Study of tumor heterogeneity and subclonality in primary pancreatic and metastatic sites from rapid autopsy patients in PDMR

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INTRODUCTION

A major set of preclinical models derived from specimens acquired from rapid autopsy patients in the National Cancer Institute Patient-Derived Models Repository (NCI PDMR, https://pdmr.cancer.gov) were from pancreatic adenocarcinoma (PAAD) patients, with metastatic specimens originating from liver, colon, omentum, and lung. Genomic characterization of these preclinical models provides a unique opportunity to study tumor heterogeneity and subclonality associated with the metastatic process and potential treatment resistance.

Pancreatic PDX models from rapid autopsy patients

- To date, 30 rapid autopsy patient-derived xenograft (PDX)/patient-derived cell (PDC)/patient-derived organoid (PDOrg) models derived from pancreatic adenocarcinoma patients (n=9) have been sequenced using whole-exome sequencing (WES) and RNASeq²,³
- Treatment history
- H&E slides
- NGS data: WES and RNAseq

METHODS

Tumor heterogeneity between primary and metastatic sites was studied based on somatic mutation, copy number alteration (CNA) and gene expression data. A bioinformatics workflow was developed to stably infer and visualize the tumor subclonality by integrating the tools of PyClone, SCHISM, and TIMESCAPE, using somatic mutations and site-specific copy number data of multiple samples generated from PDX models in primary and metastatic sites.

RESULTS

Among 30 rapid autopsy preclinical models from primary and metastatic sites, liver is the most common metastatic site in PAAD (9/19=47%) compared to other sites. Driver mutations are conserved in all preclinical model specimens derived from a given patient. KRAS p.G12D is present in 28 PDX/PDC/PDOrg models as well as the corresponding patient specimens, and BRAF p.V600E is present in other preclinical models. The fraction of the genome affected by CNA remains stable across passages (n=18, mean=7.63%, sd=5.90%). However, we found that this increased when comparing PDX models derived from metastatic sites versus the primary site (n=16, mean=19.47%, sd=9.69%). This indicates the presence of tumor heterogeneity between metastatic and primary sites.

CONCLUSION

Tumor heterogeneity and subclonality was observed in preclinical models generated from PAAD patients in the NCI PDMR. These models provide a unique resource for preclinical studies in tumor evolution, metastatic spread mediators, and drug resistance.

REFERENCES

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