

## Accelerated telomere shortening in response to life stress

### Proceedings of the National Academy of Sciences of the United States of America (PNAS)

December 7, 2004, Vol. 101, No. 49 17312-17315

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#### NOTE FROM DAN MURPHY:

Elizabeth Blackburn, from the Department of Biochemistry and Biophysics, University of California, San Francisco, was awarded the Nobel Prize in Medicine/Physiology, October 2009, for her work pertaining to telomeres.

#### BACKGROUND FROM DAN MURPHY

In 1953, Leonard Hayflick, PhD, anatomy professor at the University of California, San Francisco, discovered that human cells divided about 50 times, and then die. This is known as the *Hayflick limit*. Dr. Hayflick continues to research and publish on human aging and longevity.

About 30 years ago, scientists discovered the reason for the *Hayflick limit* was *telomeres*. *Telomeres* are short caps of DNA on the ends of chromosomes. Each time the cell divides, the *telomere* shortens a little. When most of the *telomere* disappears, the cell dies. Consequently, *telomere* length has been proposed as a marker of biological aging.

#### FROM ABSTRACT:

Numerous studies demonstrate links between chronic stress and indices of poor health, including risk factors for cardiovascular disease and poorer immune function.

Nevertheless, the exact mechanisms of how stress gets “under the skin” remain elusive. We investigated the hypothesis that stress impacts health by modulating the rate of cellular aging.

Here we provide evidence that psychological stress— both perceived stress and chronicity of stress—is significantly associated with higher oxidative stress, lower telomerase activity [telomerase is an enzyme that adds to the length of the telomere], and shorter telomere length, which are known determinants of cell senescence [state of being old; the process of becoming old] and longevity.

Women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared to low stress women.

These findings have implications for understanding how, at the cellular level, stress may promote earlier onset of age-related diseases.

#### THESE AUTHORS ALSO NOTE:

“People who are stressed over long periods tend to look haggard, and it is commonly thought that psychological stress leads to premature aging and the earlier onset of diseases of aging.”

“Numerous studies demonstrate links between chronic stress and indices of poor health, including risk factors for cardiovascular disease and poorer immune function.”

“Recent research points to the crucial roles of telomeres and telomerase in cellular aging and potentially in disease.”

“Telomeres are DNA–protein complexes that cap chromosomal ends, promoting chromosomal stability. When cells divide, the telomere is not fully replicated because of limitations of the DNA polymerases in completing the replication of the ends of the linear molecules, leading to telomere shortening with every replication. In vitro, when telomeres shorten sufficiently, the cell is arrested into senescence.”

“In people, telomeres shorten with age in all replicating somatic cells that have been examined, including fibroblasts and leukocytes. Thus, telomere length can serve as a biomarker of a cell's biological (versus chronological) ‘age’ or potential for further cell division.”

Telomerase, a cellular enzyme, adds to the length of the telomere.

Reduced telomerase activity increases cellular senescence [state of being old; the process of becoming old].

People with a genetic disease that diminishes the ability to synthesize sufficient telomerase have shortened telomeres and die prematurely.

Oxidative stress will shorten telomeres and antioxidants can decelerate this shortening.

Actual or perceived chronic psychological stress is linked to telomere shortening, lowered telomerase function, and to oxidative stress.

These authors examined 58 healthy premenopausal women who were biological mothers of either a healthy child (n = 19, “control mothers”) or a chronically ill child (n = 39, “caregiving mothers”). Age matched mean telomere length and telomerase activity was measured quantitatively. Both oxidative stress and antioxidant defenses were measured.

## RESULTS

“Within the caregiving group, the more years of caregiving, the shorter the mother’s telomere length, the lower the telomerase activity, and the greater the oxidative stress, even after controlling for the mother’s age.”

“Those with the lowest stress have the longest mean telomere length.”

A further demonstration of the relationship between stress and telomere length is seen upon comparing the two extreme groups, those in the highest and lowest quartiles of perceived stress scores. These groups were similar in age, tobacco use, and vitamin use. The high-stress group had significantly shorter telomeres than the low-stress group.

Telomere length declines during normal aging. The authors found that the telomere shortening in the high-stress group was equivalent of 9–17 additional aging years compared with the low-stress group.

“The high-stress group also had significantly lower telomerase activity and higher oxidative stress than the low-stress group.” The mean telomerase activity was 48% lower in the high-stress group.

The short telomere length group had higher stress, higher oxidative stress, and lower telomerase activity.

## DISCUSSION

Psychological stress could affect cell aging through at least three nonmutually exclusive pathways:

- 1) immune cell function or distribution
- 2) oxidative stress
- 3) telomerase activity

“Stress could potentially lead to oxidative stress by means of chronic activation of the autonomic and neuroendocrine stress responses.”

“Glucocorticoids, the primary adrenal hormones secreted during stress, increase oxidative stress damage to neurons, in part by increasing glutamate and calcium and decreasing antioxidant enzymes.”

Oxidative stress shortens telomeres.

The chronicity of caregiving stress results in shorter telomere length.

“In the elderly, telomere shortening is strongly associated with higher mortality rates.”

Patients with early myocardial infarction had telomere lengths that were equivalent to those typical of a person  $\approx$ 11 years older than controls, similar to the magnitude of accelerated cell aging observed in our high-stress group.

“The results reported here now implicate shorter telomeres in the adverse health sequelae of prolonged psychological stress.”

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#### KEY POINTS FROM DAN MURPHY:

- 1) [Elizabeth Blackburn, from the Department of Biochemistry and Biophysics, University of California, San Francisco, was awarded the Nobel Prize in Medicine/Physiology, October 2009, for her work pertaining to telomeres].
- 2) “Telomeres are DNA–protein complexes that cap chromosomal ends, promoting chromosomal stability. When cells divide, the telomere is not fully replicated because of limitations of the DNA polymerases in completing the replication of the ends of the linear molecules, leading to telomere shortening with every replication. In vitro, when telomeres shorten sufficiently, the cell is arrested into senescence.”
- 3) “In people, telomeres shorten with age in all replicating somatic cells that have been examined, including fibroblasts and leukocytes. Thus, telomere length can serve as a biomarker of a cell's biological (versus chronological) ‘age’ or potential for further cell division.”
- 4) Chronic stress is linked to poor health, including cardiovascular disease and poorer immune function.
- 5) Stress impacts health by modulating the rate of cellular aging.
- 6) Chronic stress is significantly associated with:
  - A)) Higher oxidative stress
  - B)) Lower telomerase activity [telomerase is an enzyme that adds to the length of the telomere]

C)) Shorter telomere length

These three are determinants of cell senescence [state of being old; the process of becoming old] and longevity.

7) “Women with the highest levels of perceived stress have telomeres shorter on average by the equivalent of at least one decade of additional aging compared to low stress women.”

8) “People who are stressed over long periods tend to look haggard, and it is commonly thought that psychological stress leads to premature aging and the earlier onset of diseases of aging.”

9) Telomeres and telomerase play crucial roles in cellular aging and potentially in disease.

10) Telomerase is an enzyme that adds to the length of the telomere. Reduced telomerase activity increases cellular senescence [state of being old; the process of becoming old].

11) Oxidative stress will shorten telomeres and antioxidants can decelerate this shortening.

12) Chronic psychological stress is linked to telomere shortening, lowered telomerase function, and to increased oxidative stress.

13) This study showed that:

“Those with the lowest stress have the longest mean telomere length.”

14) Telomere length declines during normal aging. The authors found that the telomere shortening in the high-stress group was equivalent of 9–17 additional aging years compared with the low-stress group.

15) “The high-stress group also had significantly lower telomerase activity and higher oxidative stress than the low-stress group.” The mean telomerase activity was 48% lower in the high-stress group.

16) The short telomere length group had higher stress, higher oxidative stress, and lower telomerase activity.

17) Stress increases oxidative stress by “means of chronic activation of the autonomic and neuroendocrine stress responses.”

**[Increased sustained sympathetic tone is deleterious to human health]**

18) “Glucocorticoids, the primary adrenal hormones secreted during stress, increase oxidative stress damage to neurons, in part by increasing glutamate and calcium and decreasing antioxidant enzymes.”

**[More evidence that excess dietary glutamate (MSG, etc.) is bad for health]**

- 19) Oxidative stress (free radical damage) shortens telomeres.
- 20) "In the elderly, telomere shortening is strongly associated with higher mortality rates."
- 21) Patients with early myocardial infarction had telomere lengths that were equivalent to those typical of a person approximately 11 years older than controls.
- 22) "The results reported here now implicate shorter telomeres in the adverse health sequelae of prolonged psychological stress."