Letter to the Editor

Genetic landscape of prognostic value in pancreas ductal adenocarcinoma microenvironment—reply

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Thank you for the constructive editorial commentaries on our recently published research, "Genetic landscape of prognostic value in pancreatic ductal adenocarcinoma microenvironment" (1).

In the editorial commentary "Prognostic value of biomarkers in the tumor microenvironment of pancreatic ductal adenocarcinoma", Mishra *et al.*, showed the experiences of their previous researches and other publications, which was consistent with our research. They also did great work on identifying the novel and potential prognostic markers of pancreatic ductal adenocarcinoma (PDAC), such as three genes (*B3GNT3*, *DMBT1*, and *DEPDC1B*), two long non-coding RNA (PVT1 and GATA6-AS), and 406 promoter methylation target loci, which were strongly correlated with survival (2). Their results provided positive feedback to our novel findings, and hoped to apply data from other public cohorts to establish the role of genes associated with higher immune and stromal scores in *in-vivo*, *in-vitro*, and PDAC patient samples.

In another recent commentary, Williams *et al.*, presented that "*In Silico analyses of host immunity and stroma provide prognostic factors in early-stage pancreatic ductal adenocarcinoma (PDAC)*". We agree that CA19-9 may help stratify patients to immune/stroma subtypes. Previous publications have demonstrated that CA19-9 is considered as a prognostic indicator in pancreatic cancer patients (3-5). Regrettably, no CA19-9 data was able to be retrieved from the database. We want to collect our samples to validate our observations, and then we can further analyze the correlations with CA19-9. In addition, they mentioned that a major limitation of our study was the lack of tumor microenvironment (TME) data from patients with advanced disease, with only 5% of the study population having stage III or IV disease. That's absolutely correct and the cases used in our cohort were all underwent surgical resection. Obvious advanced diseases confirmed by the image do not fit the criteria of the surgery. Furthermore, the first choice of the treatment for PDAC with metastatic disease is usually chemoradiotherapy (6). Locally advanced diseases or occasional occult metastatic disease underwent surgery, like those 5% of stage III/IV diseases in the cohort, does exist in clinic based on the surgeon with aggressive surgery, such as at our institution at Johns Hopkins Hospital. On the other hand, there was a bias for TME in resectable disease majorly. There is a need to investigate the TME data from patients with advanced disease using fine needle biopsies.

Another limitation was the lack of information regarding the cellularity of the tumor and its heterogeneity, contributions of genomic instability to disease heterogeneity, and the issue of low tumor cellularity when compared to the stroma, which were mentioned in the publication. It's been published that cellular heterogeneity, fibroblast heterogeneity, immune heterogeneity, and genomic heterogeneity all play a vital role in pancreatic cancer progression and metastasis (7-10). Single-cell sequencing, on the other hand, can help conquer all the limitations listed above.

Our study listed numerous genes with prognostic value in the microenvironment of PDAC from functional enrichment analysis. These genes can become auxiliary prognostic biomarkers for PDAC, and further investigation may be valuable to understand the crosstalk between tumor and microenvironment.

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Footnote

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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.

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