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Original Research

Relating pancreatic ductal adenocarcinoma tumor samples and cell lines using gene expression data in translational research

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Abstract: Cancer cell lines are useful tools to study cancer biology. Choosing proper cell lines based on experimental design for different experiments is vital. Relating tumors and cell lines, and recognizing their similarities and differences are thus very important for translational research. Abundant online databases with genomic and expression profile are suitable resources for conducting the assessment. Pancreatic ductal adenocarcinoma (PDAC) is a severe cancer with grim prognosis. Current effective treatments of PDAC remain limited. In this study, we compared the gene expression profile of 178 PDAC tumor samples from The Cancer Genome Atlas and 44 pancreatic cancer cell lines from Cancer Cell Line Encyclopedia. We showed that all pancreatic cancer cell lines resemble PDAC tumors but the correlation is different. Our study will be used to guide the selection of PDAC cell lines.

Key words: Pancreatic ductal adenocarcinoma; Cancer cell line; Gene expression correlation; TCGA; CCLE.

Introduction

Cancer cell lines are the most commonly used tool in cancer research. They are derived from cancer patients or modified from an existing cell line (1,2). Compare to animal model, cancer cell lines have irreplaceable advantages such as shorter growth cycle, clearer genetic background and easier to modify. These make cancer cell lines always be the starting choice for molecular mechanism study, drug development and phenotype screening. At present, there are over 1000 cancer cell lines and their gene expression profiles are available at the Cancer Cell Line Encyclopedia (CCLE) (3). This database provides an intuitive view of cell line comparison and guides researchers to find the suitable ones for specific experiments. Recently another very important and highly used cancer research database is The Cancer Genome Atlas (TCGA) (4). By data mining and bioinformatic analysis from TCGA, researchers can filter out key genes, miRNAs or lncRNAs, which are usually vital in cancer development. To further validate the function of these key molecules in cancer cell line is a popular work flow for researchers nowadays (5). However, an easily neglected question is that not all cancer cell lines can resemble the tumor well. Domcke *et al.* did the comparison between TCGA and CCLE about the genomic profile to evaluate ovarian cell lines as tumor models. They found that the some rarely used cell lines were actually more suitable for ovarian cancer study (6). We are curious whether this phenomenon exists for other cancer types so we choose pancreatic ductal adenocarcinoma (PDAC) for study. To our knowledge, this is the first report to compare tumor and cell line using gene expression data specially for PDAC.

Materials and Methods

Datasets

The pre-processed level 3 RNA-Seq gene expression data of PDAC were downloaded from TCGA (http://cancergenome.nih.gov/). There were 178 PDAC tumor samples with 20502 genes in total.

The cancer cell line gene expression file (CCLE_Expression_Entrez_2012-09-29.gct) and the annotation file (CCLE_sample_info_file_2012-10-18.txt) were downloaded from the CCLE (http://www.broadinstitute.org/ccle). There were 1037 cell lines with gene expression data but we only took the 44 pancreatic cancer cell lines for further analysis. The cell lines background information including sex, race, age and other characteristics from ATCC (http://www.atcc.org), KCLB (http://cellbank.snu.ac.kr) and publications (11-13). There were 18900 genes in CCLE dataset and 16765 of them were common as TCGA dataset. The following analysis were all based on these 16765 genes.

Correlation between tumor sample and cell lines

MAD (Median absolute deviation) was used to find the top 5000 genes ranked by interquartile range across all 44 pancreatic cancer cell lines. To overcome the problem that the two datasets used in this study were from two different platforms, which means the data was obtained by different technologies and normalized in different ways (7) and both of them were not normally distributed, rank-based spearman correlation was used to calculate the similarity between cancer cell lines and tumors.

Differentially expressed genes between patient similar and frequently used cell lines

Differential gene expression analysis in patient similar cell lines compared to frequently used cell lines was performed for 18900 genes by non-parameter Wilcoxon test (14). P value less than 0.01 was used as cut off.

PubMed citation analysis

PubMed search builder (http://www.pubmed.org) (15) was used to analyze the frequency of cell line usage on 23 Feb 2018. Several punctuation alternatives for the cell line names were used. By reading the abstracts mentioning one of the 44 CCLE pancreatic cancer cell lines, the number of researches that utilize a certain cell line was recorded. This method can lead to false negative results because for some publications, the cell line name was not mentioned in the abstract.

Software tools

R program language was used for most of the analysis. Pheatmap and ggplot2 were used for visualization. GO and KEGG pathway enrichment analysis was conducted in DAVID.

Results

A total number of 178 TCGA PDAC tumor profiled by RNASeq and 1019 CCLE cancer cell lines profiled by microarray were compared using top 5000 varying genes (details see methods). There are 20502 and 18900 genes in PDAC tumor and cell line respectively. The number of common genes is 16764. Out of the 1019 cell lines, 44 are derived from pancreas tissue and all of them are related to PDAC.

The heatmap for correlation between tumor and cell line is drown (Figure 1A). Distinctive difference of correlation can be seen from the hierarchical clustering, which suggests that only some of the pancreatic cancer cell lines have similar gene profile compared to PDAC patients. These cell lines can be roughly divided into 3 groups based on the heatmap. High corelated group (7) includes ASPC1, SUN8686, PANC0213, et al. Medium corelated group (8) includes SUN324, KP2, PK1, et al. Low corelated group (9) includes QGP1, KP4, PATU8988T, et al. Full grouping information is listed in Table 1. We also collected the cell line background information, including sex, ethnicity/race, age and KRAS mutation (details see method). Although for some cell lines, certain information is not available (NA), the distribution of these characteristics is even among different correlation group. It can be inferred that the correlation between patient tumor and cell line is not determined by these aspects. The variation of correlation is from 0.47 to 0.17. Dot plot for correlation grouped by cell line is shown in Figure 1B. The top10 most correlated

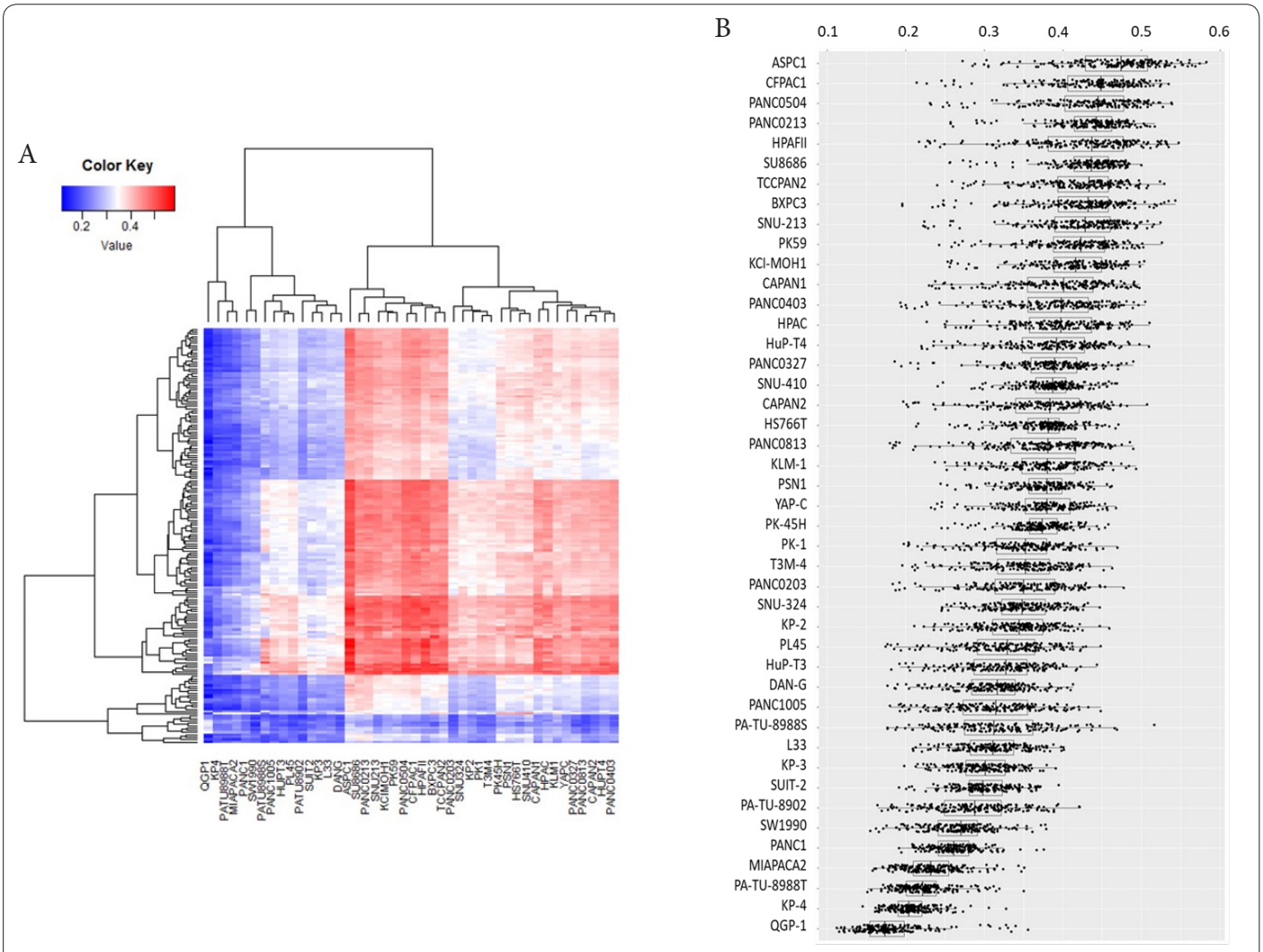

Figure 1. Spearman correlation between PDAC tumors and pancreatic cancer cell lines. In the heatmap, each row represents one tumor sample; each column represents one cell line. The correlation level is represented by color: higher correlation shown in red and low in blue. In the boxplot, each dot represents the correlation between one tumor sample and one cell line. The line shows the median.

Table 1. Pancreatic cancer cell lines background and their correlation with tumors.

	Cell line	Correlation	Sex	Ethnicity/Race	Age	KRAS mutation	Publications
High correlation	ASPC1	0.474	F	Caucasian	62	12 GGT->GAT	98
	CFPAC1	0.448	M	Caucasian	26	12 GGT->GTT	22
	PANC0504	0.445	F	White	77	12 GGT->GTT	2
	PANC0213	0.442	F	White	64	NA	0
	HPAFII	0.437	M	Caucasian	44	12 GGT->GAT	83
	SU8686	0.436	F	Caucasian	57	12 GGT->GAT	5
	TCCPAN2	0.433	F	Japanese	68	NA	3
	BXPC3	0.432	F	NA	61	Wild type	373
	SNU-213	0.428	M	Mongoloid	65	12 GGT->GTT	6
	PK59	0.422	F	NA	NA	12 GGT->GAT	3
	KCI-MOH1	0.416	F	NA	64	NA	2
Medium correlation	CAPAN1	0.400	M	Caucasian	40	12 GGT->GTT	46
	PANC0403	0.398	M	White	70	12 GGT->GAT	3
	HPAC	0.397	F	Caucasian	64	12 GGT->GAT	231
	HuP-T4	0.391	M	Japanese	60	12 GGT->GTT	7
	PANC0327	0.389	F	White	65	12 GGT->GTT	3
	SNU-410	0.387	M	Mongoloid	53	12 GGT->GTT	3
	CAPAN2	0.383	M	Caucasian	56	12 GGT->GTT	35
	HS766T	0.381	M	Caucasian	46	Wild type	60
	PANC0813	0.381	M	White	85	12 GGT->GAT	0
	KLM-1	0.380	M	NA	NA	NA	18
	PSN1	0.379	NA	NA	NA	12 GGT->CGT	28
	YAP-C	0.379	M	NA	NA	12 GGT->GTT	10
	PK-45H	0.373	NA	NA	NA	Wild type	10
	PK-1	0.352	M	NA	NA	12 GGT->GAT	42
	T3M-4	0.352	M	NA	NA	Wild type	8
	PANC0203	0.349	F	White	70	12 GGT->GAT	0
	SNU-324	0.348	M	Mongoloid	50	NA	1
	KP-2	0.344	F	Japanese	65	12 GGT->CGT	8
Low correlation	PL45	0.329	M	NA	NA	12 GGT->GAT	32
	HuP-T3	0.327	M	Japanese	66	12 GGT->CGT	5
	DAN-G	0.316	F	NA	68	12 GGT->GTT	21
	PANC1005	0.314	M	Caucasian	NA	12 GGT->GAT	1
	PA-TU-8988S	0.312	F	NA	64	12 GGT->GTT	2
	L33	0.310	F	NA	77	NA	0
	KP-3	0.301	M	Japanese	75	NA	8
	SUIT-2	0.298	M	NA	73	12 GGT->GAT	124
	PA-TU-8902	0.288	F	NA	44	12 GGT->GTT	5
	SW1990	0.270	M	Caucasian	56	12 GGT->GAT	314
	PANC1	0.261	M	Caucasian	56	12 GGT->GAT	318
	MIAPACA2	0.232	M	Caucasian	65	12 GGT->TGT	178
	PA-TU-8988T	0.221	F	NA	64	12 GGT->GTT	2
	KP-4	0.204	M	Japanese	50	NA	6
	QGP-1	0.173	M	Japanese	61	NA	47

pancreatic cell lines are ASPC1, CFPAC1, PANC0504, PANC0213, HPAFII, SU8686, TCCPAN2, BXPC3, SNU-213 and PK59, which all belong to the high correlation group. The top10 least correlated pancreatic cell lines are L33, KP-3, SUIT-2, PA-TU-8902, SW1990, PANC1, MIAPACA2, PA-TU-8988T, KP-4, QGP-1, which all belong to low correlation group.

In most publications, the selection of cell line was shown in abstract. We use cell line names to search in PubMed database and manually read the abstracts to find the frequency of the cell line usage. The top10 most frequently used pancreatic cancer cell lines were BXPC3, PANC1, SW1990, HPAC, MIAPACA2, SUIT-2, ASPC1, HPAFII, HS766T and QGP-1. The top10 least used ones were L33, PANC0203, PANC0813, TCCPAN2, PANC0213, PANC0504, PANC1005, SNU-324, PA-TU-8988T, PA-TU-8988S. Histogram of the ranking was shown in Figure 2. The exact publication number for each cell line is listed in Table1.

After we rank all the pancreatic cancer cell lines in two different ways, namely similarity to patients and frequency in usage, we are curious to see how many of the cell lines in these two groups can overlap. Result was shown in Figure 3. Interestingly, only three cell lines were common (ASPC1, HPAFII and BXPC3). For the rest most frequently used cell lines, two (HS766T and HPAC) have medium similarity and 5 (SUIT-2, QGP-1, MIAPACA2, SW1990 and PANC1) have low similarity to patients' tumor. For the rest most similar cell lines, the usage frequency ranks from 16 to 40 in all the 44 cell lines, which are also relatively medium and low. Based on the result we can conclude that at present, the commonly used pancreatic cell lines have a big difference compared to PDAC patients. Only a few of them have similar gene expression profile.

The big difference between commonly used cell lines and similar to patient cell lines raises the question whether the gene expression of the two groups of cells are also different. We use Wilcoxon test to find the differentially expressed genes and use $p<0.01$ as cut off. In total 520 genes were differentially expressed. Compared to patient similar cell lines, 270 genes were up regulated and 250 genes were down regulated in commonly used cell lines (Figure 4). This clearly showed that these two group of cells were different and the selection for pancreatic cancer cell lines for research didn't represent PADC patients well enough.

We further performed GO and KEGG pathway enrichment analysis of differentially expressed genes between the two groups using DAVID (10) For those

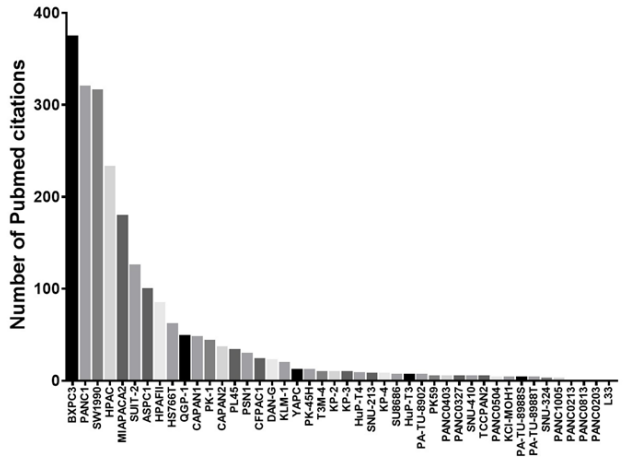

Figure 2. Pancreatic cancer cell lines usage frequency. The usage frequency for each pancreatic cancer cell line is searched by PubMed search builder.

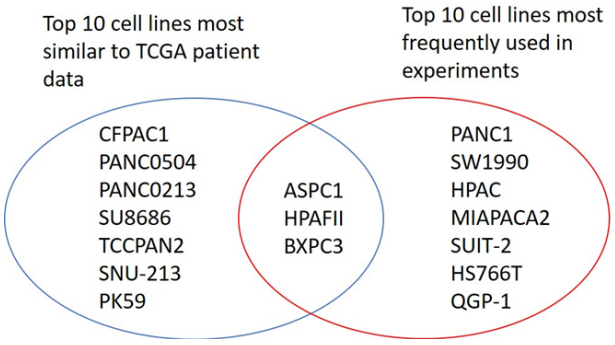

Figure 3. The common and different cell lines between top10 most similar to TCGA patient data and top10 most frequently used in experiments. Blue circle represents top10 most similar to TCGA patient data cell lines; Red circle represents top10 most frequently used cell lines; The overlay part is common in both groups.

genes over expressed in only frequently used cell lines, the top three enriched biology processes are cell division, mitotic nuclear division and mitotic sister chromatid segregation. The enriched pathways are cell cycle and splicesome (Table 2). For those genes over expressed in only patient similar cell lines, the top three enriched biology processes are immune response, proteolysis and signal transduction. The top three enriched pathways are cell adhesion molecules (CAMs), cytokine receptor interaction and Complement and coagulation cascades

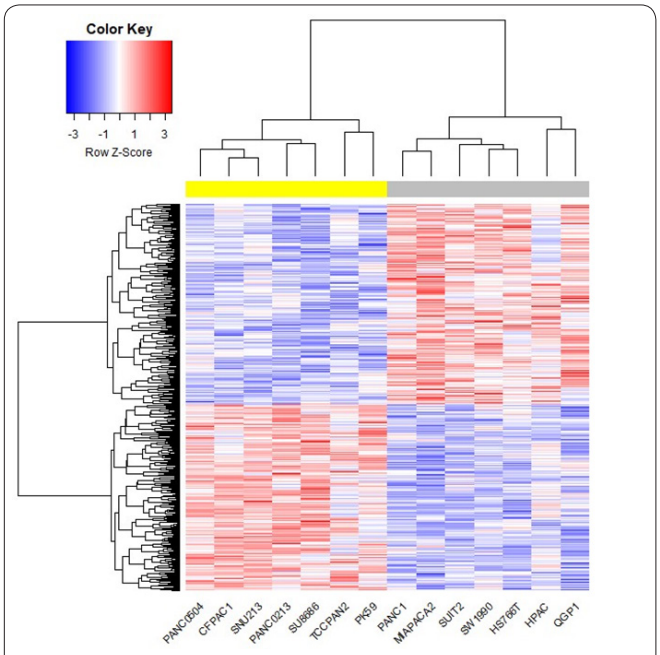

Figure 4. Differentially expressed genes between similar to TCGA patient data specific and most frequently used specific cell lines. In the heatmap, each row represents one gene; each column represents one cell line. The expression level is represented by color: upregulation shown in red and downregulation shown in blue.

(Table3). We can see that these are all important biological processes and pathways that will affect cancer progress. Attentions should be paid to these differences during experiment design.

Discussion

PDAC has a dismal prognosis, partially because of the lack of molecular information related to disease development. The established pancreatic cancer cell lines are powerful tools to investigate these molecular events (16). Although the number of existing pancreatic cancer cell lines is large, only a few cell lines are frequently used for in vitro and in vivo experiments. This may due to the limited accessibility to a large range of cells and the inadequate information about each cell line. However, the bias in choosing cell lines may not be suitable for the designed experiments. Different cell lines have different characteristics, like mutations, metastasis status, race and gene profile. These will all account for the

Table 2. Enriched GO terms and KEGG pathways for over expressed genes in only frequently used cell lines.

Category	Term	PValue	FDR
Biological process	GO:0051301~cell division	2.62E-09	4.11E-06
	GO:0007067~mitotic nuclear division	1.36E-05	2.14E-02
	GO:0000070~mitotic sister chromatid segregation	2.36E-04	3.70E-01
	GO:0006310~DNA recombination	5.74E-04	8.99E-01
	GO:0007062~sister chromatid cohesion	1.77E-03	2.75E+00
	GO:0006281~DNA repair	2.69E-03	4.14E+00
	GO:2001022~positive regulation of response to DNA damage stimulus	6.44E-03	9.65E+00
	GO:0060271~cilium morphogenesis	6.98E-03	1.04E+01
	GO:0007080~mitotic metaphase plate congression	1.07E-02	1.55E+01
	GO:0042795~snRNA transcription from RNA polymerase II promoter	1.11E-02	1.61E+01
KEGG pathway	hsa04110:Cell cycle	1.03E-03	1.20E+00
	hsa03040:Spliceosome	3.60E-02	3.50E+01

Table 3. Enriched GO terms and KEGG pathways for over expressed genes in only patient similar cell lines.

Category	Term	PValue	FDR
Biological process	GO:0006955~immune response	6.43E-06	1.06E-02
	GO:0006508~proteolysis	2.01E-04	3.32E-01
	GO:0007165~signal transduction	3.02E-04	4.99E-01
	GO:0006954~inflammatory response	3.20E-04	5.29E-01
	GO:0022617~extracellular matrix disassembly	3.86E-04	6.37E-01
	GO:0032496~response to lipopolysaccharide	1.11E-03	1.83E+00
	GO:0043011~myeloid dendritic cell differentiation	1.63E-03	2.67E+00
	GO:0016338~calcium-independent cell-cell adhesion via plasma membrane cell-adhesion molecules	2.20E-03	3.59E+00
	GO:0042127~regulation of cell proliferation	2.38E-03	3.87E+00
	GO:0043312~neutrophil degranulation	3.17E-03	5.12E+00
KEGG pathway	hsa04514:Cell adhesion molecules (CAMs)	1.25E-04	1.53E-01
	hsa04060:Cytokine-cytokine receptor interaction	4.47E-04	5.46E-01
	hsa04610:Complement and coagulation cascades	9.96E-04	1.21E+00
	hsa04360:Axon guidance	1.97E-02	2.16E+01
	hsa05202:Transcriptional misregulation in cancer	2.26E-02	2.44E+01
	hsa04530:Tight junction	2.73E-02	2.88E+01
	hsa04668:TNF signaling pathway	3.24E-02	3.33E+01

observed phenotypes.

The Cancer Genome Atlas (TCGA) is a current widely used database which contains genomic and gene expression profiles of over 10000 human tumor samples, covering 32 tumor types (9). Utilizing these data can help researchers find new vital regulators or new function of existing regulators to study the mechanism of carcinogenesis and progression. Cancer Cell Line Encyclopedia (CCLE) is launched by Novartis and the Broad Institute (17), contains genomic profiling and chemical screening data for more than 1000 cancer cell lines from 21 cancer types. These cell lines include most of the available ones in public resources. Find a potential target in TCGA and do functional validation in cell lines is a classic work flow in cancer research nowadays (8, 18-19). However, most of the time there is no clear standard for cell line selection. We believe use cell lines that are more similar to patients is a more scientific way. The public genomic and transcriptomic profiles of cancer cell lines and tumors can help us do assessment of similarity between them (20). Domcke et al related tumor samples and cancer cell lines in ovarian cancers using gene expression(6). Although gene expression is not the only factor, it can help to find out cell lines that share similar profiles.

In this study, we compared the gene profile similarity between PDAC patients and pancreatic cancer cell lines. First, we found that the correlation of tumors and cell lines varied a lot among different cell lines (from 0.474 to 0.173). Three distinct groups can be divided by the hierarchical clustering, representing high, medium and low similarity. Second, some of the widely used pancreatic cancer cell lines also have a high similarity to patient (i.e., BXPC3, HPAFII and ASPC1) but some are not (i.e., SW1990, PANC1 and MIAPACA2). This is quite surprising because the commonly used cell lines are actually not representative to patients. Then we are curious about how many of the most similar to patients and most frequently used cell lines can overlap. We choose top10 cell lines from each group to compare and the result is only 3 cell lines are common (i.e., ASPC1, HPAFII, BXPC3). Again this proves that the current frequently used pancreatic cancer cell lines are not representative to PDAC patients. ASPC1 derived from a 62 years old Caucasian with KRAS mutation (12 GGT->GAT). HPAFII derived from a 44 years old Caucasian with KRAS mutation (12 GGT->GAT). BXPC3 derived from a 61 years old female with wild type KRAS, whose race is not available. KRAS is mutated in 95% of PDACs and is a well-validated driver of PDAC growth and maintenance (21). Some PADC researches will choose cell line based on KRAS mutation status (22). As shown in Table 1, HS766T and T3M4 are also KRAS wild type cell line but the correlation to patients is low. In the rest cells, 31 have KRAS mutation and cells like CFPAC1, PANC0405 and SU8686 are all highly correlated with patients but not commonly used. In the future, if the experiment is designed based on KRAS mutation status, we suggest to use these high correlated cell lines.

Multicellular organism are genetically homogeneous but structurally and functionally heterogeneous owing to the differential expression of genes of individual cells (23). Since our result showed that only 3 of the most similar and most frequently used cells were same, we want to see whether the gene expression of those didn't overlap was different. We found 520 genes were differentially expressed between the two groups. Compared to most similar cell lines, 270 genes were upregulated and 250 genes were downregulated in most frequently used cell lines. This proves the two groups are different at gene level. Then we use these differentially expressed genes to do GO and KEGG pathways enrichment to see which biological processes and pathways are affected. Cell division, mitotic nuclear division and immune response are three significantly enriched (FDR<0.05) biological processes. Change of cell division cycle is one of the hallmarks of human malignant tumors (24). Mitosis can ensure the fidelity of cell division and is a highly regulated process. Disruption of mitotic regulators can result in aneuploidy and polyploidy, which is commonly observed in cancer cells (25). This may suggest that the

current widely used pancreatic cancer cell lines have different division properties from those can represent patients. Thus more correlated cell lines are the highly recommended for division related experiments in the future. The local and whole immune state is constantly changing during the PDAC development, reflected in immune escape. Immune suppressive cells will increase in tumor microenvironment and natural killer cells will be inhibited (26). The difference for immune response in the two groups should also be drawn attention for the experimental cell line selection.

For pathway enrichment, although FDR is above 0.05, cell cycle ($p<0.01$) pathway is coincident with biological process cell division. Cell adhesion molecules (CAMs) ($p<0.01$), Cytokine-cytokine receptor interaction ($p<0.01$) and Complement and coagulation cascades ($p<0.01$) are another three significant pathways with less strict criterion (p value). Although it's less strict, cell lines used for these experiments should also be chosen carefully, better to follow the correlation rank between tumor and cancer cell line.

In summary, by using public available gene expression data, we relate PDAC patients with pancreatic cancer cell lines. We demonstrate a big portion of the currently used pancreatic cancer cell lines are actually weak to represent patient, which may lead to bias in experiment results. We compared the differentially expressed genes between the two groups that didn't overlap with each other and found the enriched biological process and pathways. Attentions should be paid for these differences when choosing cell lines for PDAC study.

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