genes (including TBX5, GATA5, and NKX2-5) in both animal models of CAVD. In our *in vitro* system, high glucose treatment did not affect calcium deposition, while it modified osteogenic markers and significantly downregulated cardioprotective genes.
Conclusions: Diabetogenic diet induces inflammatory and immune processes, accelerating early progression of CAVD. Moreover, hyperglycemic conditions downregulate cardioprotective genes in both our *in vivo* and *in vitro* systems. These preliminary findings give new insights on the pathophysiology of diabetic CAVD and may lead to the discovery of novel therapeutic targets.

SS090 / #964, SAAG SESSION 14: NAFLD AND DIABETES, 22-05-2023 2:20 PM - 3:20 PM.
ROLE OF OPA1-MEDIATED MITOCHONDRIAL DYNAMICS IN KUPFFER CELLS ON SYSTEMIC METABOLISM

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Background and Aims: Kupffer Cells are resident macrophages that are essential for liver pathophysiology as they play a crucial role in the innate immune response. OPA1 (Optic Atrophy 1) is a dynamin-related protein located in the inner mitochondrial membrane with a pro-fusion activity that modulates mitochondrial dynamic controlling oxidative phosphorylation. Since mitochondria are pivotal for physiological energy demand by KCs, this project aims to study the role of mitochondrial dynamic within these cells and its impact on systemic lipid metabolism exploiting mice selectively lacking OPA1 in KCs.
Methods: Mice C57BL/6J OPA1 Flox/Flox Clec4F-Cre+ and control Cre- littermates (N=7:7) were fed with Chow or High Fat Diet (HFD) for 20 weeks. The metabolic phenotype was assessed by indirect calorimetry through metabolic cages. Blood and liver were collected for immunophenotyping by flow cytometry analysis and for total lipids dosages. Liver histology was characterized with tissue stainings. Statistical significance was assessed through Unpaired T-test.
Results: OPA1 Flox/Flox Clec4F-Cre+ showed less energy expenditure (-9.44%; $p<0.05$), less O_2 consumption (-9.44%; $p<0.05$), less CO_2 production (-9,48%; $p<0.01$), despite an increase in movement (+26.6%) compared to Cre- control mice under ChowD; no differences were reported under HFD. Systemic immune profile was similar, while the percentage of KCs in the liver was reduced in Cre+ mice (-25% $p<0.05$). No significant differences in cholesterol and triglycerides levels were observed as well as in liver histology, glucose and insulin sensitivity tests under ChowD or HFD.
Conclusions: Our data suggest that OPA1-mediated mitochondrial function in KCs differently impacts systemic metabolic response to Chow or HFD feeding.

SS091 / #521, SAAG SESSION 14: NAFLD AND DIABETES, 22-05-2023 2:20 PM - 3:20 PM.
AN INTEGRATED UNDERSTANDING OF THE METABOLIC BENEFITS OF A NOVEL DOUBLE-TARGETED GENETICALLY ENGINEERED PROBIOTIC EXPRESSING ALDAFERMIN INTERVENTION WITH DIETARY CHANGE ON NAFLD

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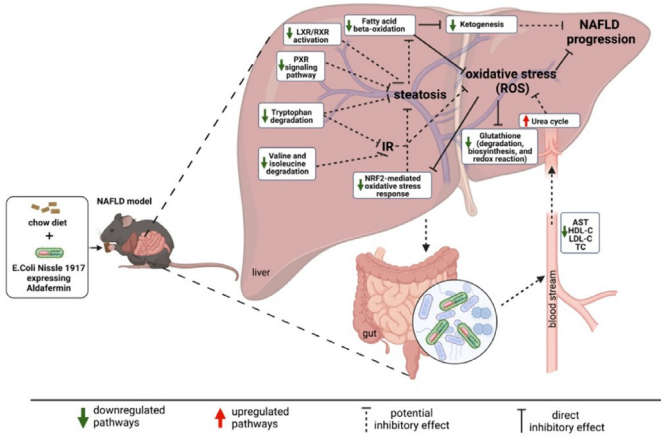
Background and Aims: Lifestyle changes toward a healthy diet and increased physical activity are the cornerstone interventions in the treatment of non-alcoholic fatty liver disease (NAFLD), the most common liver disease worldwide. However, due to its increased prevalence, new therapeutic approaches targeting the gut-liver-axis such as the use of microbial therapeutics and gut-hormonal interventions have been suggested.
Methods: The present study introduces a seven-week double-targeted intervention using the probiotic *Escherichia coli* Nissle 1917 genetically engineered to continuously express aldafermin (a non-tumorigenic analog of a human intestinal peptide hormone, fibroblast growth factor 19) along with dietary change (EcNA). The safety, efficacy, and mechanisms of action of the EcNA intervention were demonstrated using a high-fat-diet-induced NAFLD mouse model.
Results: The beneficial effects of the EcNA intervention were evidenced by the decrease in body weight, liver steatosis, and plasma concentrations of aspartate aminotransferase and cholesterol. Comprehensive integrated transcriptomics and non-targeted metabolomic analyses further revealed alterations in NAFLD-related genes and metabolites along with a switch in pathways related to the amino acid and lipid metabolism. Key alterations in gut microbial metabolism and associated receptor-signaling pathways were also observed.



Conclusions: These results suggest the potential efficacy of EcNA in ameliorating NAFLD by decreasing insulin resistance, steatosis, and oxidative stress; and highlight the potential of exploring multi-targeted interventions combining microbial therapeutics with the diet for NAFLD.

SS092 / #786, SAAG SESSION 14: NAFLD AND DIABETES, 22-05-2023 2:20 PM - 3:20 PM.
GLUCOKINASE REGULATORY PROTEIN (GCKR) IN MEDIATING THE GENETIC RISK OF NAFLD

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Background and Aims: Glucokinase regulatory protein (GCKR) is one of the most pleiotropic loci of the human genome, and is associated with T2D, NAFLD, and CAD, along with associations to blood level of lipids, lipoproteins, carbohydrates, and amino acids. Altered *GCKR* expression through CRISPR perturbation of rs780094 enhancer demonstrated a broad trans-effect on gene expression that includes genes involved in the control of carbohydrate metabolism. Prominently involved in this trans-effect are also genes that regulate cholesterol synthesis and lipoprotein uptake/secretion by the liver. In this study we try to address the current knowledge gap in understanding the functional bases for GCKR associations by studying the cellular, tissue specific and systemic effects of GCKR deficiency in mouse.
Methods: We developed a transient *GCKR* knock-down mouse model using antisense oligonucleotides (ASOs) wherein two candidate ASOs were administered for 6 weeks under specific diet. With the help of this model we try to address our aims, primarily by functional characterization of the mouse model using liver phenotyping, RNA-seq, metabolomics and histopathology.