A Multi-Omics Approach Demonstrates that Spaceflight Leads to Lipid Accumulation in Mouse Livers

Afshin Beheshti, PhD
Bioinformatician at GeneLab
Principal Investigator
Space Biosciences Division, KBRWyle
NASA Ames Research Center, Moffett Field, CA
Adjunct Assistant Professor at Department of Medicine
Rutgers Robert Wood Johnson Medical School
Visiting Researcher at Broad Institute
Cambridge, MA

afshin.beheshti@nasa.gov
abehesht@broadinstitute.org
One thing is always missing: **LIVER** as organ of interest for spaceflight related health risks!!

Select health effects due to space radiation exposures.
Welcome to NASA GeneLab - the first comprehensive space-related omics database; users can upload, download, share, store, and analyze spaceflight and spaceflight-relevant data from experiments using model organisms.
Overview of the Project

International Space Station (ISS) Missions

Liver after Spaceflight
- Lipid Metabolism
- Fatty Acid Metabolism
- NAFLD

Lipid Accumulation

Rodents Sacrificed on ISS

Liver

Rodents flown on STS and Sacrificed after Re-entry

STS-135

Space Shuttle (STS) Missions

RR1: CASIS

RR1: NASA

RR3

Time in Space for Rodents (days):
- 0
- 10
- 20
- 30
- 40
- 50
Previous Study on Liver from STS-135 Mission Revealed Lipid Accumulation in the Liver

Non-Alcoholic Fatty Liver Disease (NAFLD)

Healthy Liver

NAFLD

Steatosis

$>5-10\%$ fatty acid triglycerides

Target of SC410

Accumulation of fatty acids and triglycerides

NASH

NAFLD + Inflammation

non-alcoholic steatohepatitis (NASH)

High Risk NASH

NAFLD + Inflammation and Fibrosis

Cirrhosis

Image take from: https://micellebiopharma.com/non-alcoholic-liver-disease-and-non-alcoholic-steatohepatitis-sc410/
Lipid Accumulation Also Occurs in Livers from More Recent Missions on the ISS
Global View for Transcriptional Factors with Flight vs Ground in the Liver

Liver: Flight vs Ground Control

RR1

RR1: CASIS

STS135

RR3

RR1

RR1: CASIS

STS135

RR3
GSEA Analysis on STS-135 Liver Samples Reveals Dysregulation with Lipid Related Pathways
GSEA Analysis on RR1 and RR3 Liver Samples Reveals Common Dysregulation with Lipid Related Pathways
Common Processes and Pathways for all Datasets

- **Glucagon (GCG):** commonly downregulated across all datasets and conditions.
- **Insulin (INS):** commonly upregulated across all datasets.
- GCG and INS are more commonly found to be involved with pancreatic functions to regulate blood sugar levels.
- GCG and INS has also been shown that such signals in the liver can play a role with disease state.
  - For example, an upregulation of INS can provide the liver with high blood glucose signals.
  - In contrast GCG allows the liver to convert glycogen to glucose when the blood sugar levels are low, and thus downregulation of GCG would interrupt such conversion eventually lowering blood glucose levels.
A set of Pathways Increase with duration in space:

- The majority of these pathways are related to increases in the adaptive immune system.
- It has been previously shown that long exposure to the space environment does indeed activate persistent adaptive immune system pathways which will have potential to impact spaceflight associated health risks linked to reactivation of latent herpesviruses and increased incidence of infectious diseases.
- Oxidation of glucose and adipose tissue development are directly impacted by the adaptive immune system and both have been previously linked with adaptive immune system changes during spaceflight.
- Protein folding, translation, and ribosome pathways have been directly linked to activation of the adaptive immune system.
- The increase in the fatty acid metabolic process pathways are in agreement with our results in the previous sections indicating an increase in the lipid accumulation as a function of duration in space.
Proteomics Demonstrate Dysregulation of Lipid Related Proteins

A) Lipid Related Proteins From RR1 and RR3

- Cyp7a1
- Cyp1a2
- Fgli
- Npc2
- Soat2
- ApoC1
- ApoA2
- ApoA5
- Asah1
- C3
- Osppl8
- Tmem30a
- Acox1
- Crat
- Eci1
- Elovl2
- Esyt1
- Fabp5
- Gpdpd1
- Hadd3
- Hadh
- Hmgcs2
- Pc
- Prkkaa2
- Thrsps
- Sc5d

B) RR1

- Apoc2
- Fgli
- Cyp7a1
- Soat2

C) RR3

- Ptplad1
- Elev2
- Tmem30a
- Tnrs3
- Tnrs2
- Acx1
- Acx2
- Acox1
- Acox2
- Asah1

D) Common Functions

- Metabolism of lipids and lipoproteins
- Cholesterol metabolic process
- Steroid metabolic process
- Lipid homeostasis
- Secondary alcohol metabolic process
- Alcohol metabolic process
- Sterol metabolic process
- Organic hydroxy compound metabolic process

GO: Biological Process

Pathways

GO: Molecular Function

- Cholesterol binding
- Sterol binding
- Alcohol binding
- Steroid binding
Conclusions

Liver after Spaceflight
- Lipid Metabolism
- Fatty Acid Metabolism
- NAFLD

Rodents Sacrificed on ISS

Liver

Rodents flown on STS and Sacrificed after Re-entry

Space Shuttle (STS) Missions

International Space Station (ISS) Missions

Process after mice are sacrificed
Sample Processing
Data Sharing
Data Collection & Curation
Next Generation Research
Data Submission
Modeling and Validation

Time in Space for Rodents (days)

0 10 20 30 40 50

RR1: CASIS
RR1: Nasa
RR3

STS-135

Lipid Accumulation