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Guest Editorial

Physical Resilience: Opportunities and Challenges in Translation

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The capacity of an organism to resist and respond to a challenge, or its *resilience*, has emerged as a construct of considerable interest to the field of geroscience. Indeed, aging is associated with an increased vulnerability to diverse physical, psychological, and social challenges. A plausible hypothesis is that compromised resilience is an early manifestation of aging, evident before overt static signals of impaired organ function or chronic disease (1) (Figure 1). As such, measures of resilience could serve as predictors of future health and life span, and surrogate endpoints in clinical trials of interventions that target the fundamental biology of aging.

In this issue of the *Journal of Gerontology*, Hadley, Kuchel, and Newman provide a summary of the National Institute on Aging (NIA) Workshop on Measures of Physiologic Resiliencies in Human Aging (2). The authors nicely highlight research priorities and inherent challenges to better understand *physical resilience*, defined as the ability to resist or recover from functional decline following a health stressor (3), such as infection, surgery, fracture, bed rest, or chemotherapy. Gaps in the understanding of physical resilience exist across the across the translational continuum—from biology to epidemiology—that can be best filled through multidisciplinary approaches. Notable examples include:

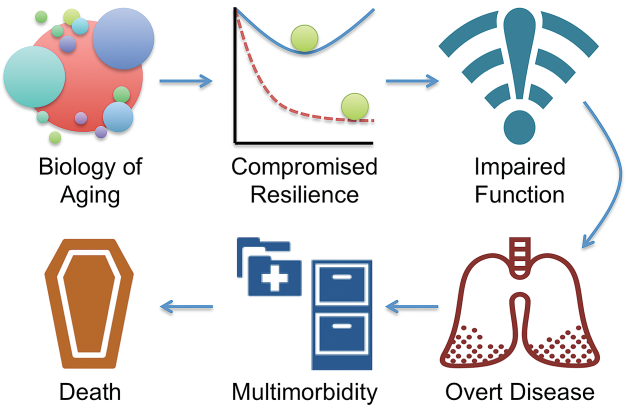

Figure 1. Aging, physical resilience, health span and life span.The geroscience hypothesis posits that the fundamental biology of aging ultimately drives chronic disease, multimorbidity, and death. Robust resilience to a health stressor in early-to-mid-life (solid line) may be indicative of healthy aging. In contrast, compromised resilience (dashed line) may signal advanced aging, before the emergence of static signals of organ or physiological dysfunction. Early-to-midlife resilience may be predictive of health span and life span.

Biology at the Bench

The interplay between the biology of aging and biology of physical resilience is of particular interest. Different forms of age-associated molecular and cellular damage, including DNA lesions, protein misfolding, mitochondrial dysfunction, and progenitor cell exhaustion, would teologically drive vulnerability, and vice versa. Intriguingly, long-lived mutant dwarf mice and calorie-restricted mice exhibit upregulation of defense or *stress response* pathways (ie, to oxidative stress, DNA damage, and apoptosis), which may contribute to their extended health and life span (4). Preclinical models (eg, mice and rats) enable tissue-to-tissue examination of the impact of genetic, pharmacological, and behavioral interventions that target aging on defense pathways. In parallel, blood, biopsy, and surgical specimens of humans of either compromised health, as evidenced by multimorbidity, frailty and disability, or of exceptional health span and longevity provide a rich opportunity for molecular phenotyping and interrogation.

Translatable Tests

There is a critical need to develop and standardize tests of physical resilience. The report emphasizes that a resilience challenge should be integrative and reflective of multiple physiologic systems. A complementary battery of challenges may be necessary for a comprehensive assessment. Resilience challenges should reveal differences both as a *function of age* and *within subjects* of similar age (most-to-least vulnerable). Optimally, assessments will be clinically relevant and

clinically feasible with respect to (a) the physical challenge (health stressor), (b) measure(s) of resistance to the challenge, and (c) measure(s) of recovery from the challenge. Preclinical models provide a valuable opportunity to determine the extent to which resiliency in early-to-midlife predicts health span and life span. Refining physical challenges and dependent variables in preclinical models also has the potential to inform the intelligent design of clinical trials. A summary of a NIA-sponsored workshop on resilience in laboratory animals, inclusive of a short-list of proposed stressors, was recently published (5).

Common health stressors experienced by humans provide an opportunity to optimize the time points and biological (eg, concentration of a biomarker), physiological (eg, echocardiography), performance-based (eg, 6-minute walk distance), and patient-reported (eg, fatigue) measures to characterize resistance and recovery. For example, for a scheduled operative procedure, a full or partial battery of assessments could be performed at or during the pre-surgical visit, perioperative period, acute hospitalization, and follow-up visit. Research is needed to better understand the trajectory of change in outcome measures of resilience. Reliable readouts may serve as informative endpoints in proof-of-concept clinical trials of aging interventions.

Clinical Criteria

Electronic medical records and natural language processing tools have enabled population-based searches for predictors of adverse health outcomes following health stressors ranging from influenza to trauma. Age, vital signs, comorbid conditions, and medication usage are examples of more consistently recorded data. However, measures of functional status or physical performance are rarely captured or documented in routine clinical practice. Hadley, Kuchel and Newman emphasize that greater incorporation of these measures in point-of-care visits would provide a rich resource to both research and healthcare communities. A key incentive for healthcare providers is that predictors of vulnerability will inform selection of the right treatment for the right patient at the right time, prehabilitation strategies to optimize outcomes, and/or more robust transitional care plans for the most vulnerable.

In summary, physical resilience represents a fertile and promising area of investigation from bench to bedside. Multiple research tracks can be pursued in parallel, and will be best served by multidisciplinary teams that span the translational continuum. These efforts promise new insights into the biology of aging, the care of older adults, and opportunities to enhance human health span.

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References

1. Huffman DM, Schafer MJ, LeBrasseur NK. Energetic interventions for healthspan and resiliency with aging. *Exp Gerontol*. 2016;71:1395–1406. doi:10.1093/gerona/glw106.
2. Hadley EC, Kuchel GA, Newman AB. Report: NIA workshop on measures of physiologic resiliencies in human aging. *J Gerontol A Biol Sci Med Sci*. 2017;72:980–990.
3. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colón-Emeric CS. Physical resilience in older adults: systematic review and development of an emerging construct. *J Gerontol A Biol Sci Med Sci*. 2016;71:489–495. doi:10.1093/gerona/glv202.
4. Schumacher B, van der Pluijm I, Moorhouse MJ, et al. Delayed and accelerated aging share common longevity assurance mechanisms. *PLoS Genet*. 2008;4:e1000161. doi:10.1371/journal.pgen.1000161.
5. Kirkland JL, Stout MB, Sierra F. Resilience in aging mice. *J Gerontol A Biol Sci Med Sci*. 2016;71:1407–1414. doi:10.1093/gerona/glw086.