INTEGRATIVE ANALYSES OF SIGNALING AND DNA DAMAGE REPAIR PATHWAYS IN PATIENT-DERIVED XENOGRAFTS (PDX) MODELS FROM NCI'S PATIENT-DERIVED MODELS REPOSITORY (PDMR)

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ABSTRACT

We have performed integrative analysis of signaling pathways in PDX models using mutation, gene expression and proteomics data. We have described therapeutically actionable biomarkers present in the NCI PDMR models. This data suggest that additional datasets generated from the PDMR models (e.g., mutational signatures, somatic tumor mutations or relevant mutational signatures) or relevant functional testing may be useful for prioritizing specific agents for preclinical drug studies.

RESULTS

We have performed integrative analysis of signaling pathways in PDX models using mutation, gene expression and proteomics data. This data suggest that additional datasets generated from the PDMR models (e.g., mutational signatures, somatic tumor mutations or relevant mutational signatures) or relevant functional testing may be useful for prioritizing specific agents for preclinical drug studies.

SIGNIFICANT ALTERATIONS IN RTK AND PI3K PATHWAYS IN PDX MODELS

- 40% of the PDX models have at least one oncogenic alteration in RTK and PI3K pathways
- 56% of the PDMR models have at least one oncogenic alteration in WNT and PI3K pathways

ONCOGENIC AND TARGETABLE ALTERATIONS IN WNT/ Catenin and SONIC HEDGEHOG PATHWAY IN PDX MODELS

- 20% of the PDX models have oncogenic alterations in major DNA damage repair pathways
- 22% of the PDX models have oncogenic alterations in SHH and/or WNT pathways
- 56% of the PDMR models have at least one targetable alteration in RTK and PI3K pathways
- 65% of the PDMR models have at least one oncogenic alteration in RTK and PI3K pathways

PERICTION ACTIVITY IN PDMR MODELS FOR A SELECTED SET OF AGENTS

- PKB inhibition
- MEK inhibition
- PI3K inhibition
- MEK/ERK kinase inhibition
- Hedgehog pathway inhibition

SUMMARY

- We have performed integrative analysis of signaling pathways in PDX models using mutation, gene expression and proteomic datasets
- Gene expression and proteomic datasets allowed us to investigate downstream effects of signaling pathways
- PDX models included in this study were generated from patients with heterogeneous pathologies
- Additional datasets generated from the PDMR models (e.g., mutational signatures, somatic tumor mutations) or relevant functional testing may be useful for prioritizing specific agents for preclinical drug studies
- We have described therapeutically actionable biomarkers present in the genomically characterized NCI PDMR models
- This data suggest using PDX models will be valuable for preclinical drug combination studies

REFERENCES

2. Taylor et al. The Path(way) Less Traveled: A Pathway Oriented Approach to Providing Information About Precision Cancer Medicine, Translational Oncology (2016), 9, 163