Systemic Microgravity Response: Utilizing GeneLab (genelab.nasa.gov) to Develop Hypotheses for Spaceflight Risks

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What is Systems Biology?

• Systems biology attempts to understand biological organisms or systems as a whole rather than researching their individual components in isolation from one another.

• NIH defines Systems Biology as: “Systems biology is an approach in biomedical research to understanding the larger picture—be it at the level of the organism, tissue, or cell—by putting its pieces together. It’s in stark contrast to decades of reductionist biology, which involves taking the pieces apart.”
General Approach to Studying a Systematic Response in the Host

An example for cancer research
GeneLab Data Used to Generate Results

- Process after mice are sacrificed
- Sample Processing
- Data Sharing
- Data Collection & Curation
- Next Generation Research
- Data Submission
- Modeling and Validation
- International Space Station (ISS) Missions
- Mice Sacrificed on ISS
- Mice flown on STS and Sacrificed after Re-entry
- Extensor Digitorum Longus Muscle
- Soleus Muscle
- Gastrocnemius Muscle
- Quadriceps
- Tibialis Anterior Muscle
- Adrenal Glands
- Kidney
- Liver
- Skin
- Time in Space for Mice (days)
- Space Shuttle (STS) Missions
Number of Significant Genes from Each Dataset

Fold-Change ≥ |1.2|

Pathway/Functional Predictions:
- Ingenuity Pathway Analysis (IPA)
- Gene Set Enrichment Analysis (GSEA)
Determination of Key Genes/Drivers

Key Genes and the Connections
General Approach to Studying a Systematic Response in the Host

Circulating miRNAs

Systemic tumor-host effects
A single miRNA has been estimated to regulate up to 500 mRNAs.
MiRNAs are single-stranded RNA sequences, of about 22 nucleotides in length, processed from longer transcripts.
MiRNAs are important regulators that repress the translation of mRNA transcripts.
Impact of Circulating microRNAs

- Circulating miRNAs can carry signals from organs to other various parts of the body through the blood stream.
- The miRNAs can be transported in Exosomes, microparticles, lipoproteins, and outside any type of packaging.
- Our preliminary data shows that a miRNA signature is carried over from the spleen to the tumor with age.

Systems Biology View of miRNAs

- **Tumor Suppressor miRNAs**
- **OncomiRNAs**

Only looking at a single miRNA:
- Tumors Inhibited

Looking at a pair of miRNAs:
- No Change in Tumors

Systems Biology Approach: Looking at how the entire system impacts the most important miRNAs
Predicted miRNAs Involved with Microgravity Effects

- miRNAs predicted from interaction from all key genes

A) Top 10 predicted miRNAs from p-values

1. mir-145-5p
2. mir-17-5p
3. mir-25
4. mir-217-5p
5. mir-223
6. mir-21
7. mir-26a-5p
8. mir-146

B) All miRNAs with Z-scores > 2 or < -2

1. mir-125b-5p
2. mir-145-5p
3. mir-34
Predicted miRNAs Involved with Microgravity Effects

Health Risk Due to miRNAs

miR-26a-5p

miR-25
mir-34
mir-21
miR-24-3p
mir-145-5p
miR-125b-5p
mir-16-5p
miR-17-5p
mir-223
mir-146

HRS = -12.79

Biological Health Risk Increased

HRS = Health Risk Score
Overall Summary of All Data

- Systems biology approach allows for systemic understanding of the impact of Microgravity.
- Circulating miRNAs can influence overall progression of health risk to the host.
- miRNAs can potentially be used for novel minimally invasive therapeutics and countermeasures
- GeneLab (genelab.nasa.gov) is a powerful tool to generate hypotheses and direct future space research
Acknowledgements

GeneLab Science Team:
Sylvain Costes, PhD
David Smith, PhD
Homer Fogle, PhD
Daniel Berrios, MD PhD MPH
Shayoni Ray, PhD
Jonathan Galazka, PhD
Egle Cekanaviciute, PhD
Sigrid Reinsch, PhD
Yared Kidane, PhD
Marla Smithwick
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genelab.nasa.gov
Thanks to Systems Biology, we now have a clear picture of complex diseases!