Assessment of the Genomic Stability and Molecular Landscape of Patient-Derived Xenograft (PDX) Models from NCI's Patient-Derived Models Repository (PDMR)

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NATIONAL CANCER INSTITUTE PATIENT-DERIVED MODELS REPOSITORY

www.pdmr.cancer.gov

ABSTRACT

Background: Patient-derived xenografts (PDXs) are a powerful tool for cancer translational research. However, it is unclear if early passage PDXs faithfully recapitulate the molecular profiles of the corresponding patient tumors. The National Cancer Institute (NCI) has developed a Patient-Derived Models Repository (PDMR; www.pdmr.cancer.gov) of PDXs with clinical annotation and comprehensive genomic data. We used this data set, which represents 9 major tumor types and other rare histologies, to conduct an in-depth investigation of the genomic stability of PDXs with early passaging.

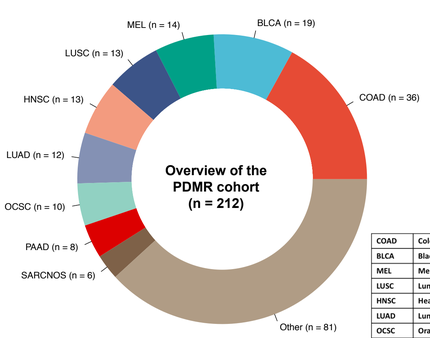
Methods: Tumors (biopsy or resection), including some from metastatic sites, were used to establish 218 PDX models from 212 patients. Whole Exome Sequencing and RNA-Seq were performed on 2-9 mice per model. Passages represented include the original clinical sample, P0, P1, P2, and less frequently > P2.

Results: By several metrics, genomic profiles of most PDMR models were stable at early passages: (1) transcriptome profiles of mice from different passages in a model were found to cluster together; (2) 75% of PDXs maintained similar copy number alteration profiles compared with the original clinical sample, with no significant differences between passages; (3) the allele frequency (AF) of clinically relevant mutations remained consistent across passages, with only 20% of models having > 15% AF range from the median. Moreover, genomic features of PDMR models were broadly comparable to those in large public patient data sets. For example, melanoma models had the highest tumor mutation burden and a 57% prevalence of BRAF V600X; 11% of colon adenocarcinoma models were MSI-H, with APC (65%), TP53 (67%) and KRAS (47%) being most frequently altered.

Conclusions: In this large and histologically diverse PDMR data set, PDXs exhibited genomic stability with early passages. The molecular landscape of PDMR models is faithfully comparable to large public patient data sets. As the PDMR collection expands additional in-depth analyses will be performed. The PDMR thus represents a valuable resource for researchers interested in pre-clinical drug or other 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

Clinical and pathological datasets:

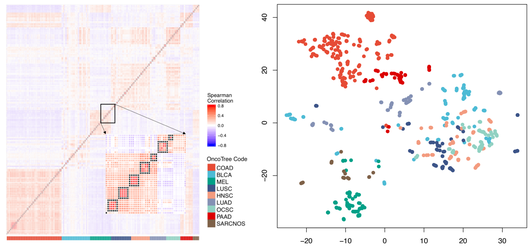
- Clinical annotation of donors
- Limited clinical history including previous treatment regimens
- Donor demographics including self-declared ethnicity, smoking history
- STR profile
- Histo-pathological annotations and images of individual PDX specimens

Genomic 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)

TRANSCRIPTOME PROFILES OF MICE FROM DIFFERENT PASSAGES WITHIN A PDX MODEL CLUSTER TOGETHER



- Pairwise Spearman correlation was conducted on gene expression profiles of PDX samples using TPM values
- Samples in several common disease types are shown
- Inset indicates specimens from 8 BLCA models
- Black boxes within the inset indicate specimens from the same model
- PDX samples were ordered by their disease types

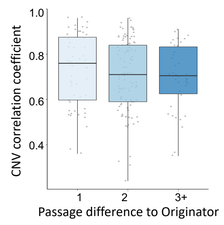
- t-SNE analysis of RNASeq gene expression data on all PDX samples show that PDX samples cluster to their own model and disease type

PDX MODELS MAINTAINED SIMILAR COPY NUMBER VARIANT (CNV) PROFILES WITH NO SIGNIFICANT DIFFERENCES BETWEEN PASSAGES

Approach
- Pearson correlation of CNA profiles was calculated between PDX samples and originator

Advantages
- No cutoff required
- Not sensitive to tumor cellularity.

Results
- ~75% of PDX models maintain similar CNV profiles between PDX samples and originator (Pearson correlation R > 0.6)
- No significant difference was observed among passages 1, 2 and 3+

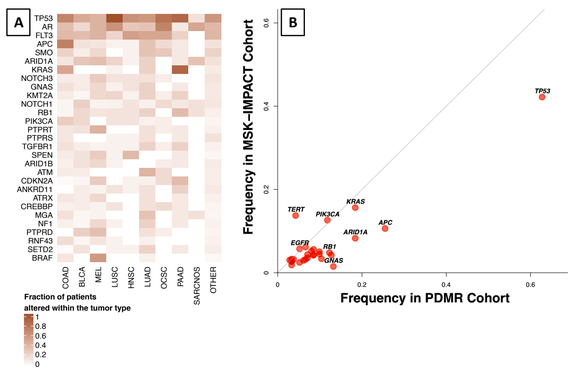


ALLELE FREQUENCIES OF CLINICALLY RELEVANT MUTATIONS REMAIN CONSISTENT ACROSS PASSAGES IN PDMR MODELS

		20% deviation from median VAF	10% deviation from median VAF
Gene	# Patients	# Outlier models	# outlier models
AKT	1	0	0
ALK	2	0	1
ATM	3	0	0
BRAF	15	1	4
CTNNB1	3	0	0
EGFR	3	0	0
ERBB2	3	0	0
FGFR3	4	1	1
HRAS	1	0	0
IDH1	4	1	2
KRAS	43	3	9
MAP2K1	2	0	0
MTOR	2	0	1
NRAS	8	2	2
PIK3CA	20	4	6
PTEN	1	0	0
TP53	15	0	1
Summary	132	9%	20%

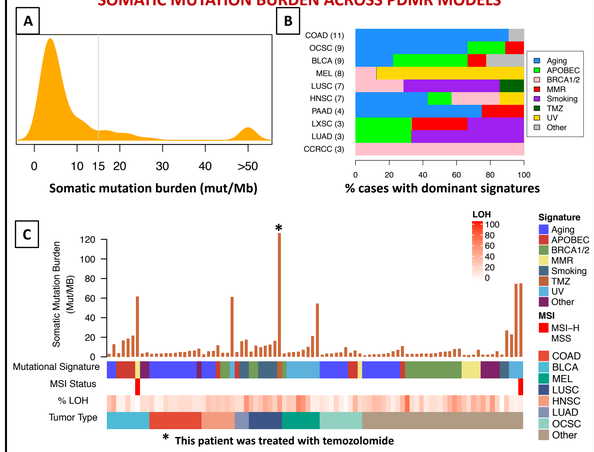
This analysis was performed on models which had above mentioned clinically relevant mutations.

FREQUENCY OF RECURRENTLY ALTERED GENES IS SIMILAR BETWEEN MSK-IMPACT AND PDMR COHORTS



Panel A: Most frequently altered genes in PDMR models.
Panel B: Frequency of recurrently altered genes between PDMR and MSK-IMPACT cohorts. The MSK-IMPACT cohort is metastatic disease cohort[1]. The PDMR cohort is a mixed population of donors with primary and metastatic disease.

CORRELATION OF MUTATIONAL SIGNATURES AND SOMATIC MUTATION BURDEN ACROSS PDMR MODELS

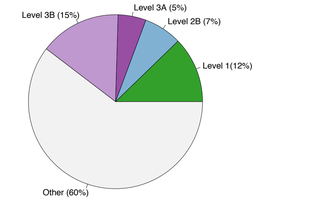


Panel A: Density plot of somatic mutational burden across PDMR models
Panel B: Dominant mutational signatures present in different histologies across PDMR models
Panel C: Distribution of somatic mutational burden, mutational signatures, MSI status, %LOH across PDMR models
Note: Data from 88 PDX models with germline DNA available was used in these panels

CLINICALLY ACTIONABLE MUTATIONS PRESENT ACROSS PDMR MODELS

OncoKB levels of evidence for clinical actionability[2]

Level 1	FDA-recognized biomarker for an FDA-approved drug in the same indication
Level 2A	Standard of care biomarker for an FDA-approved drug in the same indication
Level 2B	Standard of care biomarker for an FDA-approved drug in another indication
Level 3A	Compelling clinical evidence supporting the biomarker as being predictive of drug response in the same indication
Level 3B	Compelling clinical evidence supporting the biomarker as being predictive of drug response in another indication



SUMMARY

- PDXs exhibited genomic stability during early passages
- The genomic landscape of PDMR models is comparable to large public patient data sets
- Frequency of actionable variants in PDMR models is similar to other large public patient data sets
- 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 some models may be valuable for preclinical drug combination studies

REFERENCES

1. Zehir et al, Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients, Nature Medicine (2017), 23, 703–713
2. Chakravarty et al., OncoKB: A Precision Oncology Knowledge Base, JCO Precision Oncology (2017), 1, 1-16

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