#4144: Comprehensive Molecular Mapping of Pancreatic Ductal Adenocarcinoma Relates XPO1 mRNA Expression Levels to Potential Clinical Targets

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Background

- Encouraging pre-clinical efficacy using inhibitors targeting Exportin-1 (XPO1) - a master regulator of tumor suppressor protein export - has been reported in pancreatic ductal adenocarcinoma (PDAC) and clinical trials are currently ongoing.
- Limited data is available regarding expression and function of XPO1 in PDAC.
- Thus, we investigated XPO1 mRNA expression and its clinical and immune correlates in PDAC.

Methods

- 5,488 PDAC tumors were tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing of DNA (592-1,068 mutations/MB).
- Immune cell fraction was calculated by QuantiSeq (Phoenix, AZ) with NextGen Sequencing of DNA and RNA (whole transcriptome) (Phoenix, AZ) with NextGen Sequencing of DNA (10 mutations/MB).
- The cohort was stratified in quartiles according to XPO1 mRNA expression.
- Gene expression profiles were analyzed for transcriptomic signatures predictive of response to immune checkpoint inhibitors (T cell-inflamed score) and MAPK pathway activation (MPAS).
- The Mann-Whitney U and \( \chi^2 \) tests were applied as appropriate, with P-values adjusted for multiple comparisons.

Results

1. Genomic landscape and biomarkers

- Figure 1: (A) Disrupt of genomic alterations, immune cell infiltrate, and transcriptomic signatures (immunotherapy response (T cell-inflamed) and MAPK pathway activation (MPAS)). Prevalence of (B) genomic alteration and (C) immune biomarkers.

2. Transcriptomic signatures and immune landscape

- Figure 2: (A) Prevalence of T cell-inflamed tumors (predictive of response to immunotherapy) (B) MMA5 score, a transcriptomic signature representative of MAPK pathway activation. (C) Quantification of tumor immune infiltrate, derived via QuantiSeq (asterisks indicate statistical significance, \( * \)p<0.05).

3. Outcomes data

- Figure 3: Outcomes data for pancreatic tumors segmented by XPO1 expression.

Study Highlights

- There were no significant alterations in the genomic landscape between high and low XPO1 expression.
- Tumors with high expression of XPO1 tended to be more T cell-inflamed, had activation of the MAPK pathway and had an increase in M2 macrophage infiltrate.

Conclusions

- This is the first study comprehensively mapping XPO1 mRNA expression and immune-correlates in PDAC.
- We found that high XPO1 is linked to increased immune cell infiltration and more T cell-inflamed tumors.
- Our data provides a potential rationale to combine immune checkpoint therapy (+/- XPO1 inhibitors) in XPO1\textsuperscript{th} PDACs.