The Proteomic Landscape of Pancreatic Ductal Adenocarcinoma Liver Metastases Identifies Molecular Subtypes and Associations with Clinical Response – Response

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Keywords

We appreciate the comments by Le Large et al. regarding our article describing metastatic PDAC microenvironment subtypes using proteomics (1). As they point out, our study revealed 4 proteomic subtypes utilizing bulk PDAC liver metastases, identified subtype-specific protein associations with survival, and determined that subtypes are predictive of response to chemotherapy.

Our study is unique in its analysis of metastatic PDAC, which is important to the majority of patients who present with advanced disease and are reliant upon chemotherapy. Disseminated disease has largely been unexplored by previous subtyping efforts, which have focused primarily on treatment-naïve early-stage primary tumors. Our work was possible because of our unique biorepository of PDAC rapid autopsy samples that are of outstanding quality for molecular assays as well as generation of PDX models (https://pdmr.cancer.gov/) and organoids (2, 3). Importantly, the correlation we observed between the metastatic subtypes and those from transcriptomic studies suggests that subtype-specific therapeutic strategies may prove effective against both localized and disseminated disease.

Interestingly, our exploration of the relationship between prior treatments and PDAC subtypes failed to identify significant associations. Our analysis also included 6 liver metastases from treatment-naïve patients which identified 3 of the 4 PDAC subtypes in this group, however, larger studies are needed. Clinical longitudinal studies comparing pre- and post-treatment PDAC subtypes are also required to determine the impact of specific therapeutic pressures on subtype selection. Even with the therapeutic pressures applied in our autopsy cohort, the subtypes identified in our study correlate well with the two subtype model (Classical-Pancreatic and Squamous) that is mostly consistent across transcriptomic studies (4). Notably, this suggests that PDAC may be constrained to these subtypes even

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with therapeutic pressure, although switching between subtypes could still occur. The clinical relevance of these subtypes is evident in that subtypes mapping as Squamous (Proliferative and Inflammatory) are resistant to FOLFIRINOX, an observation supported by results from O'Kane et al. who similarly found that the basal-like/Squamous subtype is resistant to this drug combination (5). However, these compelling findings would benefit from additional validation and a deeper mechanistic understanding.

We agree that single-cell analysis and spatial technologies will provide additional insight into stromal and tumor cell subtype characteristics, and expect PDAC subtypes will continue to be refined by alternative strategies and technology advancements. Again, we thank Le Large et al. for their interest in our research and are optimistic regarding the clinical relevance of the proteomic signatures we have defined in this study.

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