not express RBMY, a marked immune-positive signal of RBMY was identified upon metastasis. Importantly, HCC patients harboring cytoplasmic RBMY generally showed early metastasis (<15 months after primary tumor resection; $p<0.001$). **Conclusion:** RBMY is a novel oncoprotein. Its regulatory roles in facilitating malignant hepatic stemness and tumor metastasis are identified in this study. Because of its absence from normal human tissues except testis, RBMY represents a feasible therapeutic target for the selective eradication of HCC cells in male patients.

Su1461

CIRCULAR RNA SLC3A2 PROMOTES HEPATOCELLULAR CARCINOMA GROWTH AND INVASION BY SPONGING MIR-490-3P AND UPREGULATING PPM1F/AKT/GSK3/β-CATENIN SIGNALING PATHWAY

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Background: Non-coding RNAs (ncRNAs) have been shown to regulate gene expression involved in tumor progression of multiple malignancies. Previous studies indicated that protein phosphatase Mg2+/Mn2+ dependent 1F (PPM1F) plays a critical role in cancer metastasis. But, the underlying mechanisms by which ncRNAs modulate PPM1F expression in hepatocellular carcinoma (HCC) remain undetermined. **Methods:** The association between PPM1F and has-miR-490-3p (miR-490) expression and the clinicopathological characteristics and prognosis of HCC patients was analyzed by TCGA RNA-sequencing data. A novel circular RNA SLC3A2 (circSLC3A2) was identified to sponge miR-490 by circRNA expression profile and bioinformatic analysis. The binding site of miR-490 with PPM1F or circSLC3A2 was validated by dual luciferase assay and RNA immunoprecipitation (RIP) assay. The expression and localization of circSLC3A2 in HCC tissue cells were investigated by fluorescence in situ hybridization (FISH). MTT, colony formation, Wound healing and Transwell assays were performed to assess the effects of miR-490 or circSLC3A2 on cell proliferation and invasion, and Western blotting analysis was conducted to evaluate their effects on PPM1F mediated AKT/GSK3/β-catenin signaling pathway. **Results:** Decreased miR-490 expression or increased PPM1F expression was correlated with unfavorable prognosis of HCC patients. Ectopic expression of miR-490 inhibited proliferation and invasion of HCC cells by targeting PPM1F gene, while knockdown of miR-490 reversed these effects. Furthermore, circSLC3A2 was mainly localized in the cytoplasm and promoted biological behaviors of HCC cells by sponging miR-490 and upregulating PPM1F mediated AKT/GSK3/ β-catenin signaling pathway. The expression of circSLC3A2 was upregulated in HCC tissues and represented an independent prognostic factor for overall survival of HCC patients. **Conclusion:** CircSLC3A2 may act as an oncogenic factor and a potential biomarker in HCC.

Su1462

TARGETED DELIVERY OF EPIGALLOCATECHIN GALLATE AND ANTI-MIR221 REGRESSED INTRAHEPATIC TUMORS IN ATHYMIC MICE

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Background and Aims: Hepatocellular carcinoma (HCC) is a primary malignant hepatic tumor and highly resistant to chemotherapy. Current treatment methods for HCC are not effective due to lack of efficient and targeted drug delivery. Here we employed milk-derived nanovesicles (MNV) for targeted delivery of anticancer agents, epigallocatechin gallate (EGCG) and anti-miR221 (microRNA 221) into intrahepatic tumors induced in athymic mice. ***Methods:*** Nanovesicles ranging from 100-200 nm were isolated from commercial skim milk using ultracentrifugation, purified, and characterized with nanoparticle tracking analysis (NTA). EGCG and anti-miR221 were introduced into MNVs using lipofectamine 2000, purified with ultracentrifugation, and further characterized. Intrahepatic tumors were induced in athymic nude mice with surgical implantation of PLC/PRF/5 HCC cells stably transfected with a mammalian expression vector carrying the luciferase gene. The animals that had uniform tumor development were injected through tail vein with either EGCG (10 µmoles/kg body weight) or anti-miR221 (500 nmoles/kg body weight) or both in combination thrice a week for four weeks. Tumor regression was monitored using in-vivo imaging system. ***Results:*** Fluorescent tracking of MNVs loaded with anticancer agents demonstrated targeted delivery into intrahepatic tumor cells. The widely opened blood stream and evasion of immunosurveillance of tumor cells facilitate transport of drug loaded MNVs into intrahepatic tumors. Significant decrease was observed in the amount photons and tumor size in the animals treated with both EGCG and anti-miR221. Combination treatment with both agents resulted in marked reduction of tumor regression and complete absence of metastasis. Furthermore, combination treatment produced synergistic effect and increased survival rate. ***Conclusions:*** The results of the present study demonstrated that MNVs can be effectively used for successful delivery of anticancer agents into intrahepatic tumors. Nanovesicle mediated targeted delivery of anticancer agents could be an efficient modality for the treatment of malignant HCC and might produce a great impact on anticancer therapy. ***Keywords:*** Extracellular vesicles, epigallocatechin gallate, EGCG, anti-miR221, targeted drug delivery, hepatocellular carcinoma

Su1463

ACID-SENSING ION CHANNEL 1 CONTRIBUTES TO ACID-INDUCED PROLIFERATION, MIGRATION, AND INVASION OF HEPATOCELLULAR CARCINOMA CELLS

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Background and Aims: Tumor microenvironment plays a key role in tumor malignance. It has been demonstrated that extracellular acidity in tumor cells contributes to malignant progression and metastatic dissemination of tumor. Acid-sensing ion channels (ASICs), which are proton-gated cation channels and can be activated by low extracellular pH, participate in pathogenesis of some tumors such as pancreatic cancer and gastric cancer. In this study, we investigated the role of ASIC in the progress of hepatocellular carcinoma (HCC). **Methods:** The proliferation and growth of HCC cells were evaluated by cell counting kit 8 (CCK8) and growth curve assay. The migration and invasion of HCC cells were determined by transwell assay. The growth and metastatic capacity of HCC cells *in vivo* were evaluated by murine hepatic orthotopic implantation and pulmonary metastatic model. **Results:** The mRNA and protein expressions of ASIC1 in human HCC tissues were markedly increased, which was mainly located in the membranes of HCC cells. The mRNA and protein expression levels of ASIC1 in human HCC cells, Huh7 and SK-Hep1, were markedly upregulated under low pH condition for 24 hours. Extracellular acidity could promote proliferation, migration and invasion of Huh7 and SK-Hep1 cells, and induce epithelial-to-mesenchymal transformation (EMT) of the HCC cells. ASIC1 inhibitor or ASIC1 shRNA inhibited the extracellular acidity-induced proliferation, migration, invasion, and EMT of Huh7 and SK-Hep1 cells. Moreover, extracellular acidity induced the increase of intracellular calcium ($[Ca^{2+}]i$) in HCC cells. ASIC1 inhibitor or ASIC1 shRNA inhibited the extracellular acidity-induced $[Ca^{2+}]i$ increase. Further results showed that intracellular Ca^{2+} chelator BAPTA-AM significantly repressed acidity-induced proliferation, migration, invasion, and EMT of HCC cells. ASIC1 shRNA in HCC cells significantly inhibited HCC cell growth in the liver and pulmonary metastasis in mice. ASIC1 expression level in human HCC tissues was positively correlated with the stage and prognosis of HCC **Conclusions:** ASIC1-mediated calcium signal mediates extracellular acidity-induced proliferation, migration and invasion of HCC cells, and promotes the progression of HCC, indicating that ASIC1 can be used as a prognostic marker and a therapeutic target for HCC.

Su1464

ACYL-COA DEHYDROGENASE 11 INHIBITION SUPPRESSES PROLIFERATION AND GROWTH OF HEPATOCELLULAR CARCINOMA CELLS

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Background & Aims: Acyl-CoA dehydrogenase 11 (ACAD11) is a newly identified long chain acyl-CoA dehydrogenase that catalyzes α, β-dehydrogenation of long chain acyl-CoA esters and participates in β-oxidation of long chain fatty acids. Recently, alteration of lipid metabolism has been increasingly recognized as a hallmark of cancer cells. It has been demonstrated that the reprogramming of lipid metabolism is critical for development and progression of hepatocellular carcinoma (HCC). Long-chain fatty acids are an important source of energy and precursors of various lipid species in cells, such as the phospholipids essential for biomembrane synthesis. In this study, we wonder whether ACAD11 participates in development and progression of HCC. **Methods**: The mRNA and protein expressions of ACAD11 in human HCC tissues were analyzed by real time PCR and western blot. The activity of ACAD11 in native human HCC cells was measure by electron transfer flavoprotein fluorescence reduction assay. The proliferation and growth of HCC cells were evaluated by cell counting kit 8 (CCK8), 5-Ethynyl-2'-deoxyuridine (EdU), growth curve assay, and hepatic orthotopic implantation model of nude mice. **Results**: The mRNA and protein expression levels of ACAD11 in human HCC tissues were markedly higher than those in pericancerous liver tissues. The activity of ACAD11 in native human HCC cells was also significantly increased. The inhibition of ACAD11 by shRNA suppressed the survival of HCC cells under glucose deprivation in vitro, the proliferation and growth of HCC cell in vitro and the growth of HCC cells in nude mice. On the other hand, overexpression of ACAD11 in HCC cells increased the survival of HCC cells and promoted the proliferation and growth of HCC cell. **Conclusions**: ACAD11 inhibition suppresses the proliferation and growth of hepatocellular carcinoma cells, implying that ACAD11 may serve as a new therapeutic target for the treatment of HCC. The further study for the mechanisms of ACAD11 alteration and action is necessary.

Su1465

THE ANTI-TUMOR EFFECTS OF A NOVEL MYD88 INHIBITOR TJ-M2010-5 ON HEPATOCELLULAR CARCINOMA GROWTH

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Objective: Compared with normal liver, MyD88 is highly expressed in hepatocellular carcinoma (HCC), promoting tumor proliferation and metastasis. In this study, we synthesized a novel MyD88 inhibitor, which is a small molecule derivative of aminothiazole, named as TJ-M2010-5 to explore its direct therapeutic effect on HCC. **Result:** We found that H22 cells have higher expression level of MyD88 than normal liver cells. In vivo, the tumor growth in the inhibitor group was significantly slower in intradermal tumor-bearing mice than that in the control group. TJ-M2010-5 was used to detect cell proliferation by CCK8 method at different concentrations. We revealed that TJ-M2010-5 inhibited the proliferation of H22 cells in a dose-dependent manner. To further elucidate the intrinsic mechanisms of TJ-M2010-5 on cell proliferation, we did cell cycle analyses and showed that G0/G1 phase H22 was 39.95% and 60.22% at the concentrations of 5 mmol/L and 10 mmol/L TJ-M2010-5 respectively, whereas the negative control group was 26.44%, indicating that TJ-M2010-5 could cause G0/G1 phase cell cycle arrest and thereby could inhibit the proliferation of H22 cells. Western blot analysis showed that TJ-M2010-5 downregulated the key factors involved in G1 to S phase transition, including cyclin D1, cyclin dependent kinases 6 (CDK6), cyclin E and CDK2. Our data also showed that TJ-M2010-5 led to decrease of both phosphor-MEK1/2 (Ser217/221) and phospho-Erk1/2 (Thr202/Tyr204) expression, suggesting that TJ-M2010-5 could modulate the Erk/MAPK signaling pathway which was recently found to be important for liver carcinogenesis. We observed a higher percentage of $F4/80^{+}CD11c^{+}$ macrophages in TJ-M2010-5-treated group than the control group. The peritoneal macrophages treated with 10 mmol/L of TJ-M2010-5 showed no significant difference in the percentage of F4/80+CD11c+ macrophages, suggesting that TJ-M2010-5 has no direct inhibitory effects on macrophages. However, the percentage of F4/80+CD11c+ macrophages was increased after they cultured with the supernatant of H22 cells treated with TJ-M2010-5. Interestingly, no difference was found in F4/80+CD206+ macrophages between two groups in this setting. We demonstrated that TJ-M2010-5 led to an increase in the proportion of M1 macrophages indirectly, while has no effect on M2 macrophages. These data confirmed the indirectly upregulation of M1 macrophages by TJ-M2010-5. **Conclusion:** In our study, we demonstrated the mechanisms by which TJ-M2010-5 inhibited the proliferation of HCC, including induction of G0/G1 phase cell cycle arrest through inhibition of Erk1/2 and MEK1/2 phosphorylation and recruitment of M1 macrophage into