0.6 in the Cancer Cell Line Encyclopedia (CCLE) project (15). However, pancreatic adenocarcinoma (PAAD) was found to exhibit a weaker correlation between cell lines and primary tumors, with a correlation coefficient of only 0.347 (15). At the same time, Deer *et al.* compared phenotype and genotype of 11 PAAD cell lines, revealing that sufficient discrepancies exist in them (17). As an extremely poor correlation between PAAD primary tumors and their cell lines was found, the empirical model of cell lines selection, and even the least accurate 1 cell line fitted all study, may be challenged. For example, if the role of KRAS mutation in pancreatic tumor is studied, then it is not reasonable to choose BxPC-3, KP-4 and Panc 10.05 cell lines; if gemcitabine-resistance pancreatic tumor is studied, the gemcitabine-sensitive cell lines BxPC-3, CFPAC and SU86.86 are not suitable (18). A more reasonable method would be to warrant scrutiny during cell line selection, to compare the gene expression profiles of a number of different cell lines to that of the patient tissues, with a focus on the most relevant pathways, in order to select the one that best matches the *in vivo* situation.

The aforementioned studies conducted by Domcke and Shuaichen had a leading find of genetic similarity between cancer cell lines and patient tumor tissue (12,14). However, more detailed information, such as correlation of individual cancer-related pathways or cancer-related functions, should be provided to suggest appropriate cell lines for *in vitro* study of the corresponding cancer. Therefore, in the present study, we conducted a comprehensive analysis of the similarity of cancer-related pathways covering 33 commonly used human PAAD cell lines and 892 patient samples. We found that the gene expression profiles of PAAD cell lines correlate weakly with those of primary pancreatic tumors. Up to 50% cancer-related pathways are not strongly recommended in PAAD cell lines, and a small proportion of cancer-related functions (12–17%) are extremely poorly correlated with PAAD cell lines. Based on the similarity of genetic profiles and bioinformatics analyses, we provide a strategy for choosing the appropriate PAAD cell line. We present the following article in accordance with the MDAR

Highlight box

Key findings

- The gene expression profiles of PAAD cell lines correlate weakly with primary pancreatic tumors, we provide a new strategy for choosing the appropriate cell lines.

What is known and what is new?

- Empirical selection of cancer cell lines may not be adequate for *in vitro* cancer studies, especially for pancreatic cancer.
- We compared the genetic similarity between PAAD cell lines and human tissue to choose the most appropriate cell lines.

What is the implication, and what should change now?

- Not all PAAD cell lines behave like human tumor tissue in *in vitro* cancer research. We could choose a more optimal PAAD cell line based on the genetic similarity between them.

reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-173/rc>).

Methods

Cell lines

The human PAAD cell lines are available at following cell line collections:

- (I) American Type Culture Collection (ATCC; Manassas, VA, USA; <http://www.atcc.org/>);
- (II) Leibniz Institute (DSMZ; Braunschweig, Germany; <http://www.dsmz.de/>);
- (III) European Collection of Authenticated Cell Cultures (ECACC; Salisbury, UK; <http://www.hpacultures.org.uk/collections/ecacc.jsp>);
- (IV) Health Sciences Research Resources Bank (HSRRB; Tokyo, Japan; <http://www.jhsf.or.jp/English/hsrrb.html>);
- (V) RIKEN of Japan (Tokyo, Japan; <http://www.brc.riken.jp/lab/cell/english/>);
- (VI) Interlab Cell Line Collection (ICLC; Genoa, Italy; <http://www.iclc.it/Listanuova.html>);
- (VII) Korean Cell Line Bank (KCLB; Seoul, Korea; <http://cellbank.snu.ac.kr/english/index.php>);
- (VIII) China Infrastructure of Cell Line Resource (CICR; Beijing, China; <http://www.cellresource.cn/>).

Private cell lines were excluded. The characteristics of cell lines were checked in database of Cellosaurus (<https://web.expasy.org/cellosaurus>). Further details are shown in [Table S1](#).

mRNA expression data

Microarray data

Data on mRNA expression in PAAD cell lines and patient tumor tissues were obtained from the Gene Expression Omnibus (GEO; <http://www.ncbi.nlm.nih.gov/geo/>). GEO datasets uploaded to the database on or before 30 June 2017 were refined using the following search terms: (I) cancer: pancreatic carcinoma, pancreatic cancer, or pancreatic tumor; OR (II) cell lines: AsPC-1, BxPC-3, PANC-1, Capan-1, Capan-2, CFPAC-1, DAN-G, Hs 766T, HuP-T3, HuP-T4, KP-2, KP-3, KP-4, MIA PaCa-2, PK-45H, PK-59, PSN1, SNU-213, SNU-324, SU.86.86, SNU-410, SUTT-2, SW1990, T3M-4, YAPC, HPAC, Panc 02.13, Panc 03.27, Panc 04.03, Panc 05.04, Panc 08.13, Panc 10.05, and PK-1. The datasets were independently

inspected and included. The study type was limited to “Expression profiling by array”, and species was defined as “*Homo sapiens*”. All datasets were independently inspected by two review authors (Gaoqi Xu and Jiao Sun), who checked the data for tumor tissues from therapy-naive patients or for untreated cell lines. Further details are shown in [Figure S1](#). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Preprocessing of microarray data

Affymetrix microarray datasets were downloaded as raw. CEL files and preprocessed using the robust multi-array average (RMA) algorithm in the Bioconductor package “affy”. Datasets from other microarray platforms were downloaded as a series matrix file with normalized data.

If a gene was detected with multiple probes in an array, the expression level was taken as the average value of all probes. Datasets from the same cell lines or from PAAD patients were pooled. Batch effect correction was performed using the function ComBat from the Bioconductor package *sva* to control for batch effects between different microarray datasets.

Cell line to patient tumor comparison

The similarity of cell lines and patient tumors was evaluated by compared the pooled data of each cell line with PAAD patients’ tumors based on the top 2,000 gene with largest interquartile range (IQR) or cancer-related pathways.

Similarity of general genes

The correlation based on general gene-profile was evaluated according to a previously reported algorithm. The average fold-changes for each gene ranked among the top 2,000 IQR genes between cell lines and tumor samples of PAAD patients were calculated by a previously fitting linear model for microarray data (*limma*) (15).

Similarity of specific pathways

Text mining search of cancer-related genes

An online text mining search engine, DiGseE (developed and available by Data Mining & Computational Biology Laboratory, Gwangju Institute of Science and Technology, Gwangju, South Korea, at <http://gcancer.org/digsee>), was used to collect the genes related to cancer from Medline abstracts for evidence sentences describing in literature (19).

Cancer-related pathways enriched via Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis

All the reported cancer-related genes were analyzed via the Database for Annotation, Visualization, and Integrated Discovery (DAVID) Bioinformatics Resources 6.8 (available at <https://david.ncifcrf.gov>). The cancer-related pathways and each pathway-involved gene were obtained. A P value <0.10 was considered to have statistical significance and to achieve significant enrichment.

Similarity evaluation of cancer-related pathways

The correlation of each pathway between an individual cell line and PAAD patient tumors was calculated by comparing normalized-expression levels of genes involved in each pathway using pairwise Pearson's correlation analysis according to the algorithm previously described (10), respectively. The pathway-similarity profiles of cell lines to human tumors were compared based on correlation coefficients of all 134 pathways using Mann-Whitney U-test. The pathways were grouped into highly ($r > 0.60$), moderately ($r = 0.30 - 0.60$), and poorly ($r < 0.30$) consistent pathways of each cell line, whereas the highly, moderately, and poorly consistent cell lines of each pathway were also collected.

Similarity evaluation of cancer-related functions

The correlation of each function between an individual cell line and PAAD patient tumors was calculated by comparing normalized-expression levels of genes involved in each function using pairwise Pearson's correlation analysis according to the algorithm previously described, respectively. The function-similarity profiles of cell lines to human tumors were compared based on correlation coefficients of all 504 functions using the Mann-Whitney U-test. The functions were grouped into highly ($r > 0.60$), moderately ($r = 0.30 - 0.60$), and poorly ($r < 0.30$) consistent functions of each cell line, and the highly, moderately, and poorly consistent cell lines of each function were also collected.

Results

A total of 479 of potentially related datasets series was found in GEO, of which 86, 48, 226, and 12 datasets were excluded for treated cell line, duplicate data-series, unavailable detail information, and too many missed data, respectively. Ultimately, 107 data series were included, among which there were 33 cell lines (AsPC-1, BxPC-3, PANC-1, Capan-1, Capan-2, CFPAC-1, DAN-G, Hs 766T, HuP-T3, HuP-T4, KP-2, KP-3, KP-4, MIA PaCa-2, PK-45H, PK-59, PSN1, SNU-213, SNU-324, SU.86.86,

SNU-410, SUT-2, SW1990, T3M-4, YAPC, HPAC, Panc 02.13, Panc 03.27, Panc 04.03, Panc 05.04, Panc 08.13, Panc 10.05, and PK-1), and 1,358 samples, respectively, as listed in [Tables S1,S2](#) and [Figure S1](#).

Cell line to primary tumor comparison

As is shown in [Figure 1](#) and [Table S1](#), high genetic divergence was observed between each PAAD cell line; and the correlation between PAAD cell lines and tumor tissue were extremely poor (correlation coefficient: median, 0.137; range, -0.416 to 0.511).

The correlation coefficients of cancer-related pathways in various pancreatic cancer cell lines are displayed in [Figure 2](#). Several key cancer-related pathways showed poor consistency between most PAAD cell lines and patient tissues, including Toll-like receptor, PI3K-Akt, NF kappa B, cAMP, p53, focal adhesion, HIF-1, Wnt, Foxo, and so on. Moreover, according to the Cellosaurus database, PAAD cell lines were divided into two groups: cell lines of primary lesion and metastatic lesion. The top 3 poor consistency PAAD cell lines with tumor tissue were all cell lines of metastatic lesion in several cancer-related pathways, such as endometrial cancer, renal cell carcinoma, and small cell lung cancer.

Although they all belonged to the same group, the genomic similarity between cell lines and tumor tissue varied greatly in the same pathway. For example, SW1990, Hup-T3, CFPAC-1, Hs766T, Capan-1, and ASPC-1 are cell lines of metastatic lesions, among which, ASPC-1 cells were poorly correlated with the HIF-1 pathway, whereas the others were highly correlated with the HIF-1 pathway. Similarly, DAN-G and Panc 10.05 were PAAD cell lines of primary lesions, the consistent value of DAN-G in the p53 pathway was 0.12, whereas that of Panc 10.05 in the p53 pathway was 0.83. In addition, there were pathways, such as mTOR, the NOD like receptor signaling pathway, and Allograft rejection, upon which the chosen of PAAD cell line had little effect. Based on these observations, we recommended the most suitable cancer-related pathways for each PAAD cell line ([Table 1](#) and [Table S3](#)). For pan-pathway analysis, the cell line showing the highest genetic correlation to patient tumors was Panc 03.27 for PAAD cell lines from primary lesion sites, and CFPAC-1 for PAAD cell lines from metastatic lesion sites.

In [Figure S2](#), although about 20% of the functions were not very different in each PAAD cell, more than 50% of the functions varied greatly between PAAD cell lines and tumor

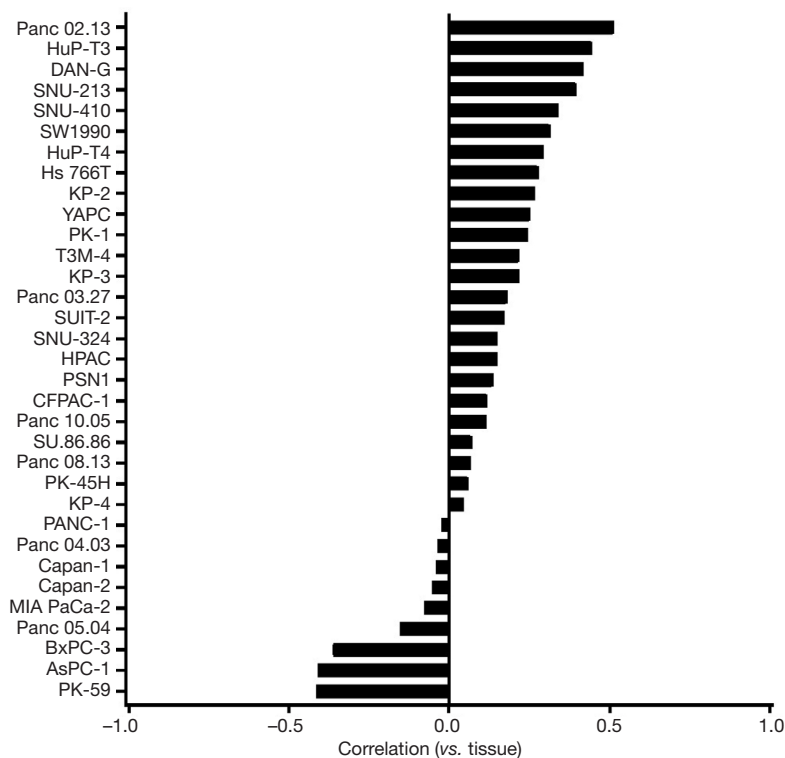


Figure 1 Correlation coefficients between PAAD cell lines and primary tumor tissue. PAAD, pancreatic adenocarcinoma.

tissue, including Epithelial to mesenchymal transition, Negative regulation of fat cell differentiation, and Cell aging, among others. To investigate these functions, selection of appropriate cell lines was quite necessary. So, we listed the top 3 suitable functions for each PAAD cell line (Table 2), to create a reference to minimize selection of an inappropriate cell line. In pan-function analysis, the cell line showing the highest genetic correlation to patient tumors was Panc 03.27 for PAAD cell lines from primary lesion sites and Capan-1 for PAAD cell lines from metastatic lesion sites.

Discussion

After the first cancer cells, HeLa, were established by Gey in 1951 (20), cancer cell lines have provided a relatively homogeneous model for *in vitro* cancer research. The first pancreatic cancer cell line was the CaPa strain established in 1963 (21). To date, more than 60 pancreatic cancer cell lines have been reported.

The use of immortalized cancer cell lines is an easy method for cancer research, not only due to the high degree of control over experimental variables, but also the role in

high-throughput screening for anti-cancer drug discovery and research on the mechanisms of disease (22,23).

Although cancer cell lines provide a convenient tool for the study of cancer biology *in vitro*, there are still some limitations. First, cancer cell lines have originated from parts of primary tumors, and have been cultured *in vitro* for a long time, which renders them prone to genetic drift. Second, some cancer cell lines have been derived from primary lesions and others derived from metastatic lesions; how this difference will affect the results of the specific research is unknown. Third, due to significant differences in both genomic alterations and expression, the selected cancer lines may not be an accurate representation or model system of primary tumors. Fourthly, PAAD cell lines cannot mimic the real immune environment in primary pancreatic tumors because not only tumor cells but also stroma, fibroblast and various immune cells are present in tumors (24). Thus, it is urgent to establish an appropriate method to compare the gene expression profiles of numbers of different cell lines to those of tumor tissues, with a focus on the most relevant pathways or function, in order to select the cell line that best matches the *in vivo* situation.

Recent study reported huge heterogeneity between

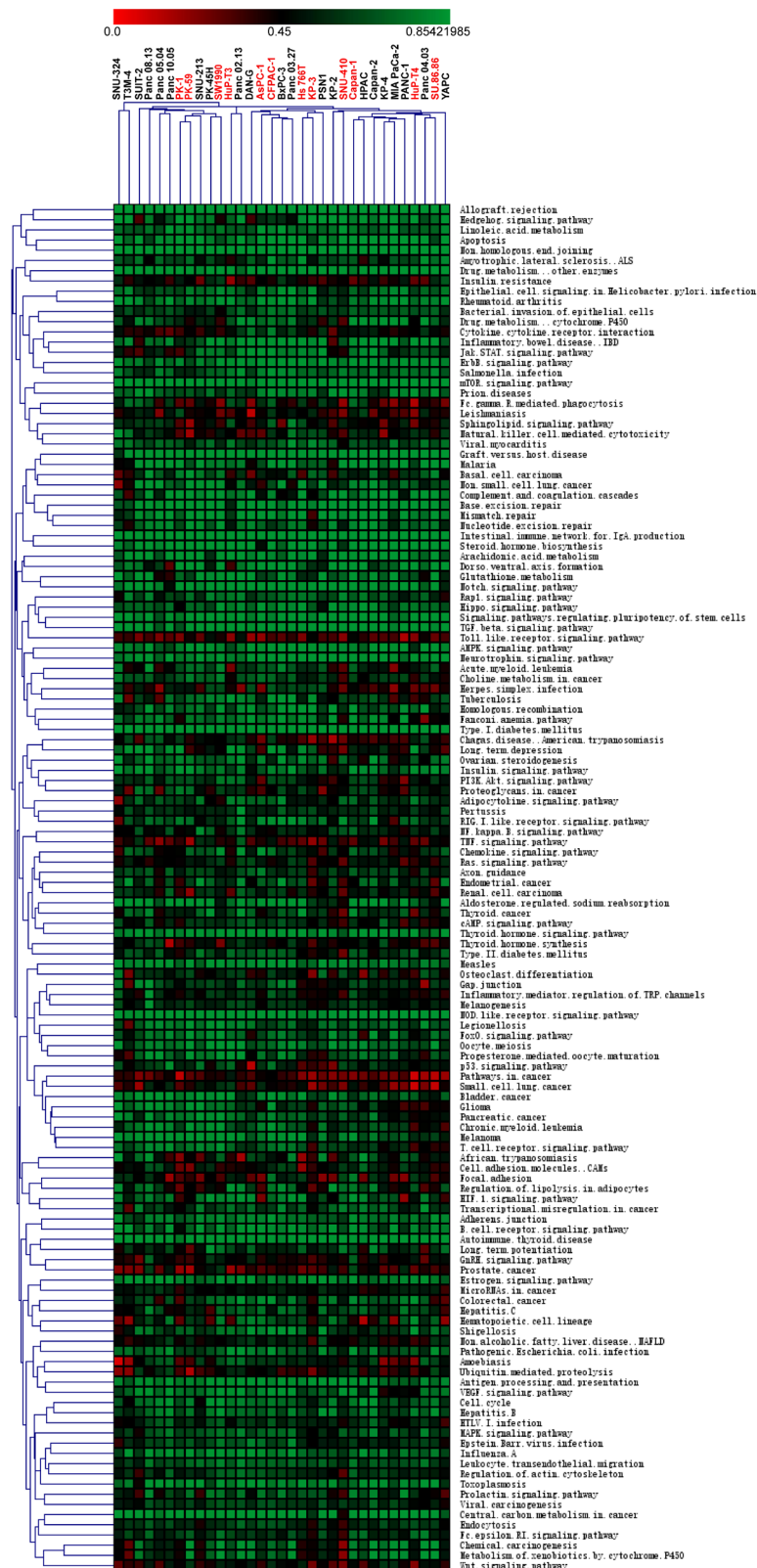


Figure 2 Correlation coefficients of cancer-related pathways in various pancreatic cancer cell lines (red font of cell lines: metastatic lesion, black font of cell lines: primary lesion).

Table 1 Cancer-related pathways highly correlated between pancreatic cell lines and the corresponding primary tumors

PAAD cell lines	Highly correlated pathways (top 3)
Panc 02.13	DNA ligation involved in DNA repair, negative regulation of acute inflammatory response, B cell proliferation
HuP-T3	Atrioventricular valve morphogenesis; positive regulation of cell adhesion mediated by integrin; microglial cell activation
DAN-G	DNA ligation involved in DNA repair; B cell proliferation; liver regeneration
HUP-T4	Positive regulation of tyrosine phosphorylation of STAT1 protein; natural killer cell activation involved in immune response; mammary gland epithelial cell proliferation
PK-59	Cell migration in hindbrain; Blood coagulation intrinsic pathway; DNA dependent DNA replication maintenance of fidelity
AsPC-1	DNA ligation involved in DNA repair; cell migration in hindbrain; positive regulation of tyrosine phosphorylation of STAT1 protein
SNU-213	Positive regulation of tyrosine phosphorylation of STAT1 protein; DNA ligation involved in DNA repair; dendritic cell chemotaxis
BxPC-3	DNA ligation involved in DNA repair; negative regulation of chondrocyte differentiation; positive regulation of cell adhesion mediated by integrin
SNU-410	DNA ligation involved in DNA repair; negative regulation of osteoblast differentiation; atrioventricular valve morphogenesis
SW1990	Positive regulation of tyrosine phosphorylation of STAT1 protein; osteoblast development; atrioventricular valve morphogenesis
HuP-T4	Natural killer cell activation involved in immune response; positive regulation of tyrosine phosphorylation of STAT1 protein; blood coagulation intrinsic pathway
Hs 766T	Blood coagulation intrinsic pathway; negative regulation of acute inflammatory response; negative regulation of osteoblast differentiation
KP-2	Cell migration in hindbrain; positive regulation of tyrosine phosphorylation of STAT1 protein; wound healing spreading of epidermal cells
YAPC	Negative regulation of acute inflammatory response; atrioventricular valve morphogenesis; negative regulation of cell cycle arrest
PK-1	Mammary gland epithelial cell proliferation; negative regulation of chondrocyte differentiation; liver regeneration
T3M-4	Liver regeneration; DNA ligation involved in DNA repair; cellular response to fluid shear stress
KP-3	Cell migration in hindbrain; blood coagulation intrinsic pathway; positive regulation of tyrosine phosphorylation of STAT1 protein
Panc 03.27	Fibrinolysis; cell migration in hindbrain; DNA ligation involved in DNA repair
SUIT-2	DNA ligation involved in DNA repair; positive regulation of tyrosine phosphorylation of STAT1 protein; negative regulation of acute inflammatory response
Panc 05.04	Cell migration in hindbrain; wound healing spreading of epidermal cells; dendritic cell chemotaxis
SNU-324	Dendritic cell chemotaxis; cellular response to fluid shear stress; DNA ligation involved in DNA repair
HPAC	DNA ligation involved in DNA repair; atrioventricular valve morphogenesis; bone mineralization
PSN1	Positive regulation of tyrosine phosphorylation of STAT1 protein; liver regeneration; negative regulation of chondrocyte differentiation
CFPAC-1	Blood coagulation intrinsic pathway; positive regulation of tyrosine phosphorylation of STAT1 protein; DNA ligation involved in DNA repair

Table 1 (continued)

Table 1 (continued)

PAAD cell lines	Highly correlated pathways (top 3)
Panc 10.05	Cell migration in hindbrain; regulation of cytokine secretion involved in immune response; atrioventricular valve morphogenesis
MIA PaCa-2	DNA ligation involved in DNA repair; positive regulation of tyrosine phosphorylation of STAT1 protein; Protein homotrimerization
SU.86.86	Positive regulation of tyrosine phosphorylation of STAT1 protein; DNA ligation involved in DNA repair; Blood coagulation intrinsic pathway
Panc 08.13	Natural killer cell activation involved in immune response; cell migration in hindbrain; positive regulation of tyrosine phosphorylation of STAT1 protein
PK-45H	Protein homotrimerization; positive regulation of tyrosine phosphorylation of STAT1 protein; fibrinolysis
Capan-2	Dendritic cell chemotaxis; cellular response to fluid shear stress; osteoblast development
KP-4	Natural killer cell activation involved in immune response; DNA ligation involved in DNA repair; Positive regulation of tyrosine phosphorylation of STAT1 protein
Capan-1	Cell migration in hindbrain; blood coagulation intrinsic pathway; DNA ligation involved in DNA repair
Panc 04.03	DNA ligation involved in DNA repair; cellular response to fluid shear stress; cell migration in hindbrain
PANC-1	Positive regulation of tyrosine phosphorylation of STAT1 protein; cell migration in hindbrain; blood coagulation intrinsic pathway

PAAD, pancreatic adenocarcinoma.

Table 2 Cancer-related functions highly correlated between PAAD cell lines and the corresponding primary tumors

Cell lines	Highly correlated functions (top 3)
Panc 02.13	DNA ligation involved in DNA repair, negative regulation of acute inflammatory response, B cell proliferation
HuP-T3	Atrioventricular valve morphogenesis; positive regulation of cell adhesion mediated by integrin; microglial cell activation
DAN-G	DNA ligation involved in DNA repair; B cell proliferation; liver regeneration
HUP-T4	Positive regulation of tyrosine phosphorylation of STAT1 protein; natural killer cell activation involved in immune response; mammary gland epithelial cell proliferation
PK-59	Cell migration in hindbrain; blood coagulation intrinsic pathway; DNA dependent DNA replication maintenance of fidelity
AsPC-1	DNA ligation involved in DNA repair; cell migration in hindbrain; positive regulation of tyrosine phosphorylation of STAT1 protein
SNU-213	Positive regulation of tyrosine phosphorylation of STAT1 protein; DNA ligation involved in DNA repair; dendritic cell chemotaxis
BxPC-3	DNA ligation involved in DNA repair; negative regulation of chondrocyte differentiation; positive regulation of cell adhesion mediated by integrin
HPDE	DNA ligation involved in DNA repair; positive regulation of cardiac muscle cell proliferation; positive regulation of tyrosine phosphorylation of STAT1 protein
SNU-410	DNA ligation involved in DNA repair; negative regulation of osteoblast differentiation; atrioventricular valve morphogenesis
SW1990	Positive regulation of tyrosine phosphorylation of STAT1 protein; osteoblast development; atrioventricular valve morphogenesis

Table 2 (continued)

Table 2 (continued)

Cell lines	Highly correlated functions (top 3)
HuP-T4	Natural killer cell activation involved in immune response; positive regulation of tyrosine phosphorylation of STAT1 protein; blood coagulation intrinsic pathway
Hs 766T	Blood coagulation intrinsic pathway; negative regulation of acute inflammatory response; negative regulation of osteoblast differentiation
KP-2	Cell migration in hindbrain; positive regulation of tyrosine phosphorylation of STAT1 protein; wound healing spreading of epidermal cells
YAPC	Negative regulation of acute inflammatory response; atrioventricular valve morphogenesis; negative regulation of cell cycle arrest
PK-1	Mammary gland epithelial cell proliferation; negative regulation of chondrocyte differentiation; liver regeneration
T3M-4	Liver regeneration; DNA ligation involved in DNA repair; cellular response to fluid shear stress
KP-3	Cell migration in hindbrain; blood coagulation intrinsic pathway; positive regulation of tyrosine phosphorylation of STAT1 protein
Panc 03.27	Fibrinolysis; cell migration in hindbrain; DNA ligation involved in DNA repair
SUIT-2	DNA ligation involved in DNA repair; positive regulation of tyrosine phosphorylation of STAT1 protein; negative regulation of acute inflammatory response
Panc 05.04	Cell migration in hindbrain; wound healing spreading of epidermal cells; dendritic cell chemotaxis
SNU-324	Dendritic cell chemotaxis; cellular response to fluid shear stress; DNA ligation involved in DNA repair
HPAC	DNA ligation involved in DNA repair; atrioventricular valve morphogenesis; bone mineralization
PSN1	Positive regulation of tyrosine phosphorylation of STAT1 protein; liver regeneration; negative regulation of chondrocyte differentiation
CFPAC-1	Blood coagulation intrinsic pathway; positive regulation of tyrosine phosphorylation of STAT1 protein; DNA ligation involved in DNA repair
Panc 10.05	Cell migration in hindbrain; regulation of cytokine secretion involved in immune response; atrioventricular valve morphogenesis
MIA PaCa-2	DNA ligation involved in DNA repair; Positive regulation of tyrosine phosphorylation of STAT1 protein; protein homotrimerization
SU.86.86	Positive regulation of tyrosine phosphorylation of STAT1 protein; DNA ligation involved in DNA repair; blood coagulation intrinsic pathway
Panc 08.13	Natural killer cell activation involved in immune response; cell migration in hindbrain; positive regulation of tyrosine phosphorylation of STAT1 protein
PK-45H	Protein homotrimerization; positive regulation of tyrosine phosphorylation of STAT1 protein; fibrinolysis
Capan-2	Dendritic cell chemotaxis; Cellular response to fluid shear stress; osteoblast development
KP-4	Natural killer cell activation involved in immune response; DNA ligation involved in DNA repair; positive regulation of tyrosine phosphorylation of STAT1 protein
Capan-1	Cell migration in hindbrain; blood coagulation intrinsic pathway; DNA ligation involved in DNA repair
Panc 04.03	DNA ligation involved in DNA repair; cellular response to fluid shear stress; cell migration in hindbrain
PANC-1	Positive regulation of tyrosine phosphorylation of STAT1 protein; cell migration in hindbrain; blood coagulation intrinsic pathway

PAAD, pancreatic adenocarcinoma.

primary pancreatic tumors and metastatic disease: primary tumors contained 7 major cell populations while the metastatic lesions contained only 3 major cell populations; Tumor cells from primary lesions showed mesenchymal phenotype while the metastatic ones showed little mesenchymal characteristics (25). Thus in our study, PAAD cell lines are also divided into two groups according to the Cellosaurus database: primary lesion and metastatic lesion. We evaluated the similarities based on total gene profiles, the top 2,000 genes with largest IQRs, and significantly differential genes in expression between human tumor samples and PAAD cell lines. The results indicated poor correlations between PAAD cell lines and primary tumor tissues.

In 134 cancer-related pathways which were identified based on KEGG analysis of gene enrichment in publications from Medline, 50% of cancer-related pathways were not recommended in neither cell lines of primary lesion nor cell lines of metastatic lesion, such as the Toll-like receptor pathway. In the pancreatic cancer pathway, all 33 cell lines were not poorly correlated with the tumor ($r > 0.3$), and they could be chosen for studying the pathway of pancreatic cancer. In addition, among 504 cancer-related functions, up to about 15% of functions were poorly correlated ($r < 0.3$) in all cell lines, including Regulation of circadian rhythm and Insulin receptor signaling pathway, among others. According to statistics, SW1990, Panc 08.13, and Panc 02.13 were the top3 PAAD cell lines that best matched to the overall cancer-related pathways, and Panc 03.27, Capan-1, and Panc 10.05 were the top3 PAAD cell lines that best matched to the overall cancer-related functions.

Correlation between PAAD cell lines and tumor tissue are varies greatly in some pathways, for example, African trypanosomiasis, Cytokine cytokine receptor interaction, Long term depression, Allograft rejection, Non homologous end joining and Type I diabetes mellitus pathways, there were no obvious selectivity tendencies among all PAAD cell lines. In Toll like receptor signaling pathway and pathways in cancer, all PAAD cell lines were poorly correlated with tumor tissue.

The same situation was observed in cancer-related functions between PAAD cell lines and tumor tissue. For example, PAAD cell lines were highly correlated in Positive regulation of tyrosine phosphorylation of stat1 protein, Response to zinc ion, and Response to fluid shear stress, among others, with tumor tissue, and were poorly correlated in Cellular response to insulin stimulus, Positive regulation of gene expression, and Regulation of circadian

rhythm *et al.* with tumor tissue, and varied greatly in Smad protein signal transduction, Negative regulation of erk1 and erk2 cascade, and Positive regulation of DNA replication and so on.

Our research provides a new strategy for selecting suitable cell lines, but it also leaves a question unanswered. Can genetic correlation between cell lines and tumor tissues reflect the “real behavioral similarity” among them? It is yet to be verified that the selected PAAD cell line would reliably mimic the biologic behavior of pancreatic cancer.

Conclusions

The gene expression profiles of PAAD cell lines correlate weakly with those of primary pancreatic tumors. We have provided a strategy for choosing the appropriate PAAD cell line, and compared the genetic similarity between PAAD cell lines and human tumor tissue.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-173/rc>

Peer Review File: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-173/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-23-173/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as

revised in 2013).

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