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Organismal stress and telomeric aging: An unexpected connection

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In a recent issue of PNAS, Epel *et al.* (1) presented an intriguing and important finding that lends support to an idea that has permeated gerontology for a century.

In the early years of the 20th century, the German physiologist Max Rubner conducted a series of magnificently obsessive investigations into phylogenetic aspects of aging (2). What he reported was landmark; across an array of species, there is a rough inverse correlation between a species' lifespan and metabolic rate (when expressed per unit of body weight). As examples from the extremes, witness the ≈ 2 -year lifespan of the rat and its resting heart rate of ≈ 400 beats per minute, and the elephant, with its 60-odd years of life and 35 beats per minute.

These studies spawned an array of "rate of living" hypotheses, focusing on the possibility that high basal metabolic rates produce shorter lifespans, both between and, more speculatively, within species (3). It was some decades later that attention shifted to the notion that perturbations of metabolism (i.e., challenges to metabolic homeostasis) could accelerate aging as well. Such "wear and tear" theories readily accommodated the birth of stress physiology, with its notion that prolonged psychological or physical challenges to homeostasis could increase the risk of disease. Specifically, this accommodation resulted in the idea that prolonged stress can accelerate aspects of aging (4).

Women who were more stressed had shorter telomeres and more oxidative stress.

Over the years, some findings have supported this intuitively appealing idea. One literature, for example, demonstrates how repeated challenges to glucose homeostasis can exacerbate adult-onset diabetes (5) and accelerate the nonenzymatic formation of advanced glycation end products (6). Other studies have shown that pro-

longed exposure to one class of stress hormones can accelerate an aspect of brain senescence (7), whereas prolonged suffering from a stress-related psychiatric disorder (i.e., major depression) increases the risk of heart disease (8). And some reports have linked stress, or the hormones of stress, to the generation of oxygen radicals (9). But, with the exception of those final studies, relatively little work has linked chronic stress with endpoints that transcend particular organ systems and, instead, concern the fundamental cell biology of aging. In the study reported by Epel *et al.* (1), an interdisciplinary team presents exciting evidence for such a link.

The finding ties together two different fields, each coming from an extreme end of the continuum stretching from the most reductive to the most integrative approaches in biomedical research. The integrative end makes use of a frequent population of study subjects in health psychology, namely humans who are primary caregivers for family members with a chronic illness. Such a caregiver role is rife with physical and psychological stressors, and numerous studies have documented how such individuals (typically women) are at a greatly increased risk for an array of stress-related maladies. For example, significant immune suppression has been reported among caregivers of dementia patients (10). In the present study, the subjects were healthy, premenopausal women (with an average age of 38) who were the mothers of children with a chronic illness; controls were age-matched mothers of healthy children.

The reductive end of this study concerns telomeres, the oligomeric DNA/protein complexes that stabilize the ends of chromosomes. In classic work, Blackburn and colleagues (11) showed that each round of cell division leads to a shortening of telomeres and that, once a critical threshold of truncation is passed, cell division ceases. Telomere shortening now stands as the most plausible molecular pacemaker of cell senescence, and feverish work has focused on the possibility that the enzyme telomerase, which can extend shortened telomeres, can decelerate or even halt features of cellular aging (12).

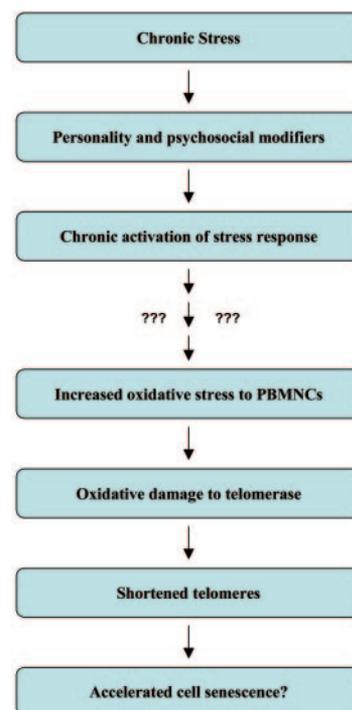


Fig. 1. A possible pathway by which chronic stress impacts telomeres. Chronic stress, in the form of caring for a chronically ill child, filtered through personality and psychosocial variables that can modulate the perception of stress, activates the stress response. Such a response, most notably, involves activation of the sympathetic nervous system and secretion of glucocorticoids, along with an array of other endocrine responses. Through a series of as yet unknown steps, this step, at the physiological level, is transduced to cellular consequences, namely increased oxidative stress to peripheral blood mononuclear cells (PBMNCs). This transduction can lead to oxidative damage to telomerase, impairing its function, thereby leading to shortened telomeres. This truncation may then translate into accelerated cell senescence.

From the intersection of these two disparate fields comes a remarkable finding, namely that those women who were more stressed, by both an objective and subjective measure, had shorter telomeres and less telomerase activity in peripheral blood mononuclear cells, and had more oxidative stress (as measured

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in urine by the amount of a marker of oxidative damage divided by a marker of antioxidant potential). The oxidative endpoint is important, given that oxidative damage to telomerase decreases its enzymatic activity and is thought to play a role in the age-related decline in telomerase activity (13).

As an objective measure, among the caregivers, the longer the duration of the child's illness (ranging from 1 to 12 years), the shorter the telomeres, the less the telomerase activity, and the more oxidative stress. And as a subjective measure, the greater the self-perceived stress (based on a questionnaire standard to the field), the worse the profile of those three endpoints. This latter relationship was observed in both caregivers and controls (whether examining data from all subjects, as well as from those at the extremes of self-assessed stress). The incorporation of both caregivers and controls in this relationship ruled out some possible confounds (such as the possibility of a biological vulnerability in some families giving rise to both the adverse telomere-related endpoints and chronic illness in children). Finally, chronic stress typically causes numerous deleterious changes in lifestyle (related to diet, substance abuse, and so on); the authors then demonstrated that these stress/telomere relationships persist after controlling for smoking, vitamin intake, and body mass index (as well as age).

Thus, prolonged and major stress, in and of itself, predicts worsening of some key cellular biomarkers of aging (Fig. 1). This is a provocative finding in the best sense of the word.

The study has many strengths, one being the magnitude of the effect. In an admittedly rough calculation, the authors estimate that the extent to which telomeres are shortened among the most self-reportedly stressed individuals (when compared with the least

stressed) approximates 9–17 years worth of accelerated cellular aging. This stress effect is unlikely to be a mere statistical phenomenon.

Another major strength is the sheer adventurousness of the interdisciplinary features of this study. Health psychology research, when moving in a reductive interdisciplinary direction, might consider the effects of caregiver status on multisystem physiological endpoints such as circulating hormone levels or blood pressure (i.e., one level more reductive than focusing on an entire organism). Meanwhile, telomere research, when moving in a more integrative interdisciplinary direction, might examine the effects of telomere length on pathways of programmed cell death (i.e., one level more integrative than focusing on chromosomal structure). Thus, the article by Epel *et al.* represents a leap across a vast interdisciplinary canyon.

The data hint at a fascinating subtext to a finding such as this, namely that there are striking individual differences in the stress/telomere connection. As noted, the article reported a relationship between self-perceived stress and telomere length that spanned both the caregiver and control populations. The relevant data (figure 1B in ref. 1) show considerable overlap in the two populations in the extent of self-perceived stress and with both groups contributing roughly equally to the stress/telomere relationship. In other words, some caregivers apparently have the means to be coping adequately, whereas some control subjects, despite being spared this major life stressor, are nonetheless not faring well.

Naturally, much more is needed. The basic finding must be replicated, of course. The bases and further consequences of the individual differences just discussed should be studied. Moreover, the generality of the finding must be examined. This takes two forms.

First, the generality must be tested at the more integrative end. Are the same telomere-related changes brought about by other chronic stressors (differing, for example, in the extent to which they are physical versus psychosocial in nature, or differing as to whether they involve frequent transients of stress or prolonged square waves)? And the generality must be tested at the more reductive end as well. As noted, the telomere-related endpoints were documented in peripheral leukocytes; other cell types must be examined, and, although it will be interesting if the basic finding extends to other cell types, it will be even more interesting if there are dramatic cell type-specific differences in the magnitude of the effect. Such a finding must then usher in studies of the downstream consequences for individual cell types, and the organism as a whole, of having telomere aging accelerated.

If the finding is replicated and generalized, the most pressing question becomes how to build a bridge across that interdisciplinary canyon. Specifically, how is stress, as experienced at the level of an individual mammal, transduced into a change in telomere biology? And one could readily imagine the answer to this constituting the careers of numerous excellent scientists.

Ultimately, the findings from the article by Epel *et al.* and those from the subsequent studies that it will hopefully spawn may reveal a detailed pathway by which stress can influence a fundamental aspect of the aging process. As an understatement, this would be a salutary bit of science. But, remarkably, a finding such as this can carry a lesson of broader and even more important significance. To answer a question as seemingly reductive and basic as, "How long are the chromosomes in this cell?," you must take into account the environment in which this cell and this cell's organism dwell.

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