Abstract:

Hepatoblastoma (HB) is the most common childhood liver cancer and occasionally presents with histological and clinical features reminiscent of hepatocellular carcinoma (HCC). Identification of molecular mechanisms that drive the neoplastic continuation towards more aggressive HCC phenotypes may help to guide the new stage of targeted therapies. We performed comprehensive studies on genetic and chromosomal alterations as well as candidate gene function and their clinical relevance. Whole-exome sequencing identified HB as a genetically very simple tumour (2.9 mutations per tumour) with recurrent mutations in β-catenin (CTNNB1) (12/15 cases) and the transcription factor NFE2L2 (2/15 cases). Their HCC-like progenies share the common CTNNB1 mutation, but additionally exhibit a significantly increased mutation number and chromosomal instability due to deletions of the genome guardians RAD17 and TP53, accompanied by telomerase reverse-transcriptase (TERT) promoter mutations. Targeted genotyping of 33 primary tumours and cell lines revealed CTNNB1, NFE2L2, and TERT mutations in 72.5%, 9.8%, and 5.9% of cases, respectively. All NFE2L2 mutations affected residues of the NFE2L2 protein that are...
recognized by the KEAP1/CUL3 complex for proteasomal degradation. Consequently, cells transfected with mutant NFE2L2 were insensitive to KEAP1-mediated downregulation of NFE2L2 signalling. Clinically, overexpression of the NFE2L2 target gene NQO1 in tumours was significantly associated with metastasis, vascular invasion, the adverse prognostic C2 gene signature, as well as poor outcome. Our study demonstrates the importance of CTNNB1 mutations and NFE2L2-KEAP1 pathway activation in HB development and defines loss of genomic stability and TERT promoter mutations as prominent characteristics of aggressive HB with HCC features.