pathogenesis, as confirmed by many studies

Conclusions: This novel homozygous ABCA1 mutation is associated with markedly decreased levels of HDL-C, plasma apoA-I as well as decreased total cellular cholesterol efflux and may play a role in the neurodegenerative condition which affect our proband. Its role in neurodegenerative disorders must be better understood.

P204 / #1056, Poster Topic: *AS02 LIPIDS AND LIPOPROTEINS / AS02.06 Cholesterol efflux and reverse cholesterol transport*

IDENTIFICATION OF NEW SIDE CHAIN OXIDIZED STEROLS AS NOVEL LIVER X RECEPTOR AGONISTS WITH THERAPEUTIC POTENTIAL IN THE TREATMENT OF CARDIOVASCULAR AND NEURODEGENERATIVE DISEASES

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Background and Aims: Nuclear liver X receptors (LXRα and β) may be potential therapeutic targets in cardiovascular and neurodegenerative diseases because of their key role in the regulation of lipid homeostasis and inflammatory processes. Among the mechanisms involved in the maintenance of macrophage cholesterol homeostasis, cholesterol efflux plays a crucial role. Specific oxy(phyto)sterols differentially modulate the transcriptional activity of LXRs, providing opportunities to develop new therapies. However, this development is precluded by unwanted side effects, such as hypertriglyceridemia and hepatic steatosis due to hepatic LXRα activation. The aim of this study was to investigate the effect of newly isolated oxyphytosterols from Sargassum Fusiforme and new synthesized side chain oxidized sterols analogs on cholesterol efflux and genes involved in this process.

Methods: Cellular cholesterol efflux was evaluated with a radioisotopic cell-based assay on human hepatocellular carcinoma cell line (HepG2) after treatment with n=5 new LXRα/β agonists at different concentration. Gene expression was assessed in HepG2 and in human astrocytoma cells (CCF-STTG1) by qPCR. T0901317 was used as positive control in all experimental evaluations.

Results: We identified two sidechain 24-oxidized sterols (S2 and S6) with a high potency for LXRα/β activation. In detail, S2 increased cholesterol efflux from HepG2 by 54.3%, 15.2%, and 24.5% in presence of isolated APOA-I and HDL, and human serum (as cholesterol acceptor), respectively, while S6 increased cholesterol efflux by 6.7% in presence of human serum. In addition, these sterols did not upregulate the expression of ABCA1 and ABCG1, but also, they didn't promote the expression of SREBF1, SCD1, FASN or ACC1 in HepG2 cells, avoiding unwanted side effects, which are usual for synthetic pan-LXR agonist. In CCF-STTG1 cells, S2 and S6 slightly increased APOE, ABCA1, and ABCG1 mRNA levels.

Conclusions: These results put the premises to identify and develop novels LXR-activating 24-oxidized sterols as potential therapeutic options in neurodegenerative and cardiovascular diseases.

P205 / #1386, Poster Topic: *AS02 LIPIDS AND LIPOPROTEINS / AS02.07 Lipidomics and metabolomics*

IDENTIFICATION OF A MOLECULAR SIGNATURE ASSOCIATED WITH COVID-19 SEVERITY USING A COMPREHENSIVE 1H-NMR SERUM METABOLOMICS PROFILING STRATEGY

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Background and Aims: Atherogenic dyslipidemia together with specific pro-inflammatory profiles have been identified as markers of severe adverse outcomes in COVID-19 disease. This study aims to evaluate nuclear magnetic resonance (NMR)-based metabolomics combined with machine learning algorithms as a strategy to identify a molecular signature associated with poor CoVID-19 prognosis.

Methods: This is a propensity risk score designed study involving a multicentric Spanish COVID-19 cohort comprising 1,280 hospitalized patients. Serum samples were collected upon hospitalization, and demographic and clinical data, including a binary classification of outcomes (severe or moderate), were recorded. A total of 318 COVID-19 patients with severe outcomes were matched 1:1 to moderate outcome patients based on age, sex, obesity, type 2 diabetes, and hypertension. NMR-based serum metabolomic analysis was conducted to characterize lipoprotein and glycoprotein profiles, the aqueous metabolome, and various lipid species. Machine learning models were trained to identify a molecular signature associated with severe outcomes.

Results: Multivariate models were explored classifying COVID severity from basal serum. Independently-validated Random Forest modelling demonstrated the highest performance in severity classification (area under the ROC curve: 0.87, 95% CI: 0.81–0.92). The selected variables for building the model were related to triglyceride metabolism, including VLDL and IDL composition, HDL-TG composition, and inflammatory-related glycoprotein parameters.

Conclusions: NMR successfully identified a molecular signature associated with COVID severity, characterized by increased triglyceride-rich particles and altered HDL composition beyond traditional factors. Metabolomic profiling describing the nature of COVID-19 demonstrated that early blood molecular changes induced by SARS-CoV-2 infection are associated with future COVID-19 severity.

P206 / #1587, Poster Topic: *AS02 LIPIDS AND LIPOPROTEINS / AS02.07 Lipidomics and metabolomics*

CHANGES IN THE HDL LIPIDOME ARE ASSOCIATED WITH THE PROGRESSION OF DIABETIC KIDNEY DISEASE

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Background and Aims: Changes in the composition and function of HDL play a role in the progression of diabetic kidney disease (DKD) and contribute to cardiovascular risk in type 2 diabetes mellitus (DM2). This study aimed to examine the HDL lipidome in individuals with DKD compared to healthy controls.

Methods: Fifty-five individuals with DM2 were classified based on their estimated glomerular filtration rate (eGFR, ml/min/1.73m^2) into stages 1 (eGFR≥90; n=4), 2 (eGFR=60-89; n=5), 3A (eGFR=45-59; n=14), 3B (eGFR=30-44; n=14), 4 (eGFR=15-29; n=13), and 5 (eGFR≤15; n=6). They were age and sex-matched with control (C) subjects (eGFR> 60; n = 7). All participants have provided written informed consent. HDL was isolated from plasma using discontinuous density gradient ultracentrifugation. Untargeted lipidomic analysis of HDL was performed using high-performance liquid chromatography coupled with mass spectrometry. Comparisons were made using one-way ANOVA or Student's t-test considering $p < 0.05$.

Results: Glycated hemoglobin, plasma total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol were similar among the groups. HDL from all groups showed 408 lipid species, with 104 of them significantly altered among groups. As compared to C, early DKD stages (1, 2, and 3A) exhibited a reduction in cholesterol ester (CE) concentrations (ranging from 1.32 to 2.81 times), while advanced stages (3B, 4, and 5) demonstrated decreased levels of phosphatidylcholine (1.55 to 1.97), sphingomyelin (1.77 to 2.13), lysophosphatidylcholine (1.68 to 1.92), and prenols (coenzyme Q10 and vitamin E; 2.09 to 2.67).

Conclusions: DKD progression is linked to remodeling in HDL lipidome, with lower CE core in early stages and reduction in several surface lipids in advanced stages. Structural changes in HDL particles may impact their functionality, thereby contributing to cardiovascular risk in DKD.The findings are original and encompass information acquired after the initial congress deadline, with no prior publication elsewhere.