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

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ABSTRACT

Background: Patient-derived xenografts (PDXs) are increasingly being used in translational cancer research for preclinical drug efficacy studies. The National Cancer Institute (NCI) has developed a Patient-Derived Models Repository (NCI PDMR; pdmr.cancer.gov) of PDXs with clinical annotation, proteomics, and comprehensive genomic datasets to facilitate these studies. Here, we present an integrative genomic, transcriptomic, and proteomic analysis of critical signaling and DNA damage repair pathways in these PDX models, which represent 9 common and multiple rare tumor histologies.

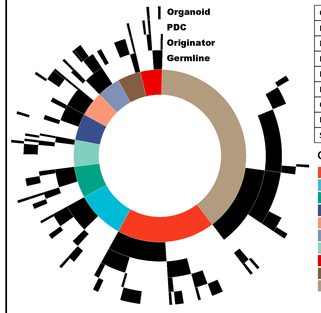
Methods: 346 PDX models from 333 patients were established from various solid tumor histologies from patients with primary or metastatic cancer. Whole Exome Sequencing, RNA-Seq and Reverse Phase Protein Array (RPPA) were performed on 2-9 PDXs per model across multiple passages. An integrative workflow was applied on multiple data sets to detect pathway activation.

Results: We profiled 5 signaling and 5 DNA repair pathways in the PDMR dataset. We observed that: (i) a large fraction (56%) of PDX models have at least 1 targetable mutation in the RTK/RAS and/or PIK3CA pathways; (ii) 131 models (45%) have putative driver and oncogenic mutations and copy number variants (CNVs) in the WNT, TGFβ, NOTCH pathways. In addition, 11% of PDX models have targetable mutations in DNA damage repair pathways and 20 PDMR models have a DNA mismatch repair defect (MSI-H). We confirmed activation of the signaling pathways in a subset of PDX models by pathway enrichment analysis on gene expression data from RNASeq and phosphoprotein-specific antibody binding data from RPPA. Activation of DNA repair processes was confirmed by enrichment of relevant mutational signatures and loss of heterozygosity in these PDX models.

Conclusions: Genomic analysis of NCI PDMR models revealed that a large fraction have clinically relevant somatic alterations in key signaling and DNA damage repair pathways. Further integrative analyses with matched transcriptomic and proteomic profiles confirmed pathway activation in a subset of these models, which may prioritize them for preclinical drug studies.

RESULTS

NCI PATIENT-DERIVED MODELS REPOSITORY DATASETS



COAD	Colon Adenocarcinoma
BLCA	Bladder Urothelial Carcinoma
MEL	Melanoma
LUSC	Lung Squamous Cell Carcinoma
HNSC	Head and Neck Squamous Cell Carcinoma
LUAD	Lung Adenocarcinoma
OCSC	Oral Cavity Squamous Cell Carcinoma
PAAD	Pancreatic Adenocarcinoma
SARCNOS	Sarcoma, not otherwise specified

ONCOTREE: COAD, BLCA, MEL, LUSC, HNSC, OCSC, LUAD, PAAD, SARCNOS, OTHER

Clinical and Histo-Pathological datasets:

- Clinical annotation of donors
- Limited clinical history including previous treatment regimens
- Donor demographics including self-declared ethnicity, smoking history
- STR profile
- Histo-pathological annotations and images of individual PDX specimens

Signaling Pathways Profile shown:

- RTK (Receptor Tyrosine Kinases)
- PI3K (PI3KCA/AKT)
- MEK/ERK kinase
- WNT/β–catenin
- Hedgehog
- DNA Damage Repair

Genomic and Proteomic Datasets:

Whole Exome:
- Raw FASTQ files
- VCF files (from our GATK pipeline)
  - Both somatic and mixed
- Variant calls from a selected set of 61 cancer-related genes
- Ethnicity determination from WES data using SNPweights

Whole transcriptome (RNASeq):
- Raw FASTQ files
- Gene expression data (RSEM pipeline)
- Transcript expression data (RSEM pipeline)

Reverse Phase Protein Array (RPPA):
- 245 antibodies (65 phospho-specific)
- z-score of a subset of specimens

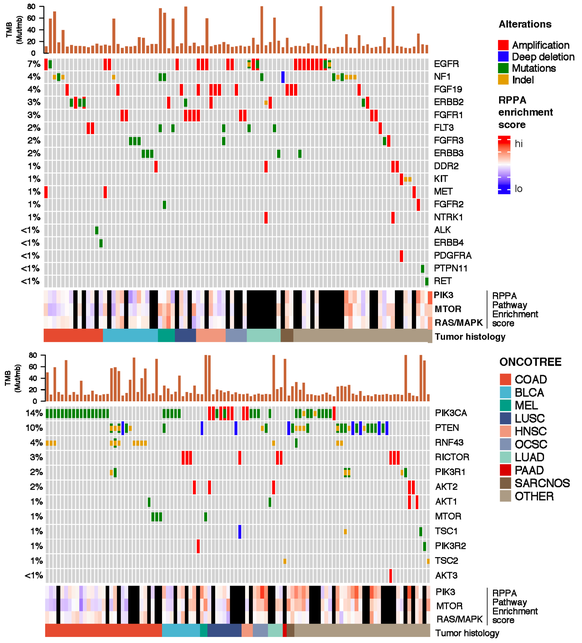
VISUALIZATION OF SIGNALING PATHWAY ACTIVATION

For each pathway, oncogenic variants[1] of constituent genes[2] are shown as oncoprints
Additionally for each pathway, relevant downstream effects and tumor histologies are shown below the oncoprint:

- for RTK and PI3K pathways, enrichment scores of PI3K, MTOR/TSC and RAS/MAPK pathways from RPPA data[3] are shown as a heatmaps
- for WNT/β-Catenin and SHH pathways, EMT score from RPPA, EMT, WNT and SHH gene set enrichment scores obtained from gene expression data are shown as a heatmaps
- for DNA damage repair pathways, mutational signature, MSI and LOH status are shown as a heatmaps

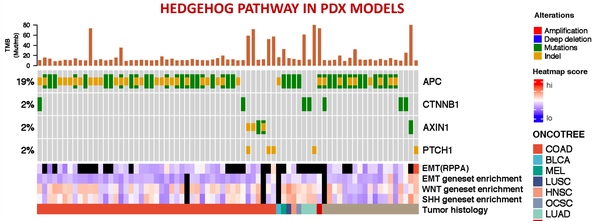
ONCOGENIC AND TARGETABLE ALTERATIONS IN RTK AND PIK3CA PATHWAYS IN PDX MODELS

- 65% of the PDMR models have at least one oncogenic alteration in RTK and PI3K pathways
- 56% the PDMR models have at least one targetable alteration in RTK and PI3K pathways



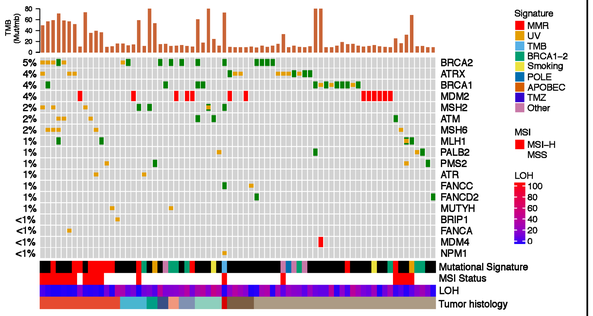
- Activity of PIK3, MTOR/TSC and RAS/MAPK pathways were determined by pathway scores calculated from RPPA data
- Activation of downstream signaling pathways were observed in some PDX models with oncogenic alterations in RTK and PI3K pathways
- PIK3CA oncogenic mutations are not associated with strong activation of downstream pathway
- PTEN mutations and homozygous deletions have correlation with downstream pathway activation

ONCOGENIC AND TARGETABLE ALTERATIONS IN WNT/β-CATENIN AND SONIC HEDGEHOG PATHWAY IN PDX MODELS



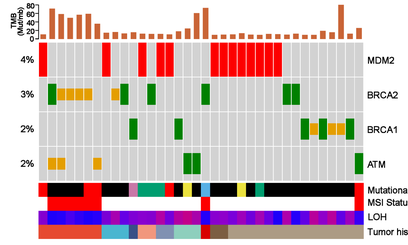
- 22% of the PDX models have oncogenic alterations in SHH and/or WNT pathways
- PDX models with PTCH1 mutations have higher EMT score and SHH gene-set enrichment scores

ONCOGENIC ALTERATIONS IN DNA DAMAGE REPAIR PATHWAYS IN PDX MODELS



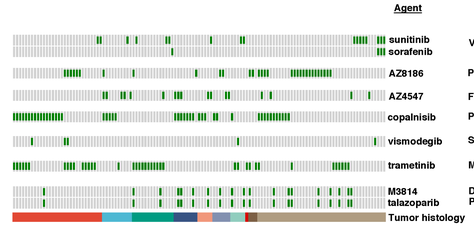
- 20% of the PDX models have oncogenic alterations in major DNA damage repair pathways
- Mutational signatures correlate well with clinical history, tumor histologies, mutational and MSI status
- In MSI-H PDX models, mutations in homologous recombination pathways don't correlate with either LOH status or relevant mutational signatures

TARGETABLE ALTERATIONS IN DNA DAMAGE REPAIR PATHWAYS IN PDX MODELS



- 11% of PDX models in PDMR may have targetable alterations in DNA damage repair pathway

PUTATIVE ACTIONABILITY IN PDMR MODELS FOR A SELECTED SET OF AGENTS



- PDMR models were queried for biomarkers for a selected set of agents
- These 9 agents represented activities across multiple signaling pathways
- We found 28% of the models may have at least one targetable biomarker for one of these agents

SUMMARY

- We have performed integrative analysis of signaling pathways in PDMR models using mutation, gene expression and proteomic datasets
- Gene expression and proteomic datasets allowed us to investigate downstream effects of signaling pathways
- PDX models in NCI PDMR exhibited activity in multiple signaling and DNA damage repair pathways
- Additional datasets generated from the PDMR models (e.g., mutational signatures, somatic tumor mutational burden, MSI status etc.) may be used to identify underlying biological processes and can be used for prioritizing preclinical study agents
- We have described therapeutically actionable biomarkers present in the genomically characterized PDX models
- This data suggest using PDMR models will be valuable for preclinical drug combination studies

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