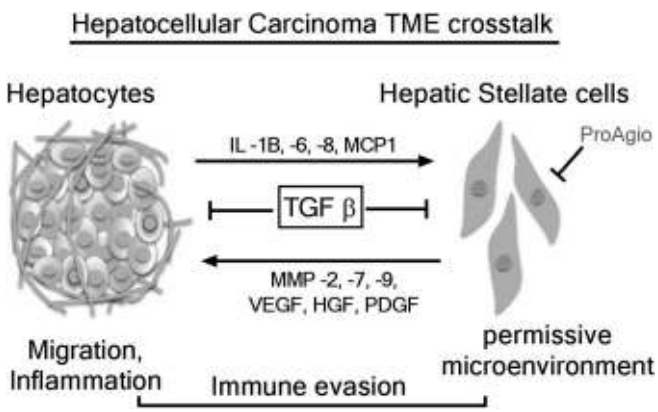
with doxorubicin significantly inhibits progression of HCC. **Methods:** B6C3F1/J mice were injected with 25mg/kg Diethylnitrosamine (DEN) intraperitoneally at 12 days of age. Mice were treated with vehicle, ProAgio (10mg/kg, i.p., 20 doses), and doxorubicin (3mg/kg, i.p., 8 doses weekly), or a combination of ProAgio and doxorubicin, all from 44 weeks of age. After 48 weeks, mice were sacrificed for gross anatomical and histological analysis. The survival benefit was also evaluated. Another *in vivo* experiment was performed with Hep G2 xenograft mouse model to evaluate the tumor growth upon treatment with vehicle, ProAgio, doxorubicin, and combination of ProAgio and doxorubicin. Hep G2 and Hep G2:LX2 (2×10^5) cells (1:1 ratio) were injected subcutaneously and the treatment was started when the average tumor size reached around 200 mm^3 in a xenograft model. **Results:** Our data demonstrate that ProAgio induces apoptosis of activated HSCs by recruiting caspase 8 to the intracellular domain of b_3. ProAgio and doxorubicin combination significantly reduced the tumor volume, number of HCC foci and prolonged the survival of DEN-induced HCC mice. IHC staining in the tumor treated with ProAgio and doxorubicin combination revealed a significant reduction in Ki67+ve cancer cells. In addition, ProAgio treated tumors demonstrated increased co-stain of cleaved caspase 3 (CC3) and a-SMA. Similar results were observed in Hep G2 xenograft experiment. Hep G2 in combination with LX2 promoted tumor growth compared to Hep G2 alone and treatment with ProAgio and combination therapy significantly inhibited the tumor growth. **Conclusion:** Elimination of activated HSCs by ProAgio inhibits HCC progression in mice and proliferation of cancer cells, potentially through modulation of the tumor microenvironment. Combination therapy of ProAgio and doxorubicin synergistically inhibits HCC progression and prolong survival of DEN-induced HCC mice. Our findings suggest that ProAgio may be a potential novel effective therapy for HCC.



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METABOLOMIC CHARACTERIZATION OF VERY EARLY HEPATOCELLULAR CARCINOMA IN CIRRHOTIC PATIENTS SUBMITTED FOR LIVER TRANSPLANTATION

Javier Bustamante[1], Enara Arretxe[2], Mikel Gastaca[3], Cristina Alonso[4], Maria Senosiain[1], Patricia Salvador[1], Patricia Ruiz Ordorica[3], Jose Ramón Fernández Ramos[1], Milagros Testillano Tarrero[1], Alberto Ventoso[3], Ibone Palomares[3], Mikel Prieto[3], Raquel Coya[5], Andres Valdivieso[3] and Maria Jesús Suarez Regueiro[1], (1)Hepatology and LT Unit, Cruces University Hospital, (2)OWL Metabolomics, (3)Liver Surgery and Transplant Unit, Cruces University Hospital, (4)OWL Metabolomics, Bizkaia Technology Park, Derio, Spain, (5) Basque Biobank

Background: Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide. Very Early HCC (BCLC 0: uninodular HCC ≤ 2 cm) is considered a distinct subgroup where truly curative therapies are possible. However, because of its asymptomatic nature and the limited performance of AFP and radiology, VE-HCC is unfrequently detected. Metabolomics, due to its ability to detect early molecular signatures of pathologic cellular processes, could be an innovative and non invasive approach to detect VE-HCC. **Methods:** 79 cirrhotics submitted for liver transplantation (43 with HCC and 36 without HCC) were prospectively studied. Sera samples obtained at the Liver Transplant Unit of Cruces University Hospital were received from Basque Biobank (Barakaldo, Spain), and classified according to HCC presence, staging and Child status. The metabolic profile was performed by ultra-high performance liquid chromatography coupled to mass spectrometry (UHPLC-MS) analysis of the chloroform/ methanol and methanol extracts obtained from sera samples extracted prior to transplantation. HCC characteristics and staging were confirmed on the explant; 3 patients with complete HCC postablation/postTACE necrosis were not considered for analysis. **Results:** 479 metabolic features were detected and included in the subsequent univariate and multivariate data analysis for the assessment of HCC characteristics (size, number of nodules, differentiation) and liver function. The circulating metabolome of HCC patients was altered when compared to cirrhotic patients without HCC, regardless of etiology. These changes included the increment of several amino acids, diglycerides, triglycerides, diacylglycerophosphatidylcholines, monoacylglycerophosphatidylcholines, ceramides and sphingomyelins in HCC patients, while some fatty acids and oxidized fatty acids were decreased. Patients with VE-HCC (uninodular ≤2 cm[n=14]) showed increased levels of several 1-ether, 2-acylglycerophosphocholines compared to the Early HCC group (uninodular >2cm uninodular/early multinodular [n=26]). No specific metabolomic profiles related to microvascular invasion or HCC differentiation have been identified, probably due to the small number of events. **Conclusion:** differential metabolomic profiles have been demonstrated in HCC vs. No-HCC cirrhotics. Additionally, a distinct metabolomic signature has been identified in VE-HCC vs. Early HCC. Although more studies are needed, this changes could represent a metabolic surrogate of the Very Early to Early HCC transition, which is associated with a higher recurrence risk.

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