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EDITORIAL

Physical resilience is a predictor of healthy aging

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Abstract

Physical resilience is defined as the ability to respond to and recover from a physically stressful event. Response to stress can be heterogeneous across lifespan and between individuals of the same age. Documentation of resilience at a young age would provide insight into how individuals across lifespan would develop resilience to physical stress at an older age and help identify individuals determined to be less resilient. Protective factors could be developed that can be engaged to promote resilience and healthy aging and provide insight as to why some individuals maintain or regain function following an insult while others do not. Preclinical animal studies will provide valuable information as to the molecular pathways involved in individual heterogeneity and help identify therapeutic targets. The concept that resilience to aging is characterized by heterogeneous response patterns unique to specific physical stressors is an excellent translational platform for determining the optimal age, scope, and intensity of physical stressors to reliably discriminate resilience.
Keywords: Resilience to aging, physical stressors, heterogeneous resilience, aging intervention, animal models

The ability to respond to and recover from a physically stressful event is defined as physical resilience. It is an individual trait throughout life, but not necessarily to the same degree from young to old. With increasing age, physical resilience declines, thereby increasing vulnerability to physical stress. However, response to stress can be heterogeneous across lifespan and between individuals within the same age. Exposure to augmented stressors can culminate in accelerated aging even in younger individuals. Accelerated aging has been shown in cancer patients undergoing chemotherapy, cancer survivors, and even younger individuals with sleep deprivation, or chronic pain.

An all-encompassing characteristic influencing resilience is the inherent individual variation in response to a specific stressor and adaptation mechanisms. Therefore, the ability to document resilience across lifespan, starting at a younger age, would provide insight into how individuals across lifespan would develop resilience to physical stress at an older age compared to an individual who was determined to be less resilient, and whether the mechanism of resilience at a younger age could be distinguished from that at an older age. Moreover, between-individual and between-organ heterogeneity in health suggests variability in response to physical stress.

A deeper understanding as to why some individuals maintain or regain function following an insult while others do not, may help to characterize protective factors that can be engaged to promote resilience and healthy aging. Thus, measuring resilience at a relatively young age through physical challenges could help classify relatively resilient and non-resilient individuals and predict health trajectories. This may require a transition to *in vitro* tests using accessible tissues such as blood and tissue biopsies. Once the molecular mechanisms that contribute to individual heterogeneity have been identified, they can be used to develop interventions focused on optimizing resilience with increasing age for each individual. Some may need little intervention, while others may need a more aggressive intervention approach.

In this regard, preclinical animal studies will provide valuable information as to the molecular pathways involved in individual heterogeneity and help identify therapeutic targets. Three physical stressors are excellent candidates to develop and characterize in laboratory mice: acute sleep disruption (ASD), the chemotherapeutic drug cyclophosphamide (CYP), and acute cutaneous trauma (ACT), that show a correlation with physiological and pathological parameters with increasing age. These stressors are translationally relevant. ASD is a major health concern and is associated with increasing age. It has recently been rec-

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ognized as an important risk factor for insulin resistance and diabetes, memory loss, heart disease, and cancer. CYP is an excellent representative chemotherapeutic agent because it is used extensively in patients for a variety of conditions, including cancers such as breast and prostate cancer and rheumatoid arthritis. ACT, in the form of a small ear punch biopsy in mice, is relevant as a model for wound healing, and is a health concern in older people because of a delay in tissue repair. Interestingly, there is evidence to suggest that middle-aged mice respond to these types of stressors in a heterogeneous manner, thereby serving as excellent animal models.

A major issue in defining responses to physical challenges is how to measure resilience and determine the optimal age, scope, and intensity of physical stressors to reliably discriminate resilience. The concept that resilience to aging is characterized by heterogeneous response patterns unique to specific physical stressors is an excellent platform for addressing this issue.

The overarching goal is to obtain a better understanding of resilience at the molecular, cellular, organ, and systemic physiological levels in order to establish aging-intervention strategies on an individual basis.

Declarations

Conflicts of interest: Warren Ladiges is a member of the Editorial Board of Aging Pathobiology and Therapeutics. All authors declare no conflict of interest and were not involved in the journal's review or decisions related to this manuscript.

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