Biology of resilience: predicting mouse aging?

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Short-term Measurements of Physical Resilience as a Predictor of Healthspan in Mice: RFA-AG-17-040

• “The goal of this Funding Opportunity Announcement (FOA) is to develop a panel of tests to measure resilience in young or middle-aged animals that can be used to predict: 1) individual future health outcomes, and 2) whether an intervention might result in increased longevity and/or healthspan in an animal model as a population.”

CHALLENGE

• What physical challenges or stresses and return to cellular, tissue and/or organismal homeostasis would have limited effect on future health outcomes?

RATIONALE OF OUR STUDY

• If there are biological mechanisms of resilience, they should exist throughout the organism
Predicting longevity & functional resilience from cellular resilience
Selection of primary cells (fibroblasts) as a model?

• Minimally invasive biopsy collection (tail snip); can be repeated
• Readily expandable in culture; multiple assessments from a single cell “line”
• Primary fibroblasts retain “in vivo” characteristics even after growth and expansion in culture
  • Fibroblasts from long-lived mutant mice (i.e., dwarf mice, GHR-knockout) are resistant to multiple forms of cellular stress
  • Fibroblasts from long-lived species tend to be stress resistant compared to those from short-lived species
  • Cellular resilience to one form of stress predicts resilience to others

*REMINDER*
If there are biological mechanisms of resilience, they should exist throughout the organism (i.e., they should be agnostic to cell type, origin or role in physiology)
What is cellular resilience and how can it be leveraged?
Variability \textit{(predictive power)} among mice in cellular resilience

- Live cell imaging (Incucyte)
- 0.5\textmu M Cadmium
- 50\textmu M MDIVI-1
- 4\textmu M Thapsigargin

- Cell death
- Autophagy
- Respiration
- Oxidative stress
- Senescence/SASP
Variability (*predictive power*) among mice at cellular level

**Metabolic function (Seahorse Bioanalyzer)**

- Basal respiration
- ATP-linked Respiration ( oligomycin)
- Max respiration (FCCP)
- Non-mito respiration (rotenone & antimycin A)

**Maximum respiration**

- Oxygen consumption (AUC)
- Female
- Male

Measured mitochondrial response to uncoupler FCCP
Can cellular resiliency predict longevity or healthspan in normally aging mice?

~260 UM-HET3 mice; M/F
Tail biopsy @ 6, 18 mo.

Genetic heterogeneity (i.e., not inbred)
Grand-offspring of 4 different inbred lines (C57BL/6, DBA/2, C3H, BALB/C)
Males and females; testing at different ages
Can cellular resiliency predict physiological resilience?

Isolation of primary cells

HIGH FAT DIET

METABOLIC RESILIENCE

Basal resp VS weight gain

Basal resp VS ITT change

R = 0.47
P < 0.01

R = 0.53
P < 0.01

Weight Gain 4 wk HFD

Change in ITT (AUC)
Harnessing cellular variability in resilience

PROTEOSTATIC  ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯  CELL GROWTH  ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯  LONGEVITY HEALTHSPAN
METABOLIC  ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯  SENESCENCE  ⎯⎯⎯⎯⎯⎯⎯⎯⎯⎯  CYTOTOXIC
Harnessing cellular variability in resilience

CRI: Cellular Resilience Index
Translational opportunities?

• Can we identify Cellular Resilience Index across species?
  • Non-human primates (marmosets, baboons), humans

• Can cellular resilience be modified?

• Does cellular resilience exist across cell types?
  • How do tissue-derived cells compare to blood cells?

• Personalized medicine?
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