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

Bruno de Souza Basso[1],
Thaliane Carvalho de Oliveira[1],
Rachel Pinto Dornelles[1], Daiane Dias Cabeleira[1],
Elisa Carolina Lange[1], Cristiane Gisele Gomes[1],
Emanuela Tureta Cagnini[1], Luca Prá Scherer[1],
Henrique Mombach Barreto[1],
Leonardo Priesnitz Friedrich[1], Gustavo Santos Lucca[1],
Maria Alice Smielevski Gomes[1],
Carolina Fischer Nadvorny[1], Jessica Sindo[1],
Maria Ines Gonzales Solari[1],
Patricia Bencke Grudzinski[1], Laura Alvarez[2],
Ezequiel Ridruejo[3], Simone Macagnin Wajner[1],
Mario Reis Alvares-da-Silva[1]

[1] *Federal do Rio Grande do Sul. PO, Porto Alegre. Brasil*
[2] *Universidad de Buenos Aires. Buenos Aires. Argentina.*
[3] *CEMIC. Buenos Aires. Argentina.*

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

Mario Reis Alvares-da-Silva[1],
Melina Keingeski Belén[1], Larisse Longo[1],
Bruno de Souza Basso[1], Jose Tadeu Stefano[2],
Claudia Pinto Oliveira[2], Carolina Uribe-Cruz[3],
Juan Pablo Arab Verdugo[4]

[1] *Universidade Federal do Rio Grande do Sul. PO, Brasil.*
[2] *Universidade de São Paulo, Brasil.*
[3] *Universidad Católica de Misiones, Argentina.*
[4] *Virginia Commonwealth University, USA.*

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.

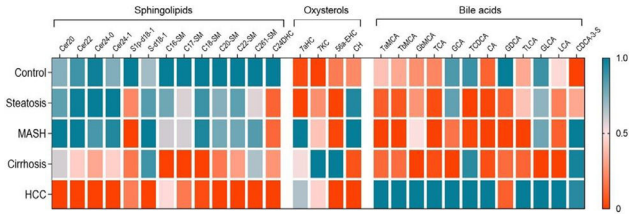
Patients and Methods: EVs were isolated from patients with STE (n=25), MASH without fibrosis (MASH; n=25), CIR (n=25) and HCC (n=18), and compared to controls (CON; n=25). Lipidomics was performed by mass spectrometric analysis of sphingolipids, oxysterols and bile acids.

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

Emanuela Tureta Cagnini[1], Bruno de Souza Basso[1],
Elisa Carolina Lange[1], Thaliane Carvalho de Oliveira[1],
Milla Paim Dreher[1], Daiane Dias Cabeleira[1],
Jessica Sindo[1], Maria Ines Gonzales Solari[1],
Rachel Pinto Dornelles[1], Simone Macagnin Wajner[1],
Mario Alvares-da-Silva Reis[1]

[1] *Universidade Federal do Rio Grande do Sul. PO, Brasil.*

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