Identification of a robust functional subpathway signature for pancreatic ductal adenocarcinoma by comprehensive and integrated analyses

CURRENT STATUS: ACCEPTED

Cell Communication & Signaling BMC

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DOI:

10.21203/rs.2.17455/v1

SUBJECT AREAS

Cell Communication and Signaling *Cancer Biology*

KEYWORDS

Pancreatic ductal adenocarcinoma, prognosis signature, subpathway activity, comprehensive analysis, meta-analysis

Abstract

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy and its mortality continues to rise globally. Because of its high heterogeneity and complex molecular landscapes, published gene signatures have shown low specificity and robustness. Functional signatures containing a group of genes involved in similar biological functions display a more robust performance.

Methods: The present study was designed to excavate potential functional signatures for PDAC by analyzing maximal number of datasets extracted from available databases with a recently developed method of FAIME (Functional Analysis of Individual Microarray Expression) in a comprehensive and integrated way.

Results: By using appropriate search strategies, we extracted 11 PDAC datasets from GEO, ICGC and TCGA databases. By systemically analyzing these datasets, we identified a robust functional signature of subpathway (path:00982_1), which belongs to the drug metabolism-cytochrome P450 pathway. The functional signature has displayed a more powerful and robust capacity in predicting prognosis, drug response and chemotherapeutic efficacy for PDAC, particularly for the classical subtype, in comparison with published gene signatures and clinically used TNM staging system. This signature was further verified by meta-analyses and validated in cell line databases and available clinical datasets.

Conclusion: This is the first functional signature for PDAC identified from the largest number of datasets by using comprehensive and integrated analyses. The novel signature warrants a further investigation, since it is like to improve the current systems for predicting the prognosis and monitoring drug response, and to serve a potential linkage to therapeutic options for combating PDAC.

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed. However, the manuscript can be downloaded and accessed as a PDF.

Figures

Figure 1

Outline of comprehensive and integrated analyses. An integrated prognostic score (ipScore) for each signature at gene, subpathway and pathway levels was calculated as described in Materials and Methods. An analysis at subpathway level by using a combination of 5 training sets is shown as an example.

Figure 2

Excavation of potential signatures associated with PDAC. (a) The integrated prognostic score for each signature is calculated and assessed as described in Materials and Methods.

P-value is calculated and -log₁₀ of P-value used as Y-axis. (b-d) Top-counted signatures identified at levels of gene (b), subpathway (c) and pathway (d). Percentages of cancer- and PDAC-related genes are calculated and P-values, determined by a hypergeometric test in (c) and (d). Significant results are marked by red color.

Figure 3

Analysis of the overlapping relationship and predictive ability of signatures. (a) Overlapping genes of pathways and subpathways. “n” indicates the number of genes. (b) The predictive ability of signatures in the 11 datasets. Hazard ratio and P-value are calculated by using a univariate Cox analysis.

Figure 4

Meta-analysis of the predictive capacity of path:00982_1 signature. (a) Forest plots of pooled hazard ratio for analyzing the impact of path:00982_1 signature on the survival in each dataset. (b) Funnel plots of meta-analysis. (c) Sensitivity analysis of meta-analysis. (d)

Forest plots for analyzing the impact of path:00982_1 signature in two subgroups, microarray (the upper panel) and RNA sequencing (the middle panel). I-square and P-value in each subgroup (subtotal) and for all datasets (overall, the lower panel) are calculated. ES, estimates; CI, confidence interval.

Figure 5

The prognostic capacity of path:00982_1 signature in different PDAC subtypes. PDAC patients in each dataset are stratified into three subtypes: Classical, Quasi-mesenchymal (QM-PDA) and Exocrine-like, with the classification (Collisson, et al., 2011). Hazard ratio and P-value for each subtype are calculated. Data from 5 training datasets and 4 testing datasets are shown in the upper and lower panels, respectively. A number in red color indicates a significance.

Figure 6

Correlation of path:00982_1 signature and chemotherapeutic effects. (a) Correlation of path:00982_1 activity and the IC50 of each chemotherapeutic drug against PDAC cell lines derived from CCLE and GDSC databases. R value is calculated by using a Spearman method.

(b, c) Correlation of path:00982_1 activity and chemotherapeutic efficacy in the ICGC.CA.Seq (b) and TCGA (c) databases. Tumor responses are classified into complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). P-values are calculated by using a Wilcoxon rank sum test. “n” in brackets refers to the number of patients. “Classical” indicates “classical subtype” according to the classification (Collisson, et al., 2011), and “Second chemotherapy” indicates that patients received a

second chemotherapy regimen.

Supplementary Files

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