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The stress field ages: A close look into cellular aging processes

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This special issue on Stress and Aging Mechanisms is devoted to the memory of Bruce McEwen, PhD, 1938–2020. Bruce was a pioneer in understanding stress, brain and peripheral health interrelationships at the cellular and systemic levels. He coined the term “allostatic load” which is a model that has helped shape the field including understanding aging processes. His legacy lives on, in science, and in society

1. The Stress Field Ages: A timely special issue on stress and aging mechanisms

The roots of stress research lie in the belief that stress can accelerate biological aging. Hans Selye, a father of stress research, first showed organisms mounted a common graded response to diverse stressors such as cold, surgery, or pharmacological agents (Selye, 1936). After an acute response over days, he observed habituation and a return to almost normal functioning, what we might think of as homeostasis or healthy allostasis—the changing balance of regulatory systems to meet the demands of the external environment and maintain internal stability. However, if the noxious stimuli continued on for months, there was ‘exhaustion’ and signs of physiological damage in organs that regulate adaptation. This effect of chronic stress might be thought of as early disease states—more easily observable in short lived animals like rodents than in long lived humans. In humans, stressors accumulate over decades, and can have mostly invisible damaging effects on regulatory systems and organs long before disease states can be measured and labeled. While homeostasis may describe how simple systems respond to acute stressors, ending with a return to a normal baseline value of function, the modern concept of allostasis is critical to understanding stress and aging. We need both concepts, homeostasis and allostasis, to better understand aging. For humans in our modern context, we are exposed to conditions we were not evolved for that reveal *fragility in homeostasis* and dysregulation and damage to

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regulatory systems, thus resulting in “allostatic load” (McEwen, 1998; Ramsay and Woods, 2014). One example is the chronicity of abundant palatable calories which results in obesity and premature aging of metabolic regulation, the rise in glucose and insulin. In the case of social stress, the extent of allostatic load is becoming well characterized, especially in terms of biological aging at a cellular and molecular level. Even back then, Selye viewed stress as an inherent part of the nonspecific process of biological aging and famously stated “*Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older*.” (Selye, 1976). The earliest changes due to stress can be observed in various ways at the cellular level, leaving imprints that now, 75 years later, we have the technology and insights to see more clearly. The stress field has matured, and we now know that chronic stress is intimately involved in the process of biological aging.

Volumes of careful studies demonstrate that traumatic or chronic psychosocial adversity, including low socioeconomic status, predict higher allostatic load, whereas higher psychosocial resources are associated with lower allostatic load, with reliable but small effects (Danese and McEwen, 2012; Wiley et al., 2017). Allostatic load is an early developmental step toward developing diagnosable disease. Therefore, it is useful to have an even earlier marker of aging that we could track starting at birth or childhood, long before systemic allostatic load develops. Hence we can look at indices of cellular health, to foresee wear and tear of life experience at the molecular level, in order to be able to predict with some reliability the likelihood that disease will develop. Now that we know more about how cells age, we can measure cellular health and aging related processes using many different markers.

Our guiding question for this special issue is – how can we better understand how exposure to stress across the life span might accelerate aging processes? This large question cannot be answered by any one study or set of papers, given the diverse nature of types of stressors and responses, and the multiple pathways through which stress works. Further, there is not just one measure of biological aging, and in fact there is little agreement about what might be the most important causal aging mechanisms. There is, however, some agreement about what several of the important cellular aging mechanisms are. For example, aging is reflected in senescent cells, and it is unclear how early in life these accumulate. Inflammation, telomeres, and mitochondria are coregulated systems that can lead to early senescent cells, which in turn have their own independent effects on tissue health. These are common drivers of cell aging that make the cells and tissue vulnerable to aberrant pathways and multiple disease states. Therefore, a focus on the early causes of cellular aging should pay off in spades for our understanding of disease etiology and prevention regardless of disease type, which is also a goal of the geroscience agenda. This issue focuses on several cellular processes of aging that are interrelated: Telomere biology, mitochondrial function, and epigenetic aging. Many expert groups in related fields have provided exciting novel findings as well as important conceptual and methodological reviews.

2. Aged cells in population based studies

Many population-based studies have added DNA based measures of aging such as measures of leukocyte telomere length. Since most cohort studies have saved epigenomic markers of

immune cell DNA, more studies in the future will likely include epigenetics, gene expression and mitochondrial DNA copy number. So far, we have learned sociodemographic factors appear to pattern onto telomere length, although there have not been consistent patterns of findings across studies. For example, income may matter in one group or sex. Telomere length appears to be associated with lower education in western countries (Robertson et al., 2013), and in some studies with indices of neighborhood low quality or deprivation (Ellaway et al., 2019; Geronimus et al., 2015; Needham et al., 2014; Theall et al., 2013). There have been less consistent findings of telomere length or attrition with racial and ethnic differences. This may be due in part to the use of different measures, variance across labs, and the error inherent in currently available measures. The measurement issues are addressed in Lin et al., this issue. It is also important to examine changes over time, and there have been too few studies that were able to address this reliably in a planned way.

In this issue, we see several new patterns emerge from longitudinal cohort studies. Chronic life stress and discrimination were specifically explored. Meier et al. examined chronic life stress as well as neighborhood stress exposures in the MESA study. They found in part that increases in chronic stress were associated with greater attrition over ten years (Meier et al., 2019). Rentscher et al. found that among healthy midlife adults, chronic stress was associated with greater levels of $p16^{INK4a}$, a marker of senescent immune cells, but not with shorter LTL (Rentscher et al., 2019).

Sullivan and colleagues, examining a cohort of men and women with heart disease, find that everyday discrimination is associated with shorter telomeres in women, both African Americans and white, but not men (Sullivan et al., 2019). This adds to a rapidly emerging body of studies examining links between discrimination and telomere length, primarily in African Americans.

Sociodemographic factors are proxies for a set of exposures, of which life stress is only one. Huang and colleagues find in a Singaporean sample that the relationship between chronological age and telomere length is partly explained by cognitive aging (Huang et al., 2019), and relationships vary by socioeconomic status. Needham and colleagues examine telomere attrition over time and show that whether or not one controls for baseline levels can actually reverse findings on effects of sex and age, showing how important it is to reach consensus in this field on analytic and reporting methods (Needham et al., 2019).

Lastly, Liu et al. examined the Levine measure of epigenetic aging and sociodemographic patterns in the Women's Health Initiative, and found that there was older age among those with lower education and among non-Hispanic blacks (Liu et al., 2019). Other epigenetic clock measures were not examined as they appear not to show gradients with sociodemographic factors.

Experimental studies in animals suggest a causal relationship between stress and telomere attrition (Epel and Prather, 2018). However, it is not clear yet from human studies how much of this relationship is bidirectional. Verhoeven et al. demonstrate that a higher genetic load for depression does not predict telomere attrition, and vice versa, pointing to more

environmental or acquired causes for the shorter telomeres found associated with distress measures rather than shared genetic causes (Verhoeven et al., 2019).

3. Aging starts early in life

The establishment of the integrity of key cellular aging-related processes that determine variation across individuals in the onset and progression of age-related disorders originate very early in life (in utero) and are plastic and influenced by developmental conditions. It is well established that the initial (newborn and early life) settings of telomere length and telomerase expression capacity represent critically important aspects of the integrity of our telomere system as we age. The first study in this area examined maternal stress exposure during pregnancy in a retrospective manner, and found shorter telomere length in the healthy adult children, suggesting there may have been effects embedded during pregnancy (Entringer et al., 2011). Since then, there is a body of literature showing maternal systemic and intrauterine effects as well as experiences during early postnatal life seem to play a major role in this initial set-up of telomere length. Many animal and human studies suggest that adverse conditions such as stress and trauma exposure in intrauterine and early postnatal life are associated with shorter offspring TL at birth, during childhood and in adult life (Entringer et al., 2018). Two papers in this issue contribute to this growing body of literature. Ridout et al. measured telomere length and mitochondrial DNA copy number (mtDNAcn) in saliva DNA in young children with and without child welfare documentation of maltreatment in the past six months thereby examining immediate embedding effects of traumatic experiences (Ridout et al., 2019). In line with recent studies in adults, mtDNAcn was positively associated with trauma experiences, however children who experienced maltreatment had longer telomeres which is in contrast to previously published studies. The authors discuss the observed positive association between maltreatment and telomere length as potential compensatory biological changes in response to recent trauma. Adversity during childhood may not only affect the directly exposed individual, but through alterations in placental telomere length may be passed on to the next generation with implications for offspring development (Jones et al., 2019), adding biological evidence to the growing notion of the intergenerational transmission of the effects of early life trauma.

In an aging society, common age-related disorders are among the most important public health issues because they are the leading cause of mortality and morbidity globally. If these health risks begin in the earliest years of life, even before birth, and they accumulate over time, this has long-term consequences for susceptibility to common, age-related disorders. We urgently need a better understanding of underlying mechanisms that alter risk early during development for subsequent age-related disease risks. Therefore, we call for more comprehensive studies that include longitudinal measures of newborn and infant cellular aging-related processes to then transition to translational research on early identification of risk/vulnerable populations and to subsequent development of primary and secondary intervention strategies.

4. Biochemical mechanisms and interrelations between aging systems

Four papers in this issue investigated mechanistic pathways underlying the association between stress and cellular aging with an emphasis on immune cells. One of the mechanisms through which chronic stress may be associated with shortened telomere length is chronic inflammation. Lin et al. provide evidence that in healthy young people, chronic stress is associated with an exaggerated NF- κB mediated inflammatory response in PBMCs when stimulated in vitro, which in turn predicted shorter telomere length measured 15 months later (Lin et al., 2018). This is the first demonstration of a specific potential mechanism of immune inflammatory reactivity for telomere shortening.

Besides telomere biology, another important and closely related molecular aspect of cellular aging is mitochondrial respiratory function. When mitochondrial (mt) DNA end up outside the cell in the blood, this is thought to be due to cellular stress. Using experimental paradigms in humans, Trumpff et al. (Trumpff et al., 2019a) show that acute psychosocial stress exposure increases serum circulating cell-free (ccf) mtDNA within 30 min, and that glucocorticoid signaling in primary fibroblasts induce mtDNA extrusion also within minutes. Using a machine-learning approach they then explore determinants of inter- and within-person differences in this so-called “stress-induced mtDNA reactivity” paradigm (Trumpff et al., 2019b). This study opens up a potentially important new measure of acute stress vulnerability.

Lastly, a meta-analysis shows a consistent relationship between greater cortisol reactivity to acute stress and shorter telomere length, supporting a stress vulnerability pathway or at least association (Jiang et al., 2019). Few studies examine aging systems simultaneously and thus we have an incomplete picture of the interrelations between inflammation, mitochondrial activity and mitochondrial DNA expulsion, or the stress mechanisms that may precede them.

5. Next generation of research

The stress field indeed has aged. As shown in this broad spanning issue, the conceptual and empirical papers provide further evidence that exposure to stress across the life span accelerates the aging processes and shed light on the underlying biological mechanisms. This supports the importance of both fragile homeostasis and allostatic load in understanding the stress related wear and tear of aging. This issue underscores the importance of early human development as a time for biological embedding of a faster trajectory of aging. Further knowledge gaps remain regarding the long-term effects of developmental conditions on the early life setting of cellular aging related biological systems and the clinical significance of these observed effects. Specifically, are cellular markers assessed at birth or during early childhood predictive in later life of susceptibility for common age-related disorders and longevity, and may alterations in these systems even confer higher disease risk in the next generation? To answer these questions, longitudinal studies are warranted that track the effects of early life conditions on the telomere biology system from prenatal life and birth onwards through childhood until adulthood and beyond.

We focused this issue on a specific set of measures that can be examined in immune cells – telomere biology, mitochondria, and epigenetic aging, rapidly growing areas where the research needs to come together to be better integrated by examining the determinants and interrelations and consequences within the same cohorts and reports. There are numerous potentially helpful indices of biological aging that were not included, such as patterns of inflammatory gene expression that underlie disease. Future studies should assess and integrate cellular based measures of aging with other indicators of health and disease to determine their role in the disease processes. Studies by Belsky et al. (Belsky et al., 2018) and Hastings et al. (this issue) (Hastings et al., 2019) were among the first that took a pass at integrating and comparing measures. Hastings et al. compared four different measures of biological aging (3 composites and telomere length) in a large cohort study. Their study emphasized the importance of including different measures of aging, showing that they are not interchangeable, but rather have different effects. Similarly, Marioni et al. found that epigenetic clock and telomere length both predict mortality but they were independent – they worked through mostly non overlapping pathways (Marioni et al., 2016). These types of studies suggest we should move beyond labeling one measure as proof of 'biological aging' but rather each one is *one index of biological aging, in the complexity of interrelated but largely independent measures*. Further, we should avoid the simplicity of a horse race mentality that focuses solely on the factors that most strongly predict mortality. While that is an important practical question, there are basic scientific questions about aging that are more relevant to other measures. The strongest predictors of mortality will inevitably be algorithm based measures of clinical markers that are more proximal to disease. Molecular based markers like telomere length have known mechanistic roles in aging (Blackburn et al., 2015), and while they appear to have reliable effects on predicting mortality (Mons et al., 2017) their effects are small. However, we know they are transmitted across generations in both a prenatal programming and an epigenetic like fashion, making them important in understanding intergenerational transmission of sociodemographic patterns of population health.

As laid out in a conceptual paper on current challenges and future directions of this research field (Han et al., 2019), effort should be put into establishing the best objective and predictive biological age indicators or combinations of indicators (e.g., based on measures of telomere biology, mitochondrial biology, epigenetic aging) and examining to what extent interventions can delay, halt or temporarily reverse biological aging trajectories in the long term. This group of experts in mental health and cellular aging points to several methodological advances the field needs: The importance of collecting longitudinal data, using experimental designs (e.g., cellular or animal models to allow the direct manipulation of a specific set of variables), using machine learning and other artificial intelligence techniques to create composite indices and panels of biological age indicators relevant to mental health, and considering tissue specificity because stress-related effects on aging may be tissue- and cell-type specific.

Using aging biomarkers as barometers for successful interventions is becoming more important, given the increasing interest in geroscience, with its focus on slowing aging. It is critical to recognize the role of stress and health behaviors, because while there will hopefully be pharmacological agents for slowing aging in the future (Vaiserman and

Lushchak, 2017), it is unlikely they will prevent the strong detrimental effects of stress and poor lifestyle on accelerating aging biology. While we need to mitigate societal and social sources of stress, we can also utilize mechanistic findings for tempering their effects, such as compensating for stress suppression of salutary hormones. Stevenson et al. (Stevenson et al., 2019) show that chronic isolation of a social mammal (prairie voles) leads to oxidative stress and shortened telomeres. However, the social stress effects could be prevented by administration of oxytocin, pointing to an important pathway for understanding social stress effects on cellular aging.

The stress field is now an interdisciplinary field, where we can take advantage of the careful mechanistic work by basic stress scientists, and examine these in intervention and population based studies. We can examine social and geographic trends in aging. This makes measurement issues absolutely critical. Reliability within methods, cell types, and across labs must be addressed. We need to continuously make efforts to improve our measures of cellular aging markers. This is laid out in two papers with specific recommendations for the assessment of telomerase activity (de Punder et al., 2019) and of telomere length (Lin et al., 2019) in the context of human studies on stress and cellular aging. This is such an important issue to the future of health that the National Institutes of Health (NIH) just funded a Telomere Research Network, with a focus on improving available measurements in the field and developing best practices for the larger field of population health. This initiative will involve many key members of this special issue as well as others in related fields.

In addition to improving our measures of biological stress and aging, we need to improve and harmonize our measures of psychological stress. Again, this is of such importance to advance the stress field that NIA has supported a Stress Network to address these issues. The network will benefit from the expertise of interdisciplinary researchers in social stress related fields, both using and adding to the stress measurement toolbox, as well as utilizing the stress measures harmonized across longitudinal cohort studies of aging in different countries https://stresscenter.ucsf.edu/. These cohort studies could benefit from the addition of more causal biomarkers of aging, in order to meet the goals described above. This type of biodemographical epidemiology is also an important practical path toward identifying best targets of interventions (Newman et al., 2019).

The “indelible scars” from stress that Selye described can now be understood in a larger context: We do not just function as independent organisms, but rather as social groups, scarred by common neighborhood and social stressors, and we transmit these social scars across generations. It is a time to work harder collaboratively across measures, and disciplines, and to apply the implications of this work. We are in a critical time in history with stress exposures at multiple levels – political stress, environmental stress from population growth and global warming along with climate crises, high levels of income inequality, and the social stress inherent in the oppression of marginalized social groups. It is thus important to bring together the best science of stress mechanisms with a better understanding and thus better prevention of severe stress at a personal, community, and population level.

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