Molecular Underpinnings of Resilience During Aging

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Ken Seldeen, Ram Thiyagarajan, Nik Satchidanand, Jessica Reynolds
Frailty Prevalence During Aging

What is the trajectory of resilience during aging?

Ahmad et al. PLOS One 2018
Loss of Resilience ⇒ Frailty Progression

Frail cellular, metabolic, epigenetic

Resilient Pre-Frail Frail

Physiologic Reserve
challenge
Recovery

Incomplete Recovery (i.e., disability/death)

Resilience Trajectory

Functional Independence → Impairment → Disability

Resilience

Independence Aging, Disease Successful compensation

Difficulty with tasks Compensation partly successful

IADL dependence 1-2 ADLs dependence ≥3 ADLs NH/CLC

Time
Resilience for a given challenge

- $R_1$: limit decline
- $R_2$: restore function towards baseline

Mechanistic spectrum (frailty)

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Perazza et al. Compr Physiol 2022
Loss of Resilience – Tip of the Iceberg?

Biomarkers Associated with Physical Resilience After Hip Fracture

- Physical resilience after hip fracture—the expected recovery differential (ERD)
- Used biomarkers associated with physical performance, morbidity, mortality, and hip fracture
- Baltimore Hip Studies (N = 304): biomarkers of inflammation (TNFR-I, TNFR-II, sVCAM-1, and IL-6), metabolic and mitochondrial function (non-esterified fatty acids, lactate, ketones, acylcarnitines, free amino acids, and IGF-1), and epigenetic dysregulation (circulating microRNAs)
- Complete biomarker set explained 37% of the variance in ERD (p < .001)
- Biomarker subset ⇒ 27% of the ERD variance and included metabolic factors (aspartate/asparagine, C22, C5:1, lactate, glutamate/mine), TNFR-I, miR-376a-3p, and miR-16-5p

Parker et al. J Gerontol 2020
Phenotype may be all we need???

The frailty index outperforms DNA methylation age and its derivatives as an indicator of biological age

Sangkyu Kim, Leann Myers, Jennifer Wyckoff, Katie E. Cherry, S. Michal Jazwinski

- Fl34 was a significant predictor of mortality, whereas none of the DNA methylation age-based metrics were.
- Fl34 outperformed DNA methylation, remaining significant with chronological age when DNA methylation measures were not.
- Fl34 is a robust predictor of biological age, while DNA methylation measures are largely a statistical reflection of the passage of chronological time.

Baseline miRNA profiles predict loss of muscle, declines in physical function, and decreased energy 17 years later

Reynolds et al. Preliminary Results
Questions / Future Strategies

• Measures of frailty may be too late – the horse may have left the barn?
• Though, we have demonstrated that frailty (in mice and likely people) can be reduced with HIIT – is resilience modifiable?
• Will resilience measures be specific to pathways and molecular systems and/or correlate to clinical outcomes?
• Need models that permit prognostication and prevention: keep the horse in the barn rather than just bringing it back?

References