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ATORVASTATIN AND RIFAXIMIN IN THYROID PREVENT LIVER THYROID METABOLISM ABNORMALITIES IN HEPATOCELLULAR CARCINOMA: IN VITRO AND IN VIVO STUDY

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Introduction and Objectives: Metabolic-associated steatotic liver disease (MASLD) is one of the leading causes of hepatocellular carcinoma (HCC) worldwide. We evaluated tumoral processes and thyroid metabolism alterations in experimental HCC.

Materials and Methods: Atorvastatin (AT) and Rifaximin (RIFA) were evaluated in vitro and in vivo. Huh7 cells were pretreated with AT (20μM) or RIFA (10μM), subsequently treated with endocrine disrupting tumor promoter (HCB5μM). Sprague-Dawley rats received diethylnitrosamine (135mg/l) in drinking water for 16 weeks, high-fat diet and AT (5mg/Kg) or RIFA (5ml/Kg).

Results: In vitro results revealed that HCB increased colony formation (39%), TGFB1 (45%), COX-2 (25%), cytochrome-c (35%) and caspase-3 (25%) compared to control (CON) - AT and RIFA prevent the increase. AT and RIFA also prevented T3 levels from decreasing. Animals showed 88% higher TGFB1 expression in tumoral areas compared with normal adjacent tissue. AT or RIFA diminished TGFB by 10 and 30% respectively. Fibrosis area was reduced with RIFA by 30%, compared to HCC. AT did not induce significant decrease. HIF1 augmented 200% in tumor areas while AT or RIFA diminished 75% and 50% respectively. DIO3 augmented by 50% in tumor and DIO1 expression did not change.

Conclusions: In conclusion, tumor growth and dedifferentiation seem to diminish with AT or RIFA in both models. Thyroid hormone metabolism changes in different forms: in cells, T3 seems to be altered by D1 and in animals by D3 alterations. These differences can be due to diverse stages of tumor growth and aggressiveness in the models.

Conflict of interest: None

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DIFFERENT LIPIDOMIC SIGNATURE IN EXTRACELLULAR VESICLES IN PATIENTS WITH MASLD- HCC: ANALYSIS OF DIFFERENT STAGES OF MASLD

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Introduction and Objectives: MASLD ranges from isolated steatosis (STE) to steatohepatitis (MASH), cirrhosis (CIR) and hepatocellular carcinoma (HCC). Non-invasive markers have limited ability to identify different stages. Extracellular vesicles (EVs) could be a useful tool. This study aims to evaluate EVs lipid signature in disease progression.

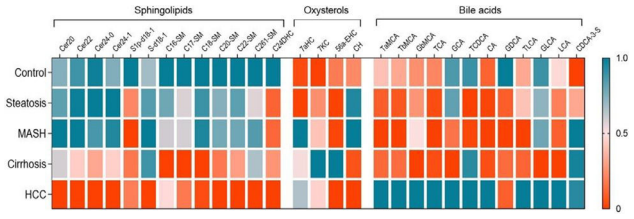
Patients and Methods: EVs were isolated from patients with STE (n=25), MASH without fibrosis (MASH; n=25), CIR (n=25) and HCC (n=18), and compared to controls (CON; n=25). Lipidomics was performed by mass spectrometric analysis of sphingolipids, oxysterols and bile acids.

Results: Figure 1 shows a heatmap of lipid profiles. C24DHC was lower in MASLD vs CON, suggesting early alterations in membrane lipid homeostasis. C18-SM, C20-SM, C22-SM and Cer24-0 decreased in CIR and HCC vs others, indicating progressive disruption of sphingolipid metabolism with progression. C17-SM and C261-SM were significantly reduced in HCC vs CON, reflecting extensive lipid remodeling in late-stage. 7KC levels were significantly increased in HCC vs others, consistent with enhanced oxidative stress specifically associated with hepatocarcinogenesis. Bile acids TCA and CA were higher in HCC vs others, pointing to dysregulation of bile acid pathways in late-stage disease. All differences, $p<0.05$.

Conclusions: Lipid composition of EVs may reflect key molecular changes during MASLD progression. The reduction of sphingolipids and accumulation of oxysterols and bile acids in advanced stages suggest disrupted lipid metabolism, oxidative stress, and hepatocellular dysfunction. These findings support the potential of EV lipidomics as a non-invasive tool for disease staging and mechanistic insight.

Conflict of interest: None

Lipidomics heatmap



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#121

NEW INSIGHTS INTO THYROID HORMONE METABOLISM AND AMMONIA DETOXIFICATION IN MASLD USING N-ACETYLCYSTEINE (NAC) AND L-ORNITHINE L-ASPARTATE (LOLA)

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Introduction and Objectives: Thyroid hormones (THs) are fundamental to liver physiology. TH dysfunction, particularly due to alterations in deiodinase enzymes such as D3, plays a critical role in the progression of MASLD. In MASLD, the Urea Cycle and Krebs Cycle shift

their enzymes to alternative pathways for ammonia detoxification, disrupting normal energy metabolism.

Materials and Methods: Adult male Sprague Dawley rats were randomly assigned to a control group on a standard diet (2.93 kcal/g, n=10), an intervention group on a high-fat diet deficient in choline (MASLD, HDCF, 4.3 kcal/g, n=10), and two treatment groups, MASLD +NAC (n=12) and MASLD+LOLA (n=12), over a period of 16 weeks.

Results: In MASLD, there was an increase in the expression of D3, colocalized with M1 macrophages and TR beta protein levels, while MCT8 levels remained unchanged. Additionally, mitochondrial respiration decreased, and no effects were observed with treatments. Furthermore, Glutamate Dehydrogenase (GDH) activity diminished, whereas α-Ketoglutarate Dehydrogenase (α-KGDH) activity increased. It was also determined that Grp78 (decreased by 74%) and Grp75 (increased by 60%) are regulated by T3 and are endoplasmic reticulum (ER) chaperones meaning ER stress.

Conclusions: Our study corroborates the interaction between TH metabolism and compensatory mechanisms that counteract elevated ammonia levels, as well as the enzymes regulating this process in MASLD. Both NAC and LOLA demonstrated potential in correcting TH metabolism and enhancing ammonia detoxification in MASLD, which may help alleviate symptoms or slow the progression of the disease.

Conflict of interest: None

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#128

EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS PREVIOUSLY TREATED WITH FIBRATES OR OBETICHOLIC ACID

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Introduction and Objectives: Seladelpar was evaluated as monotherapy or with ursodeoxycholic acid in RESPONSE (NCT04620733) among patients with primary biliary cholangitis. Patients completing RESPONSE could roll over into ASSURE (NCT03301506).

Here, we present 18-month (M) data (6M of ASSURE) in patients with or without prior use of fibrates or obeticholic acid (OCA) continuing into ASSURE from RESPONSE.

Patients and Methods: Patients received oral seladelpar 10 mg or placebo during RESPONSE, followed by open-label seladelpar in ASSURE. Fibrates/OCA were prohibited during RESPONSE. Analyses included patients with or without prior fibrates/OCA use, categorized by RESPONSE assignment: continuous seladelpar or crossover from placebo. Efficacy included the proportion of patients achieving a composite biochemical response (CBR; ALP $<1.67 \times$ ULN, ALP decrease $\geq$15%, and total bilirubin $\leq$ULN). Safety evaluations included adverse events (AEs).

Results: Among patients who continued into ASSURE from RESPONSE (n=158), 16 continuous seladelpar and 11 crossover patients reported prior use of fibrates/OCA (n=27; 17%); 88 continuous seladelpar and 43 crossover patients reported no prior use of fibrates/OCA (n=131; 83%). At 18M, 9/15 (60%) continuous seladelpar patients with prior fibrates/OCA use achieved a CBR vs 54/87 (62%) patients without prior fibrates/OCA use. Among crossover patients, 7/11 (64%) patients with prior fibrates/OCA use vs 32/41 (78%) patients without prior fibrates/OCA use achieved a CBR at 6M of ASSURE. From ASSURE initiation to 6M, AE incidence was similar across all patients, regardless of prior fibrates/OCA use; no treatment-related serious AEs were reported.

Conclusions: Interim results show seladelpar achieved comparable, sustained biochemical responses and favorable safety irrespective of prior fibrates/OCA use.

Conflict of interest: Yes, Gilead Sciences, Inc.

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EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND COMPENSATED CIRRHOSIS IN THE PHASE 3 PLACEBO-CONTROLLED RESPONSE TRIAL

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Introduction and Objectives: In the Phase 3 RESPONSE trial (NCT04620733), seladelpar, a first-in-class delpar (selective peroxisome proliferator–activated receptor delta agonist), significantly improved biomarkers of cholestasis in patients with primary biliary cholangitis (PBC) over 12 months vs placebo. More patients with cirrhosis met the primary endpoint in the seladelpar arm (39%) vs placebo (22%).

We now report data on additional biochemical results and safety in patients with or without cirrhosis in RESPONSE.

Patients and Methods: Eligible patients had an inadequate response or intolerance to ursodeoxycholic acid, alkaline