Subtyping of pancreatic cancer patient-derived xenograft tumors and implications for anti-cancer agent testing

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1 INTRODUCTION

Despite improvements in treatment, pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal cancers with a continuous increase in incidence, emphasizing the need for further research and therapeutic development. Facing the need to test new anti-cancer agents, we report here the development of 42 patient-derived xenograft (PDX) models of PDAC for pharmacogenomics investigations. In order to show the suitability of these models for pre-clinical studies, we performed an integrative analysis to highlight model features and subtypes by combining histology, genomic and transcriptomic profiles.

2 PDX-PDX ESTABLISHMENT

• PDAC from 65 patients were implanted into female, 4-6 weeks old, NMR1/nu nu (Harlan, The Netherlands) immune-compromised mice.

• 42 PDAC-PDX were stably established (success rate 64%).

• Patient survival (Fig 1) and lymph node invasion were associated with model establishment (P=0.026 and P=0.03, respectively).

3 RESULTS

PDAC-PDX MORPHOLOGY FEATURES

- As with patient tumors, grades and stroma content of PDAC-PDX were heterogeneous, both correlating inversely (p=0.0006; Fig 2A).

- PDAC-PDX grades usually correlated with those of parental tumors, however some models shifted to a higher grade (Fig 2B).

- PDAC-PDX demonstrated the capability to develop low to high mural stromal content. Part of PDAC-PDX models, correlated with corresponding parental tumors (Fig 2C).

- As recently described in patient tumors, parts of PDAC-PDX showed stromal activation consisting of fibroblasts with small spindle cell morphology, a thin and wavy body structure and a symmetric/partial orientation (Fig 2D).

PDAC-PDX TRANSCRIPTOME SUBTYPE

The 62-gene expression signature established by Collisson et al., classified PDAC-PDX and patient tumors into distinct transcriptomic subtypes. 22 models were of the classical subtype (52%), 15 of the squamous-adenocarcinoma (38%) and 5 of the exocrine-like subtype (12%).

PDAC-PDX INTEGRATIVE ANALYSIS

4 CONCLUSIONS

Comprehensive characterization of our PDAC-PDX collection revealed similarities with patient tumors with regards to histology features including stroma content and fibrolast activation. At the molecular level, the models demonstrated similar genomic and transcriptomic patterns to those reported for patient tumors, demonstrating the preservation of patient tumor features and the suitability of this collection for pharmacogenomics investigations.

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