PDX models generated from a patient with metastatic colon adenocarcinoma display both spatial and temporal tumor heterogeneity

Biswajit Das1, Chris Karlovich1, Corinne Camaliier1, Rajesh Patidar1, Li Chen1, Vivekananda Datta1, William Walsh1, Palmer Fliss1, Sean McDermott1, Tomas Villimas1, Palmer Fliss1, Justine N. McCutcheon1, Amanda Peach1, Michelle Ahalt-Gotholm2, Carrie Bonomi3, Kelly Dougery3, John Carter1, Yvonne A. Evrard3, Shivaani Kummard2, Melinda G. Hollingshead4,5, P. Mickey Williams1 and James H. Doroshow1

1Leidos Biomedical Research Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, 2Biological Testing Branch, Developmental Therapeutics Program, National Cancer Institute at Frederick, Frederick, MD, 3Division of Medical Oncology, Stanford University School of Medicine, Palo Alto, CA and 4National Cancer Institute, Division of Cancer Treatment and Diagnosis, Bethesda, MD

Abstract

Patient-derived xenograft (PDX) models are being widely used in preclinical studies to identify mechanisms of drug resistance and drug combinations that improve outcomes for patients with cancer. However, the extent to which tumors maintain spatial and temporal heterogeneity within their microenvironment remains largely unexplored. Specifically, it is unclear how PDX models represent a tumor microenvironment in the spatial and temporal resolution that is relevant to clinical treatment. In this study, we generated four patient-derived xenograft (PDX) models from a patient with metastatic colon adenocarcinoma (MET-2) and examined the tumor heterogeneity of these models using a range of spatially and temporally sensitive methods. We find that PDX lines are heterogeneous for not only the genome, but also for spatial and temporal tumor heterogeneity. We observe a high concordance of genomic alterations across PDX models and a discordance of drug susceptibility profiles. These findings indicate that PDX model heterogeneity may confound the development and testing of new therapy.

Introduction

1. PDX models capture the disease complexity present in corresponding primary tumors, including the tumor heterogeneity obtained from different sub-clones.
2. PDX models can be used to explore the impact of genetic changes in different sub-clones.

To inform our understanding of the role of tumor heterogeneity, we generated four PDX models (MET-2) from the same patient with metastatic colon adenocarcinoma (MET-2). We analyzed these models for spatial and temporal heterogeneity using a range of spatially and temporally sensitive methods. We found a high concordance of genomic alterations across PDX models and a discordance of drug susceptibility profiles.

Clinical History of Patient 172845

Patient 172845 (MET-2) was diagnosed with metastatic colon adenocarcinoma in 2009 and underwent surgery to remove a metastatic tumor from the liver in 2010. He was then treated with FOLFIRI chemotherapy and bevacizumab. During the course of treatment, he developed liver metastases, and survived for several years despite multiple chemotherapy treatments. In 2016, the patient underwent surgery to remove a metastatic tumor from the liver, and was found to have both spatial and temporal tumor heterogeneity.

Methods

We generated four PDX models (MET-2) from the same patient with metastatic colon adenocarcinoma (MET-2). We analyzed these models for spatial and temporal heterogeneity using a range of spatially and temporally sensitive methods. We found a high concordance of genomic alterations across PDX models and a discordance of drug susceptibility profiles. These findings indicate that PDX model heterogeneity may confound the development and testing of new therapy.

Conclusion

Patient-derived xenograft (PDX) models from the same patient with metastatic colon adenocarcinoma display both spatial and temporal tumor heterogeneity. These findings indicate that PDX model heterogeneity may confound the development and testing of new therapy.

Resources and References

1. NCI-PDMR website: https://clinicalancer.gov
2. Genomic profiling data, SOPs, data analysis pipeline SOPs available at NCI-PDMR website

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