Orthotopic patient-derived xenografts (O-PDX) are effective precision oncology models in predicting therapeutic response and acquired drug resistance

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ABSTRACT

Patient-derived xenografts are a functional test system in a living organism, making them the leading assay for precision oncology and drug development.[1,2] In vivo pharmacology studies are widely performed using subcutaneous implantation; however, due to significant changes in the tumor microenvironment, this methodology falls short of modeling the full complexities of human cancer. Recently evidence has shown different engraftment and growth rates and therapeutic responses if engrafted orthotopically (O-PDX).[3] In this study we sought to compare the differences in pharmacological response between a subcutaneous PDX and O-PDX and apply O-PDX to predict therapeutic response and acquired resistance to therapy.

METHODS

Patient biopsies were surgically implanted into subcutaneous and orthotopic sites of female NOG mice, and serially passaged orthotopically. Animals were imaged with the M3™ compact MRI from Aspect Imaging to monitor tumor growth. Drugs were formulated and administered per manufacturer's instructions or past publications. Tumors were formalin-fixed, paraffin embedded, sectioned, and stained with hematoxylin and eosin. Tissue slides were digitally scanned using the 3DHistech Panoramic Scan II. For RNAseq analysis, clean reads were aligned to the Ensembl Human GRCh38 genome using STAR/RSEM, and gene expression was quantified using Transcripts Per Kilobase Million (TPM). Statistical analysis was performed with log2-transformed TPM data, and genes with p-values <= 0.025, and absolute fold changes >=0.75 were considered to have significant changes in mRNA expression between subcutaneous implantation and orthotopic implantation. Pathway analysis was conducted with DAVID Bioinformatics Resources 6.8 using Gene Ontology.

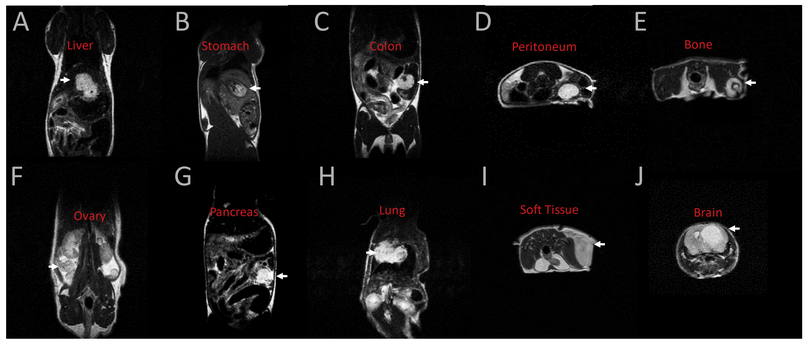

Figure 1. O-PDX implantation visualized by MRI. White arrow indicate tumor. A. Metastatic colorectal adenocarcinoma. B. Gastric adenocarcinoma. C. Colorectal adenocarcinoma. D. Liposarcoma. E. Osteosarcoma. F. Ovarian carcinoma. G. Pancreatic ductal adenocarcinoma. H. Lung adenocarcinoma. I. Myxofibrosarcoma. J. Glioblastoma multiforme.

RESULTS

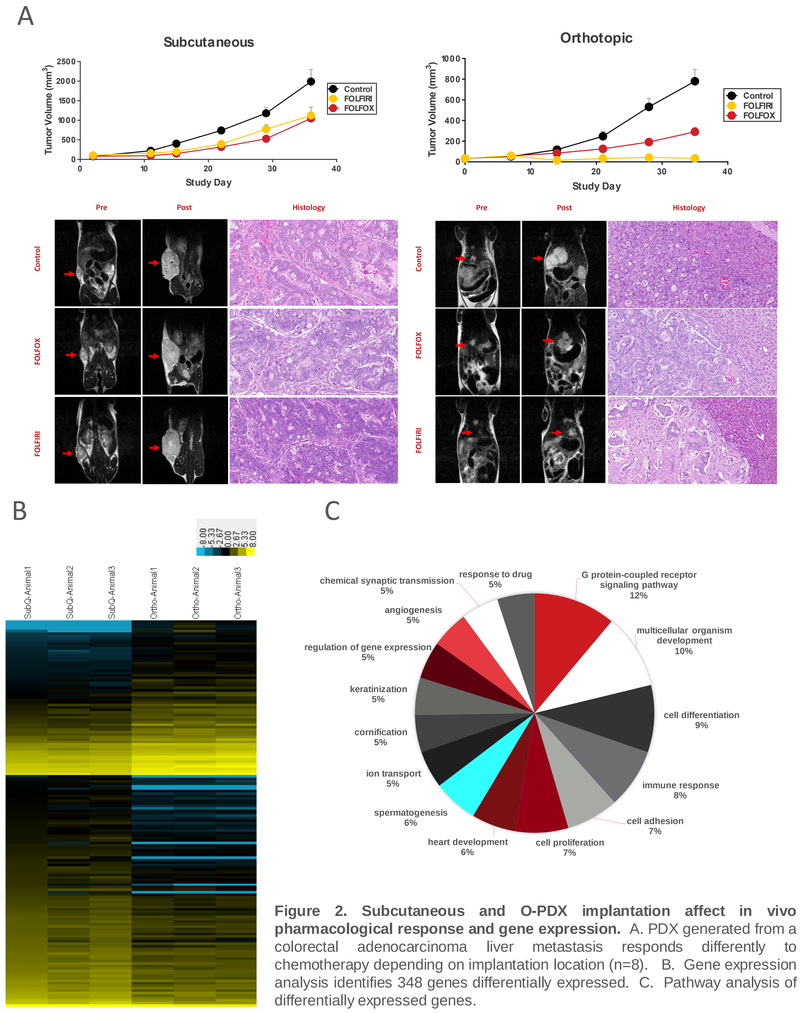

Figure 2. Subcutaneous and O-PDX implantation affect in vivo pharmacological response and gene expression. A. PDX generated from a colorectal adenocarcinoma liver metastasis responds differently to chemotherapy depending on implantation location (n=8). B. Gene expression analysis identifies 348 genes differentially expressed. C. Pathway analysis of differentially expressed genes.

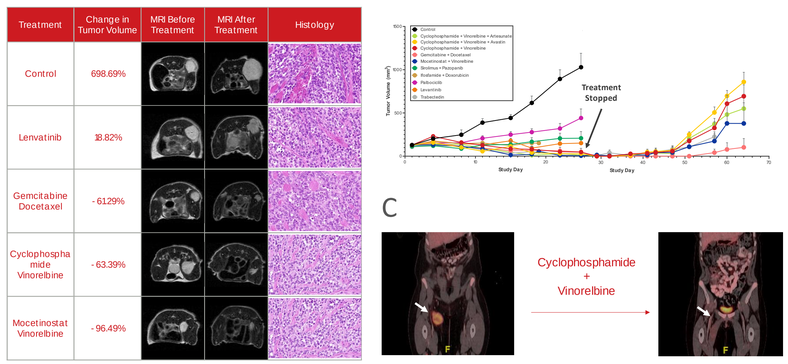

Figure 3. Individualized testing in a pediatric rhabdomyosarcoma O-PDX model identifies promising therapies. A. Summary of results. B. Tumor volumes over time indicated the best therapies and show tumor recurrence upon treatment discontinuation (n=8). C. PET scan of patient showing no evidence of disease after 4 months of treatment (white arrow), demonstrating concordance with O-PDX study.

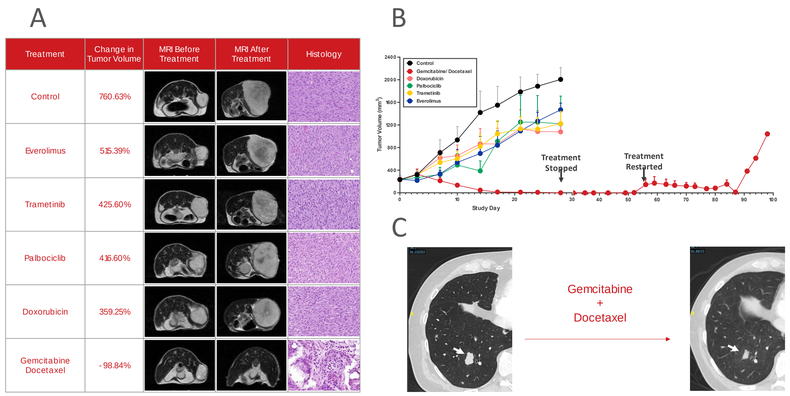

Figure 4. Individualized testing on a recurrent metastatic cancer identifies a promising therapy and predicts acquired resistance. A. Summary of results. B. Tumor volumes over time reveal the best therapies and show tumor recurrence upon treatment discontinuation (n=5). Tumors grew during retreatment, indicating tumors acquired resistance to the therapy. C. CT scan of patient showing stable disease after 5 cycles of treatment (white arrow), demonstrating concordance with O-PDX study.

CONCLUSIONS

O-PDX implantation affects in vivo pharmacological response and gene expression. O-PDX models can predict effective treatment strategies for individual patients and forecast tumor recurrence after therapy. Furthermore, we use this approach to develop in-vivo models of acquired drug resistance to strategize future treatment options and aid in drug development.

CITATIONS AND ACKNOWLEDGMENTS

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