correlates with poor outcome in HCC patients and more aggressive phenotype and function of HCC cells.

**P64**

**THE ULTRACONSERVED NON CODING RNA UC.158 IS DOWNSTREAM OF THE WNT/β-CATENIN PATHWAY IN LIVER CANCERS**


**Background and Aims:** We aimed at investigating the effect of the Wnt/β-catenin signalling on Transcribed-Ultranscribed-Regions (T-UCR), a class of 481 non-coding-RNAs, which are identical across the genome of human mouse and rat and play a role in carcinogenesis. These may be explored as therapeutic targets.

**Methods:** APC<sup>−/−</sup> mice develop Wnt/β-catenin dependent HCC. Expression of T-UCR was assessed by microarray-analysis with sense and antisense probes, and by specific real-time-PCR.

**Results:** Twenty-two T-UCRs were aberrantly expressed, with 4 up- and 18 down-regulated >2 fold in tumour tissues from APC<sup>−/−</sup> mice compared to normal liver from WT. Over-expression of uc.158 could differentiate APC<sup>−/−</sup>-HCC from DEN-induced-HCC. uc.158 is over-expressed in HepG2 vs Huh7 and in HSC vs normal hepatocytes, in line with the activation of the Wnt pathway. Treatment with Lithium-Chloride that increased nuclear localization of β-catenin increased uc.158 in Huh-7 cells. Uc.158 was reduced after inhibition of β-catenin by siRNA or ICG-001 in HepG2. Uc.158 expression was not increased in PLC/PRF-5 cells (AXIN1-mutated), as well as no differences were observed between the liver of AXIN1<sup>−/−</sup> and WT mice, in line with the absence of β-catenin activation in these tumours. Recent findings suggest that Wnt/β-cat pathway is activated in cholangiocarcinoma (CCA). We found increased expression of uc.158 in human CCA. Tumour tissue from rat model of thioacetamide-induced CCA expressed uc.158, which was reduced after in vivo treatment with ICG-001 or C59 (Wnt/β-catenin inhibitors).

**Conclusions:** uc.158 is activated by Wnt/β-catenin pathway in primary liver cancers across three species and may represent a promising target for developing novel therapeutics in a subset of cancers.

**P65**

**MUTATION SPECTRUM ASSOCIATED WITH THE PROGRESSION OF HBV-RELATED HEPATOCELLULAR CARCINOMA**

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**Background and Aims:** Recent advance of sequencing technology has revealed genome-wide mutation profiles in numerous cancer types. However, its heterogeneous landscape of somatic mutations associated with the progression of liver cancer is not fully understood.

**Methods:** We profiled mutation spectrum of whole-exome in 12 cases of Hepatitis B-related hepatocellular carcinoma (HCC) and paired non-tumoral adjacent liver tissues with heterogeneous differentiation status. Tumor-specific variations (TSV) and 535 non-tumor-specific variations (NSV) were profiled in the early and advanced HCC, respectively.

**Results:** Enriched cancer-specific mutations at chromosome 1q were observed in the advanced HCC compared to those in the early HCC. Functional difference of the mutation spectrum was also identified between early and advanced HCC. The early HCCs were frequently mutated in the genes related to immune-related and protein transport functions, while the advanced HCC had mutations in proliferation-related genes.

**Conclusions:** This suggests the differential mutations in gene functions may contribute to the heterogeneous progression of HCC. Our whole-exome sequencing analysis revealed mutation profiles which might be associated with the heterogeneous progression of HCC.

**P66**

**IMPDH2-TARGETED CONSTRAINT OF CELL GROWTH IN HEPATOCellular CARCINOMA BY MYCOPHENOLIC ACID**

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**Background and Aims:** Immunosuppressants have significant impact on hepatocellular carcinoma (HCC) recurrence after liver transplantation. This study evaluated the effects and mechanism-of-action of mycophenolic acid (MPA), an immunosuppressant commonly used after liver transplantation, in experimental HCC models.

**Methods:** Five HCC cell lines and nude mice with partial immunodeficiency were used.

**Results:** With clinically achievable concentrations, MPA potently inhibited cell proliferation in five HCC cell lines determined by the MTT assay. Flowcytometric analysis showed induction of apoptosis in 54%±2.8% (n=3) cells after treatment with 20μg/ml MPA for 5 days. In colony formation assays, MPA profoundly suppressed the number and size of formed colonies by treatment with only 1μg/ml MPA, whereas colony formation was completely prevented by higher concentrations. Cell cycle analysis demonstrated that MPA arrested a considerable portion (22%±3%, at 5 μg/ml) of HCC cells in the G0/G1 phase. Ectopic over-expression of IMPDH2 that lacks the binding site of MPA but retains its enzyme activity resulted in complete resistance to MPA. In nude mice subcutaneously engrafted with a HCC cell line, MPA significantly delayed tumor formation. Low dose (60mg/kg) of MPA slightly promoted tumor growth (conceivably due to immunosuppression) but a high dose (250mg/kg) constrained tumor growth, compared with PBS treated mice.

**Conclusions:** MPA can specifically inhibit HCC cell growth by targeting IMPDH2. Besides immunosuppression-mediated tumor promotion which is observed with virtually all types of immunosuppressants, MPA can on the other hand specifically constrain HCC growth in mice. Clinical studies are encouraged to further validate in patients.