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Abstract:
Hepatoblastoma (HB) is the main pediatric liver tumor with limited treatment options for more aggressive types. The current lack of suitable HB models compromises its investigation. Here we describe the development of patient-derived organoids as a novel tool to explore HB molecular mechanisms and to design new therapeutic approaches.

Primary tumor (T) and non-tumor (NT) tissues collected from Spanish hospitals were used to generate organoids. Organoids were characterized by: CTNNB1 mutation; immunofluorescence; total- and small-RNA transcriptomic profiles; mouse NSG subcutaneous injection; drug response.

We have developed 14 T and 17 NT organoids from 27 patients, which showed patient-specific morphology and maintained the CTNNB1 mutation of the primary tumor. T organoids showed

nuclei β-catenin, increased expression of progenitor (LGR5, Sox9) and HB (DLK1, AFP) markers and lower hepatocyte (HNF4a, CYP2E1) markers. Transcriptomic profiling confirmed that HB organoids mimicked the gene expression profile of the tumor tissue of origin. Enrichment analysis identified conserved pathways between T tissues and T organoids, which differed from NT samples. Notably, pathways involved in epigenetic modification, proliferation, WNT activation and altered metabolism were found altered in T organoids. Subcutaneous injection of T organoids confirms their tumorigenic potential with different HB-like histology. Finally, drug assay with 4 chemotherapeutic agents revealed organoid-specific drug response.

We have developed a new patient-derived ex vivo 3D system based on organoid cultures that recapitulate HB molecular features. This reliable model provides an extremely useful tool to test novel drugs to move forward to personalized treatments.