

New Technologies - Bioengineering II

Hepatic organoids for cancer risk prediction

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Major genomic drivers of hepatocellular carcinoma (HCC) are nowadays well recognized, although models to establish their roles in cancer initiation remain scarce. Here, we used liver organoids that were directly generated from human liver tissues in experiments to mimic the early steps of carcinogenesis from the genetic lesions of TP53 loss and L3 loop R249S mutation. In addition, we used ChIP-seq results to shed important functional insights into the consequential loss of tumor suppressive function from TP53 deficiency and gain-of-function activities from mutant p53. CRISPR knockout of TP53 in liver organoids demonstrated tumor-like morphological changes, increased in stemness and unrestricted in-vitro propagation. Overexpression of mutant R249S in TP53 knockout organoids further showed spontaneous increase in tumorigenic potentials and bona fide HCC histology in xenotransplants. Our ChIP-seq analysis underscored gain-of-function properties from L3 loop p53 mutants in chromatin remodeling and overcoming extrinsic stress. More importantly, direct transcriptional activation of PSMF1 by mutant R249S could increase organoid resistance to ER stress, which was readily abrogated by PSMF1 knockdown in rescue experiments. In conclusion, we showed liver organoids can recapitulate cancer supporting phenotypes ex-vivo. Furthermore, differential tumorigenic effects from TP53 loss and L3 mutations, together highlight pro-tumoral changes and early clonal advantages that provided normal hepatocytes with survival signals.