

# Comparative genomic analysis of head and body/tail of pancreatic ductal adenocarcinoma at early and late stages

**Xueyou Zhang**

Department of Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine

**Shi Feng**

Department of Pathology, the First Affiliated Hospital, Zhejiang University School of Medicine

**Qian Wang**

OrigiMed, Inc. China

**Haitao Huang**

Department of Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine

**Qinfen Xie**

Department of Surgery, Shulan(Hangzhou) Hospital, China

**Wu Zhang**

Department of Surgery, Shulan(Hangzhou) Hospital, China

**Aodi Wang**

OrigiMed, Inc. China

**Shuirong Zhang**

OrigiMed, Inc. China

**Lingjian Wang**

OrigiMed, Inc. China

**Ming Yao**

OrigiMed, Inc. China

**Qi Ling** (✉ [lingqi@zju.edu.cn](mailto:lingqi@zju.edu.cn))

Zhejiang University School of Medicine First Affiliated Hospital <https://orcid.org/0000-0002-7377-2381>

---

## Primary research

**Keywords:** pancreatic ductal adenocarcinoma, tumor location, head, body/tail, genomic profiling, druggable

**Posted Date:** June 29th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-36713/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

**Version of Record:** A version of this preprint was published at Journal of Cellular and Molecular Medicine on January 16th, 2021. See the published version at <https://doi.org/10.1111/jcmm.16281>.

# Abstract

## Background

Pancreatic ductal adenocarcinoma (PDAC), one of the most lethal human cancers, can be divided into head and body/tail cancers according to the anatomy. We previously reported a prognostic relevance of tumor location in resectable PDAC. This study is aimed to further explore the mechanism underlying the molecular diversity between the head and body/tail of PDACs.

## Methods

We detected tumor genomes in 154 resectable (surgery) and non-resectable (biopsy) PDACs using a next-generation sequencing panel. Wilcoxon rank test or Fisher exact test was used for evaluating associations between clinical characteristics, mutation frequency, and survival probability between the two cohorts.

## Results

Compared with pancreatic head cancers, pancreatic body/tail cancers showed significantly more enriched genomic alterations in KRAS (97.1% vs. 82.4%,  $p = 0.004$ ) and SMAD4 (42.0% vs. 21.2%,  $p = 0.008$ ). At early stages (I-II), the SMAD4 mutation rate was significantly higher in pancreatic body/tail cancers than pancreatic head cancers (56.0% vs. 26.5%,  $p = 0.021$ ). At late stages (III-IV), pancreatic body/tail cancers presented significantly higher KRAS mutation rate (100.0% vs. 75.8%,  $p = 0.001$ ), higher frequency of MAPK pathway mutation (100% vs. 87.8%,  $p = 0.040$ ) and lower rates of druggable genomic alterations (30.8% vs. 57.6%,  $p = 0.030$ ) than pancreatic head cancers.

## Conclusions

The molecular diversity exists between pancreatic head and body/tail cancers in both tumor initiation and progression. Pancreatic body/tail cancer seems to be more malignant than pancreatic head cancer at late stages.

## Background

Pancreatic ductal adenocarcinoma (PDAC), one of the most lethal human cancers, can be divided into head and body/tail cancers according to the anatomy. We previously made a comprehensive review on the diversity between pancreatic head and body/tail cancers in tissue ontogeny (e.g., cell composition, blood supply, lymphatic and venous backflow), clinical parameters (e.g., presentation, treatment, and prognosis), and in vitro genetic and tumor biology[1]. We assumed that pancreatic body/tail cancer might be a less malignant phenotype compared with pancreatic head cancer. The conclusion was further

supported by a recent large cohort database analysis which indicated that patients with pancreatic body/tail cancers had a better prognosis compared to those with head cancers among resectable PDACs[2].

Because of the genomic heterogeneity of PDACs, identification of the genetic and epigenetic profile of pancreatic head and body/tail cancers could be of great help to better understand the prognostic relevance of primary tumor location. We previously demonstrated that pancreatic body/tail cancer had less invasiveness and metastasis potential than pancreatic head cancer possibly via miR-501-3p/E-cadherin signaling by using strictly matched resectable pancreatic head and body/tail cancers in both, in vitro and in vivo models[3]. In contrast, Birnbaum et al [4] and Dreyer et al [5] identified genomic and transcriptional diversities between the two subtypes of resectable PDACs and drew an opposite conclusion that pancreatic body/tail cancer had aggressive tumor biology and worse clinical outcomes. The shortcoming of these previous studies was that almost all of the tissue samples were obtained from an early stage (I-II) resectable PDACs. To further clarify different genomic signatures between pancreatic head and body/tail cancers, we included PDAC samples from both early-stage and late-stage and analyzed in-depth molecular characterization in an independent Chinese PDAC cohort by targeted next-generation sequencing (NGS). Our research might provide another picture of the molecular aspect for a better understanding of PDACs, and the potential strategies for targeted therapy for patients with PDACs.

## Materials And Methods

### Patients

Tumor and matched peripheral blood samples from 154 patients with treatment-naive PDACs, including 85 pancreatic head cancers and 69 pancreatic body/tail cancers, were involved in the research. Surgery and biopsy tumor samples were available in early and advanced-stage patients, respectively. A total of 103 and 51 patients were collected from the First Affiliated Hospital of Zhejiang University School of Medicine and Shulan (Hangzhou) Hospital, respectively. The study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine and the Ethics Committee of Shulan Hospital, and following the declaration of Helsinki. All patients had signed the informed consent.

### Sequencing experiment

A total of 154 specimens and matched normal blood were detected and analyzed in a College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) certified laboratory at OrigiMedforCSYS assay[6] with a mean coverage of 900 × for tumor samples (minimum 700×) and 300 × for matched normal blood samples. We analyzed multiple genomic variant types, including single nucleotide variants (SNVs), copy number variations (CNVs), short and long insertions/deletions (indels), and gene rearrangements by bioinformatics workflows described previously[6].

# Statistics analysis

Wilcoxon rank test or Fisher exact test was used for evaluating associations between clinical characteristics, mutation frequency and survival probability between the two cohorts.  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using R 3.3.1.

## Results

### Patient characteristics and overall survival

The patient clinicopathological data are summarized in Table 1. At the initial diagnosis, compared with pancreatic head cancers, pancreatic body/tail cancers showed more advanced stage (III-IV) and distant metastasis, but less local invasion. There is no significant difference in overall patient survival between the two subgroups (Fig. 1a). The median survival time was 23 and 28 months for patients with pancreatic head cancers and pancreatic body/tail cancers respectively with no statistic difference. Also, there was no significant difference in survival for tumors at early stages (I-II) ( $p = 0.180$ , Fig. 1b) and late stages (III-IV) ( $p = 0.240$ , Fig. 1c).

Table 1  
Overview of patients' clinicopathological characteristics

Characteristic	Head of PDAC ( <i>n</i> = 85)	Body/Tail of PDAC ( <i>n</i> = 69)	<i>p</i>
Age (years)	61 (38–86)	62 (42–78)	0.540
Male, <i>n</i> (%)	55 (64.7)	45 (65.2)	1.000
Tumor stage, <i>n</i> (%)			0.040
I	21 (24.7)	13 (17.4)	
II	28 (32.9)	13 (17.4)	
III	10 (11.8)	6 (8.7)	
IV	23 (27.1)	33 (47.8)	
Undefined	3 (3.5)	4 (5.8)	
Tumor grade, <i>n</i> (%)			0.845
High	1 (1.2)	1 (1.4)	
Moderate	15 (17.6)	12 (17.4)	
Low	32 (37.6)	20 (30.0)	
Undefined	37 (43.5)	36 (52.2)	
Metastasis, <i>n</i> (%)			
Lymph node	25 (54.3)	16 (53.3)	1.000
Liver	12 (21.4)	17 (39.5)	0.074
Other	3 (5.5)	8 (19.5)	0.050
Local invasion, <i>n</i> (%)	52 (96.3)	35 (83.3)	0.039

## The landscape of genomic alterations

There were 216 genes found to be mutated in PDAC samples, with a mutation rate ranging from 0.6–89.0%. Thirteen genes showed mutation frequencies over 5%, and the TOP 5 most frequently mutated gene were *KRAS* (89.0%), *TP53* (81.8%), *SMAD4* (30.5%), *CDKN2A* (29.9%) and *ARID1A* (16.2%).

The comparison of gene alteration frequencies between pancreatic head and body/tail cancers is shown in Fig. 2a. Compared with pancreatic head cancers, pancreatic body/tail cancers showed significant higher clinically relevant mutation frequency in *KRAS* (97.1% vs. 82.4%,  $p = 0.004$ ) and *SMAD4* (42.0% vs. 21.3%,  $p = 0.008$ ) (Fig. 2b). The mutation frequencies of these two genes were further analyzed according

to tumor stage (Fig. 2c). The statistical significance in *KRAS* and *SMAD4* mutation rates was achieved only at late stages and early stages, respectively. Interestingly, all *MAP2K4* mutations ( $n = 6$ ) occurred in advanced PDACs.

The comparison of hot spot mutation sites is shown in Additional file 1:Figure S1. Codon 12 and 13 were the major hotspots of *KRAS* in solid tumors. In this study, G12V/D/R contributed 87.7% of *KRAS* mutations. However, there were no significant difference in the detail composition of G12V/D/R between the pancreatic head and body/tail cancers.

## Pathway analysis

Seven primarily signaling pathways influencing tumor initiation and progression were involved in the pathway comparison analysis, including MAPK signaling, Wnt signaling, cell cycle signaling, Homologous Recombination (HR) pathway, PI3K-AKT-mTOR signaling, ERBB family pathway, and Notch signaling. Among these pathways, the mutation frequency of Wnt signaling was significantly different higher in pancreatic body/tail cancers than pancreatic head cancers (56.5% vs. 36.5%,  $P = 0.020$ ) (Fig. 3a). The mutation frequency of the Wnt pathway did not show the distinctive difference both in early stage (42.9% vs. 65.4%,  $p = 0.090$ ) and late stage (30.3% vs. 48.7%,  $p = 0.150$ ) pancreatic head and body/tail cancers. MAPK pathway was the most dominant mutated pathway both in pancreatic head and body/tail cancers (91.8% vs. 97.1%,  $p = 0.188$ ), although no significant difference. Of note, the mutation frequency of MAPK pathway showed the apparently difference in advanced pancreatic body/tail and head cancers (100% vs. 87.8%,  $p = 0.040$ ), but not in early stage cancers (92.3% vs. 95.9%,  $p = 0.600$ ).

Besides, we focused on TOP 2 frequently mutated pathways, Wnt and MAPK signaling at the gene levels (Fig. 3b). Higher mutated frequency in Wnt signaling of pancreatic body/tail cancers mainly resulted from distinctly enriched *SMAD4* mutations ( $p = 0.008$ ), and more abundant *LRP1/1B* and *CTNNB1* mutations. Interestingly, we found that *RNF43* mutations ( $n = 8$ ) were mutually exclusive to *SMAD4* in pancreatic head cancers but 3 of 4 *RNF43* mutations co-occurred with *SMAD4* in pancreatic body/tail cancers.

## Clinical druggable genes

To compare potential clinical benefits among pancreatic head and body/tail cancers in terms of targeted drugs, we analyzed actionable alterations from 16 clinical relevant genes with 43 potential therapies according to the widely accepted rule (Fig. 4a) [7]. Overall, 43.5% of pancreatic head cancer and 34.8% of pancreatic body/tail cancer carried at least one genomic alteration that could potentially benefit from the targeted drugs, but no significant difference was achieved. In late stages (III-IV), pancreatic body/tail cancer showed significant less druggable mutation than pancreatic head cancer (30.8% vs. 57.6%,  $p = 0.030$ ) (Fig. 4b).

The TOP 3 frequently mutated targets were *CDKN2A* (21.2%), *KRAS* wild type (17.6%) and *KDM6A/ATM* (3.5%) in pancreatic head cancers and *CDKN2A* (21.7%), *KDM6A* (4.3%) and *KRAS* wild type/*BRCA2/PIK3CA/NTRK3* (2.9%) in pancreatic body/tail cancers. There was significantly less *KRAS* wild type in pancreatic body/tail cancers than pancreatic head cancers (2.9% vs. 17.6%,  $p = 0.004$ ). In late

stages (III-IV), the difference in *KRAS* wild type druggable mutation frequency between the two subtypes was increased (0% vs. 24.2%,  $p = 0.001$ ). In addition, patient with TMB-H (> 10 mutations/Mb) patients accounted for 4.7% ( $n = 4$ ) and 1.4% ( $n = 1$ ), in pancreatic body/tail and head cancers respectively ( $p = 0.381$ ).

## Discussion

It is well-known that patients with pancreatic body/tail cancer usually have a poorer prognosis than those with pancreatic head cancer probably due to more advanced pathologic stages at initial diagnosis[1]. To better understand the prognostic relevance and distinct tumor biology, we should compare the two subtypes of PDACs in comparable conditions such as AJCC TNM stages and pathology grade. A large cohort analysis using the National Cancer Database of the United States from 1998 to 2011 demonstrated that among 40,980 cases of resected PDAC, pancreatic head cancers had advanced tumor stage, higher nodal positivity, worse tumor grade and poorer overall survival than pancreatic body/tail cancers[2]. A recent strictly propensity score-matched (e.g., race, gender, marital status, TMN stage and pathology grade) study including 4,571 resected T1 stage PDACs from Surveillance, Epidemiology, and End Results (SEER) database (2004–2014) provided the best evidence showing the prognostic value of tumor location in early-stage PDACs up to now[8]. They found that patients with pancreatic head cancer had a worse prognosis compared to those with pancreatic body/tail cancers. Body/tail location was further proved to be an independent indicator for better chances of survival in T1 PDAC patients. In this sense, pancreatic body/tail cancer seems to be a less malignant phenotype as compared to pancreatic head cancer.

However, the genomic and transcriptomic profiling comparison between pancreatic head and body/tail cancers using resected PDAC samples provided the opposite results. Both Birnaum's[4] and Dreyer's[5] studies showed pancreatic body/tail cancers were associated with 'squamous phenotype'[9] and presented more aggressive tumor biology such as epithelial-to-mesenchymal transition (EMT), inflammation and metabolic reprogramming. This study displayed a 2-fold higher *SMAD4* mutation rate in pancreatic body/tail cancers than pancreatic head cancers among early-stage tumors (I-II). Inactivating mutation in *SMAD4* does not initiate the tumor genes in PDAC but serve as secondary genetic alterations following *KRAS* mutation[10]. Interestingly, *SMAD4*/TGF-beta signaling is involved in squamous/EMT transition in PDAC[11]. Therefore, our results supported the previous two studies that pancreatic body/tail cancers might be more 'squamous phenotype' than pancreatic head cancers. We also assume that the molecular diversity between pancreatic head and body/tail cancers starts from the clonal expansion phase[10] but not the tumor initiation.

When PDAC developed to the late stages (III-IV), there was a remarkable difference in cancer genome between the two subtypes. We found significantly higher *KRAS* mutations (e.g., substitution, indels, and gene amplification), more enriched mutation frequencies in MAPK pathway and a lower rate of druggable genomic alterations in pancreatic body/tail cancers than pancreatic head cancers. Activating mutation of *KRAS* is almost ubiquitous (~ 95%) in PDAC and is an essential event in both tumor initiation and

progression[12]. Mutant *KRAS* drives PDAC development and promotes tumor cell proliferation via altered metabolic pathways including stimulation of glucose uptake and utilization, reprogrammed glutamine metabolism and increased autophagy[12]. Furthermore, *KRAS* driver mutations lead to the activation of Wnt and MAPK pathways, which controls tumor cell proliferation, motility, metabolism and survival[13]. The results were consistent with a large cohort study including 9,952 patients with metastasized PDAC from the Netherlands Cancer Registry (2005–2015), which demonstrated that pancreatic tail cancers had more metastatic sites and worse survival[14]. It seems that pancreatic body/tail cancers are more biological aggressive than pancreatic head cancers as PDAC has progressed to late stage.

Besides, the genomic variant results indicated that the choice of therapy strategies could refer to tumor location as well as mutated genes. Birnbaum et al[4] suggested checkpoint inhibitors as neoadjuvant treatment for pancreatic head cancers and anti-EGFR targeted therapies for pancreatic body/tail cancers. This study displayed a significantly lower rate of *KRAS* wild type in pancreatic body/tail cancers than pancreatic head cancers, indicating a low efficiency of Regorafenib, Panitumumab, and Cetuximab, which is FDA approved drugs for the treatment of colorectal cancer patients with *KRAS* wild type. A novel small-molecular inhibitor AMG510 targeting to a *KRAS* mutation G12C presented valid anti-cancer ability for patients with non-small cell lung cancer in the phase I clinical trial [15] and may be of help for the 100% *KRAS* mutated late-stage pancreatic body/tail cancers. Anti-EGFR or BRAF targeted therapies were not recommended in either pancreatic head or body/tail cancers because of the extremely low druggable mutation frequencies.

There were strengths as well as limitations in this study. This was the first study including both early and late stages PDACs and comparing the genomic profiles between pancreatic head and body/tail cancers. Thus, it is a more comprehensive comparison than the previous studies. But the sample size was rather small. Moreover, this study used ultra-deep panel sequencing to detect extremely low frequencies. But the panel was limited to 450 genes and the previously defined molecular subtypes [16] could not be analyzed.

## Conclusions

The molecular pathophysiology diversity existed between pancreatic head and body/tail cancers. The distinct genomes may not occur at initial step but at stepwise progression stages such as cell clonal expansion (*SMAD4* in I-II stage PDACs), interaction with microenvironment and metabolic reprogram (*KRAS* in III-IV stage PDACs) (Fig. 5). Consequently, pancreatic body/tail cancer presents as a more malignant phenotype than pancreatic head cancer in advanced stages. In contrast, whether pancreatic body/tail cancer has more aggressive tumor biology than pancreatic head cancer in the early stages is still under debate and needs to be further explored.

## Abbreviations

PDAC :Pancreatic ductal adenocarcinoma; NGS :next-generation sequencing; SNVs :single nucleotide variants, CNVs :copy number variations; SEER :Surveillance, Epidemiology, and End Results database

## Declarations

## Ethics approval and consent to participate:

The study was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine and the Ethics Committee of Shulan Hospital, and following the declaration of Helsinki. All patients had signed the informed consent.

### Consent for publication:

Authors confirmed that this work can be published. Also, all authors ensured that this manuscript is original and has not yet been accepted or published elsewhere.

### Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Competing interests:

Q.W., A.W., S.Z., L.W. and M.Y. are employees of OrigiMed.

## Funding:

This research was funded by the National Natural Science Foundation of China (81771713), Zhejiang Provincial Natural Science Foundation of China (LR18H030001), and the Fundamental Research Funds for the Central Universities (2019QNA7030).

## Author Contributions:

Conceptualization, Q.L.; methodology, X.Z.; formal analysis, S.F., Q.W. and H.H.; investigation, Q.X. and W.Z; data curation, Q.W., A.W., S.Z., L.W., and M.Y.; writing—original draft preparation, X.Z.; writing—review and editing, Q.L.; supervision, Q.L.; funding acquisition, Q.L.. All authors have read and agreed to the published version of the manuscript.

## Acknowledgments:

Not applicable.

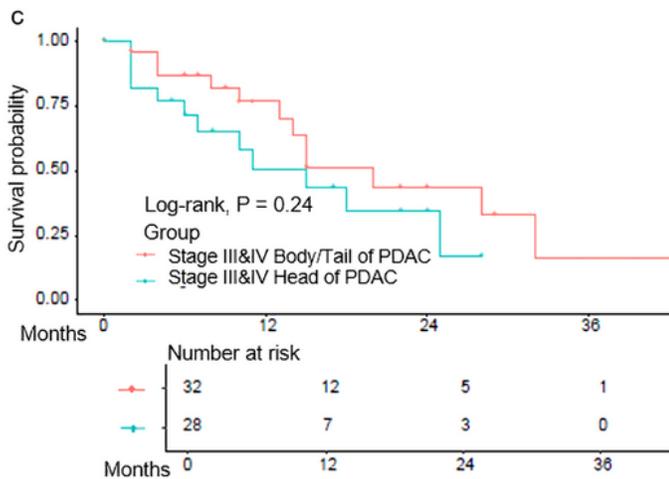
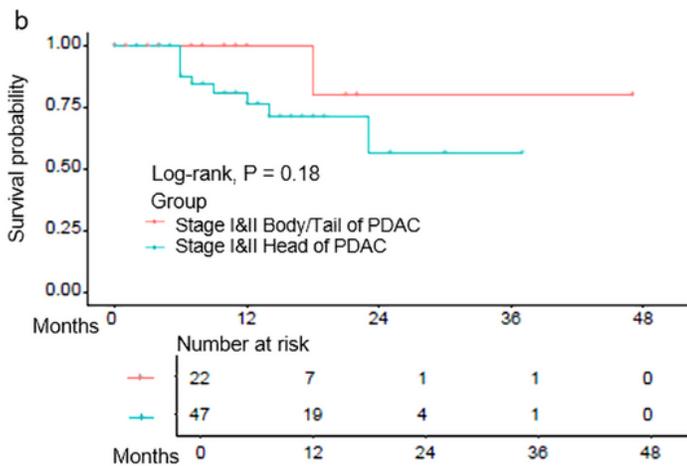
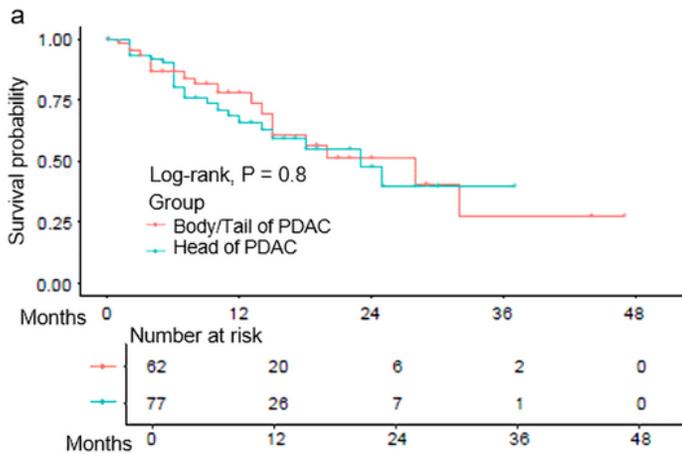
## References

1. Ling Q, Xu X, Zheng SS, Kalthoff H. The diversity between pancreatic head and body/tail cancers: clinical parameters and in vitro models. *Hepatobiliary Pancreat Dis Int.* 2013;12(5):480–7.
2. Winer LK, Dhar VK, Wima K, Morris MC, Lee TC, Shah SA, Ahmad SA, Patel SH. The Impact of Tumor Location on Resection and Survival for Pancreatic Ductal Adenocarcinoma. *J Surg Res.* 2019;239:60–6.
3. Ling Q, Xu X, Ye P, Xie H, Gao F, Hu Q, Liu Z, Wei X, Röder C, Trauzold A, et al. The prognostic relevance of primary tumor location in patients undergoing resection for pancreatic ductal adenocarcinoma. *Oncotarget.* 2017;8(9):15159–67.
4. Birnbaum DJ, Bertucci F, Finetti P, Birnbaum D, Mamessier E. **Head and Body/Tail Pancreatic Carcinomas Are Not the Same Tumors.** *Cancers (Basel)* 2019, 11(4).
5. Dreyer SB, Jamieson NB, Upstill-Goddard R, Bailey PJ, McKay CJ, Biankin AV, Chang DK. Defining the molecular pathology of pancreatic body and tail adenocarcinoma. *Br J Surg.* 2018;105(2):e183–91.
6. Cao J, Chen L, Li H, Chen H, Yao J, Mu S, Liu W, Zhang P, Cheng Y, Liu B, et al. An Accurate and Comprehensive Clinical Sequencing Assay for Cancer Targeted and Immunotherapies. *Oncologist.* 2019;24(12):e1294–302.
7. Chakravarty D, Gao J, Phillips SM, Kundra R, Zhang H, Wang J, Rudolph JE, Yaeger R, Soumerai T, Nissan MH, et al: **OncoKB: A Precision Oncology Knowledge Base.** *JCO Precis Oncol* 2017, **2017**.
8. Meng Z, Cao M, Zhang Y, Liu Z, Wu S, Wu H. Tumor location as an indicator of survival in T1 resectable pancreatic ductal adenocarcinoma: a propensity score-matched analysis. *BMC Gastroenterol.* 2019;19(1):59.
9. Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, Miller DK, Christ AN, Bruxner TJ, Quinn MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature.* 2016;531(7592):47–52.
10. Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. *Nat Rev Cancer.* 2016;16(9):553–65.
11. Huang PH, Lu PJ, Ding LY, Chu PC, Hsu WY, Chen CS, Tsao CC, Chen BH, Lee CT, Shan YS, et al. TGF $\beta$  promotes mesenchymal phenotype of pancreatic cancer cells, in part, through epigenetic activation of VAV1. *Oncogene.* 2017;36(16):2202–14.
12. Bryant KL, Mancias JD, Kimmelman AC, Der CJ. KRAS: feeding pancreatic cancer proliferation. *Trends Biochem Sci.* 2014;39(2):91–100.
13. Wee P, Wang Z. **Epidermal Growth Factor Receptor Cell Proliferation Signaling Pathways.** *Cancers (Basel)* 2017, 9(5).
14. Mackay TM, van Erning FN, van der Geest LGM, de Groot JWB, Haj Mohammad N, Lemmens VE, van Laarhoven HW, Besselink MG, Wilmink JW. Association between primary origin (head, body and tail) of metastasised pancreatic ductal adenocarcinoma and oncologic outcome: A population-based analysis. *Eur J Cancer.* 2019;106:99–105.

15. **AMG**. 510 First to Inhibit "Undruggable" KRAS. *Cancer Discov.* 2019;9(8):988–9.

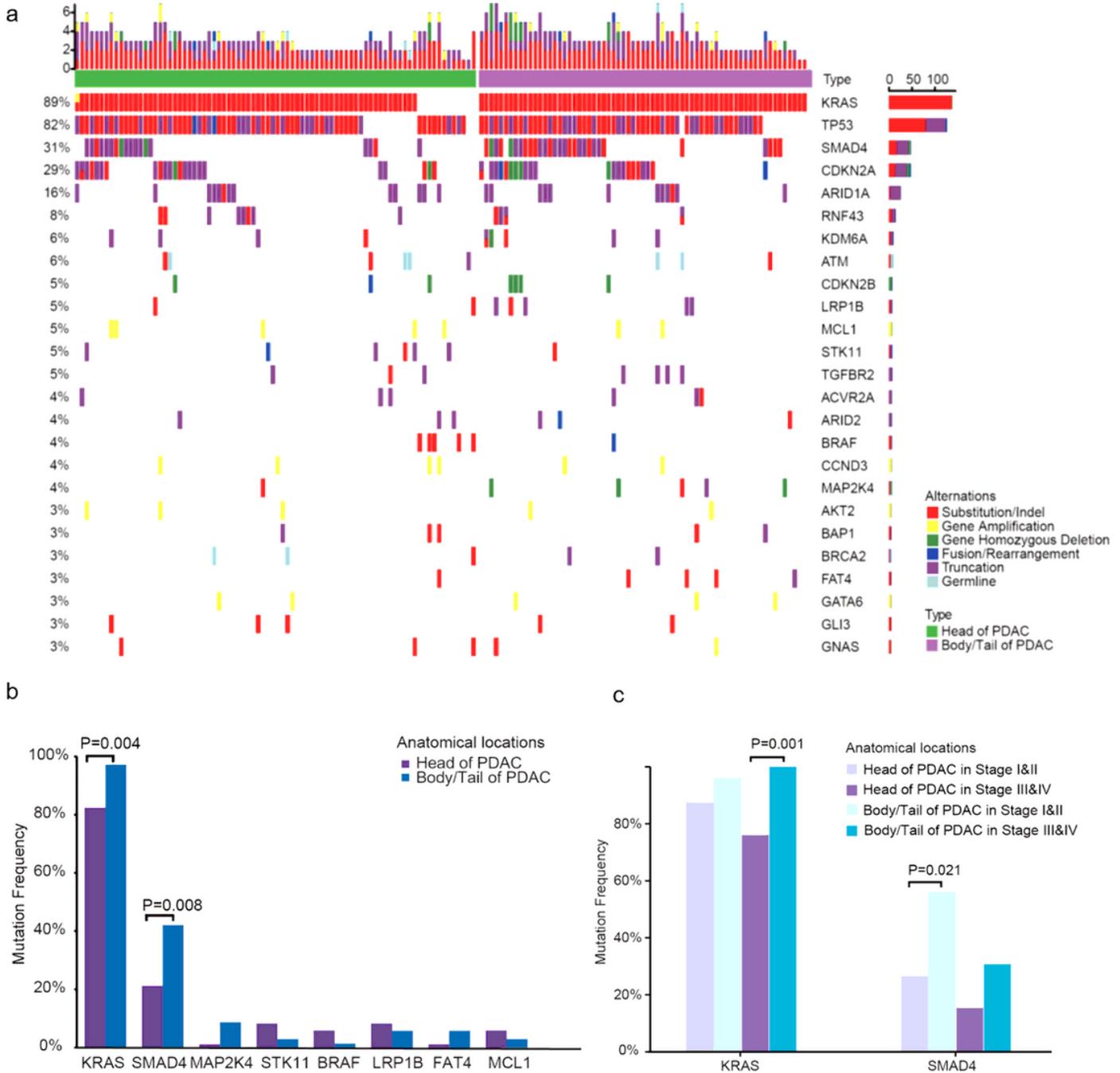
16. Collisson EA, Bailey P, Chang DK, Biankin AV. Molecular subtypes of pancreatic cancer. *Nat Rev Gastroenterol Hepatol.* 2019;16(4):207–20.

## Figures



**Figure 1**

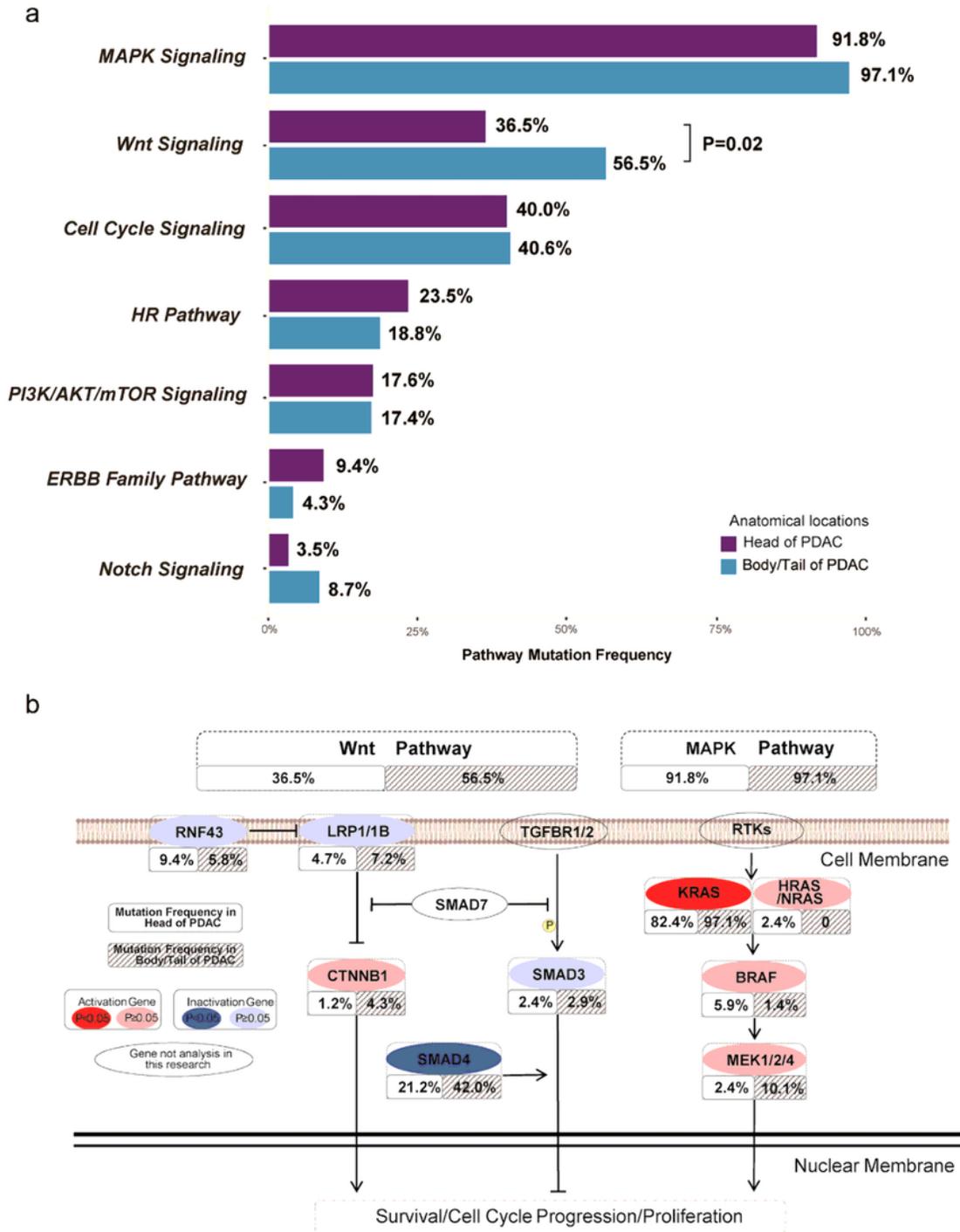
The comparison of patient survival between pancreatic head and body/tail cancers. (a) The comparison of overall survival in all PDACs; (b) The comparison of overall survival in early (I-II) pancreatic head and body/tail cancer; (c) The comparison of overall survival in the late stage (III-IV) pancreatic head and body/tail cancer. PDAC indicates pancreatic ductal adenocarcinoma.



**Figure 2**

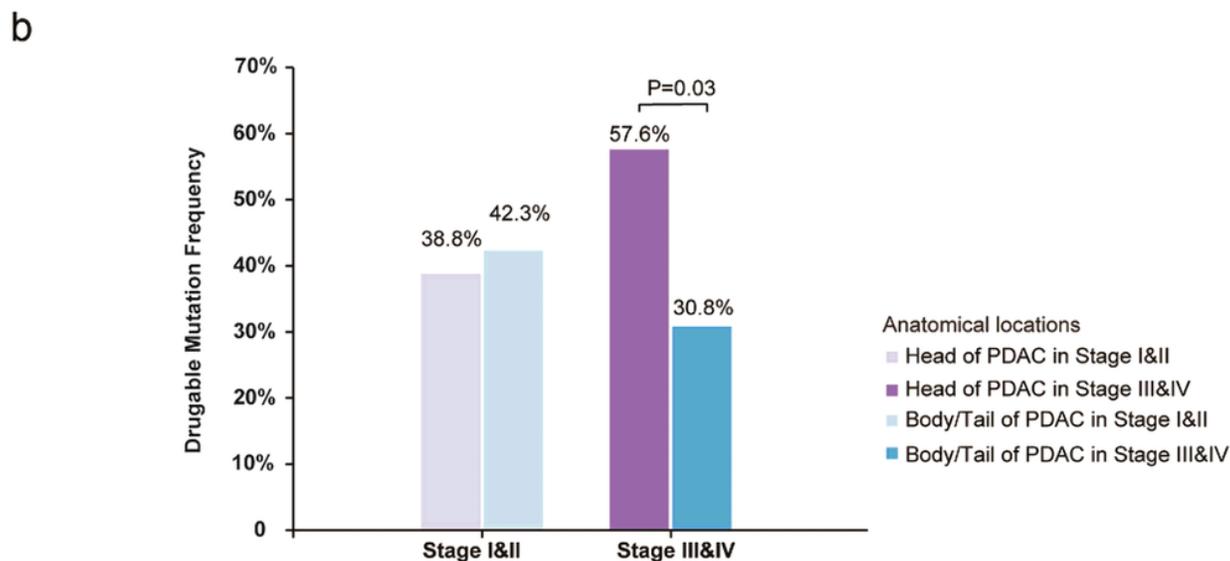
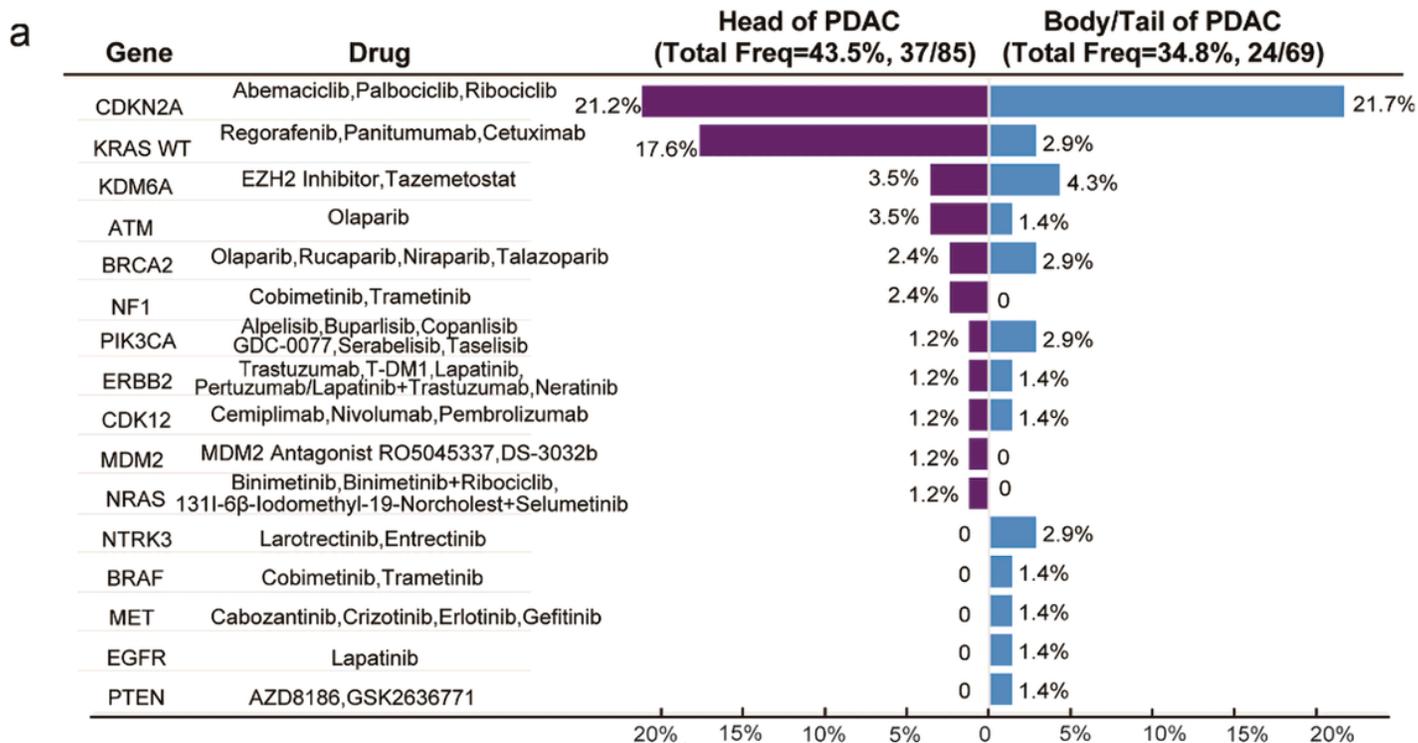
The comparison of genomic alterations between pancreatic head and body/tail cancers. (a) The genomic landscape in head (n = 85) and body/tail (n = 69) of PDACs; (b) Eight gene alteration frequencies in head and body/tail of PDACs. The comparison of overall survival in all PDACs; (c) KRAS and SMAD4 alteration

frequencies in head and body/tail of PDACs related to early (I-II) and advanced (III-IV) stages. PDAC indicates pancreatic ductal adenocarcinoma.



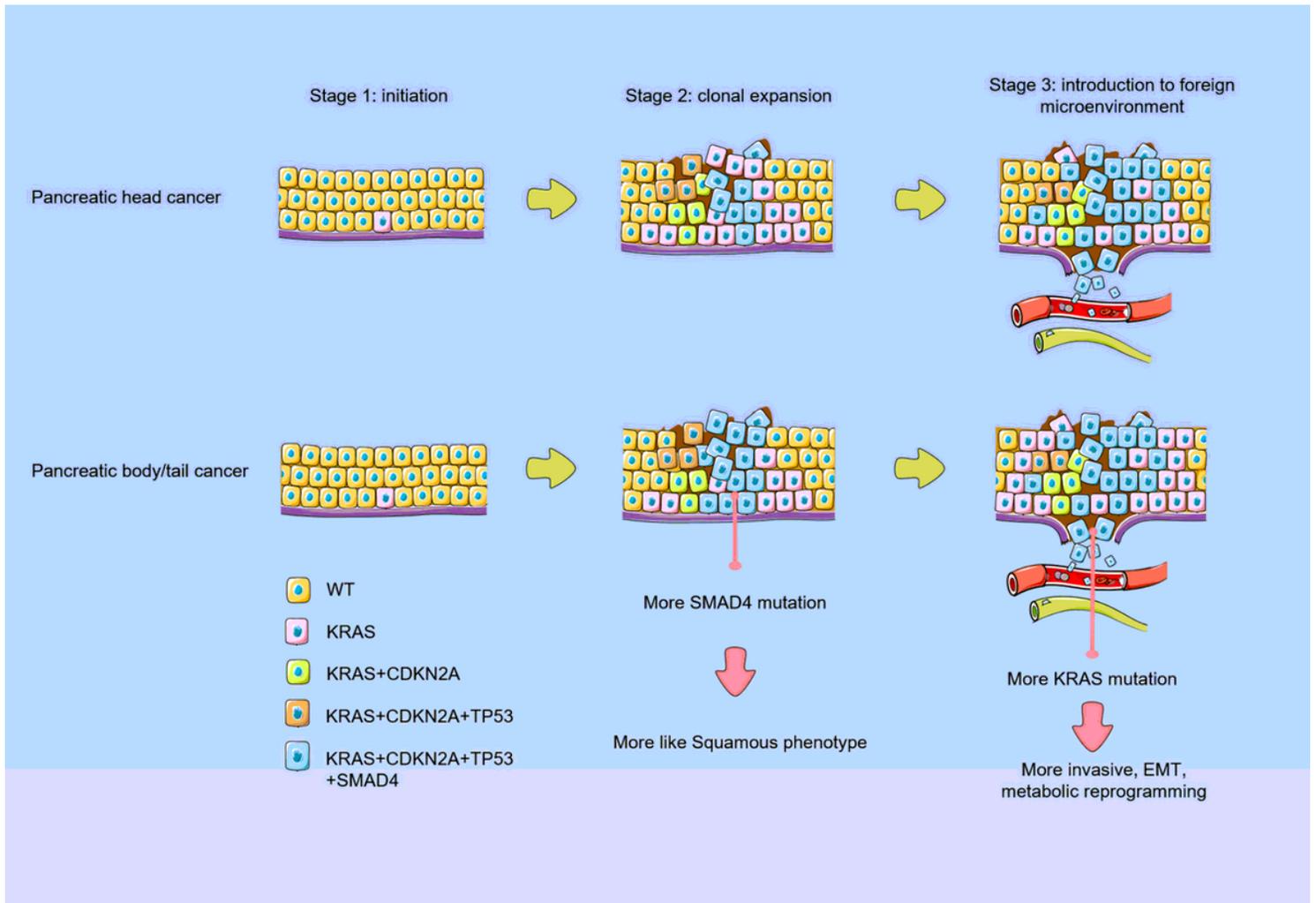
**Figure 3**

The comparison of mutation frequencies in pathways. (a) Seven gene pathways mutation frequencies in head and body/tail PDAC; (b) TOP 2 mutated pathways in gene level



**Figure 4**

The comparison of putative druggable genome in head and body/tail PDAC (a) and druggable mutation frequency in head and body/tail of PDAC according to early and advanced stages (b). PDAC indicates pancreatic ductal adenocarcinoma.



**Figure 5**

Schematic illustration showing the molecular diversity between pancreatic head and body/tail cancers. The tumor staging (Stage 1, tumor initiation; Stage 2, the clonal expansion phase; Stage 3, interaction with microenvironment) was defined according to Makohon-Moore's study[11].

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supportinginformationR0.docx](#)
- [FigureS1.tif](#)