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EDITORIAL

Predicting resilience to aging with physical stressors

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Abstract

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 heterogenous across lifespan and between individuals within the same age. 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. Examples of clinically relevant physical stressors include cold, sleep deprivation, the chemotherapeutic drug cyclophosphamide, rate of wound healing, recovery from anesthesia, and degree of antibody response to a commonly used vaccine. Research is needed to identify panels of these stressors capable of predicting resilience to aging and those individuals with more accelerated rates of aging requiring intervention approaches.

Keywords: Physical resilience, aging, clinical stressors, aging intervention

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 heterogenous 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 on how individuals across lifespan would develop resilience to physical stress at an older age, and compared to an individual that was determined to be less resilient and whether the mechanism of resilience at a younger age could be distinguished from 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 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.

Unfortunately, parameters for resilience are not well defined, and no single standardized stress test exists. In order to inform about health status, integrative responses involving multiple tissues, organs, and activities need to be measured to reveal the overall resilience status. Therefore, a battery of stress tests, rather than a single all-encompassing one, would be more informative. An ideal battery of tests should have enough dynamic range in the response to allow characterization of an individual in easily distinguishable groups as being resilient or non-resilient. Each test should also be simple, reliable, and inexpensive so the panel can easily be duplicated by many different groups. As a panel, three stressors- cold, sleep deprivation and the chemotherapeutic drug cyclophosphamide, fit these criteria. The mechanisms of response to cold are multifacto-

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rial. Sleep deprivation is a risk factor for insulin resistance and diabetes, memory loss, heart disease, and cancer. Cyclophosphamide targets several different systems but most specifically the hematopoietic system.

These three stressors combined could be an attractive perturbation for resilience testing to measure the effectiveness of interventions that target basic aging processes. These stressors are relevant to clinical medicine and aging. For example, humans can develop intolerance to cold with increased sensitivity to hypothermia with increasing age. Sleep deprivation is a major health concern in developed countries and is associated with increasing age. Sleep disturbances including sleep fragmentation and sleep loss can occur. Cyclophosphamide as a representative chemotherapeutic agent is used extensively in patients for a variety of conditions including cancer and rheumatoid arthritis. Short term side effects are more severe with increasing age and intermediate and long-term effects are associated with a general accelerated aging-like state. Additional clinical stressors to be considered are rate of wound healing, recovery from anesthesia, and degree of antibody response to a commonly used vaccine. Respective responses are different in different individuals and change with increasing age. Further investigations are necessary to validate stressor panels capable of predicting resilient and susceptible individuals to determine if aging intervention approaches are options for enhancing healthy aging.

Declarations

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