Telomeres and telomerase in human health and disease

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What are telomeres and why should we care?
Telomeres cap ends of chromosomes.
Telomeric DNA Structure

Chromosome

Telomere

Simple repeated DNA sequence

Blackburn and Gall, 1978
The Telomere – the protective cap at every chromosome end

![Diagram of telomere with a protective protein sheath]
Predicted, if DNA replication alone acts on DNA:
Loss of DNA from the chromosome end

Eventual senescence

Watson, 1972, Olovnikov, 1971
DISCOVERY OF TELOMERASE

SYNTHETIC TELOMERE IN TEST TUBE

5' G G G G T T T G G G G G T T T G G G G G T T T 3' OH

Tetrahymena cell extract
Mg++
dGTP + TTP

Greider and Blackburn, 1985
**Tetrahymena thermophila**

Telomeres provide a reservoir of replenishable DNA. Telomeres are replenished by telomerase.

- **Tetrahymena thermophila**
  - Plenty of telomerase
  - Genetically inactivate telomerase
  - Telomeres progressively shorten

**Cells are immortal**

- Genetically inactivate telomerase
- Telomeres progressively shorten
- They become "mortal"

**Yu, Bradley, Attardi and Blackburn, 1990**
“Immortal”

Mutate telomerase

“Mortal”

Yu, Bradley, Attardi and Blackburn, 1990
Telomerase maintains the ends of chromosomes

Telomeres replenished by telomerase

Cells keep dividing
Without telomerase

Senescence; cell malfunction; genomic instability

STOP After a delay
How do we age?

A multi-faceted process
- increased susceptibility to diseases
Many normal human cells have limiting or no telomerase and their telomeres shorten with age.

Senescence  Death?

WHAT CAN SAVE THE CELLS? Telomerase:
- Active: stem cells, germ cells
- Low/none: many normal adult cell types
Plenty of telomerase:

Addition and shortening stay balanced
Plenty of telomerase:

Addition and shortening stay balanced

Cells keep dividing
Upregulated telomerase in humans: telomeres can grow in vivo

Weng, Granger and Hodes, 1997
Predicted, if some telomerase:
Slow loss of DNA from chromosome ends

Slower net loss/cell division

Senescence/malfunction comes later
Predicted, if less telomerase:
Faster loss of DNA from chromosome ends

- genetic
- environment/life factors
Measure telomere length

Telomeric DNA
In the **general** population telomere shortness is associated with diseases.

After correcting for age and multiple factors, major common diseases of aging have been linked to shorter telomeres in normal cells (many independent studies and cohorts).

Impaired immune fn. Cancers Lung Disease Heart disease Diabetes Vascular. dementia Osteoarthritis Risk factors eg smoking
In *general* populations, telomere shortness *precedes* the future onset of diseases of aging and earlier mortality.

After correcting for age and multiple factors, major *common* diseases of aging are anticipated by shorter telomeres in normal cells (many independent studies and cohorts).

Earlier Mortality
Impaired immune fn.
Cancers
Lung Disease
Heart disease
Diabetes
Dementias
TELOMERE LENGTH AND MORTALITY
Cross sectional relationship of mean human telomere length with age. N = 100,000 people
Mean Telomere Length (cells in saliva). Error bars are 1 s.e. of mean

Kaiser Permanente Research Program in Genes, Environment and Health (RPGEH) Genetic Epidemiology Research on Aging (GERA) Cohort

Lapham, Kvale et al, unpubl.
Cross sectional relationship of mean human telomere length with age, separately for males and females.

Mean Telomere Length (cells in saliva). Error bars are 1 s.e. of mean

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Kaiser Permanente Research Program in Genes, Environment and Health (RPGEH) Genetic Epidemiology Research on Aging (GERA) Cohort

Lapham, Kvale et al, unpubl.
Odds of all-causes mortality within 3 yrs of telomere measure

Telomere length at this time was measured (N= 100,000)

Who had died within the 3 years since telomere length measure (N= ~ 2,500)

Compare to Mean Baseline Telomere Length

* Adjusted for age, gender, race-ethnicity, education, cigarette pack years, physical activity, alcohol drinks per week, and BMI

Unpubl.
Telomere shortness predicts all-cause mortality in the 3 yrs since telomere measure

- Quartile 1 = Shortest

- Adjusted for age, gender, race-ethnicity, education, cigarette packyears, physical activity, alcohol drinks per week, and BMI

Unpubl.
Short mean telomere length predicts all-cause mortality in the 3 yrs since telomere measure.

Decile 1 = Shortest telomeres

Telomere length at this time was measured

Unpubl.
Short Mean Baseline Telomere Length in White Blood Cells Predicted All-causes Death

Community-based study  Age range 66 – 101  N=1900

Telomere length measured at this time

42%
CAUSALITY
CAUSALITY
– Part 1
patterns of inheritance
Disease impact

Telomere shortness in the general population is associated with diseases of aging.

Too-short Telomeres

Disease impact
How do human beings respond if they have a mutation causing only half the usual telomerase level?
Lessons learned from Rare Mutations in People’s Telomerase Genes

Disease impact

Rare genetic mutations that cause telomere shortness cause diseases of aging

Early death

Certain cancers

Immune system failure

Pulm. Fibrosis

Cirrhosis

Diabetes

Lessons learned 1:

GENETICS tells us:
Just
2x too little
telomerase
causes some
cancers
Lessons learned 2:

Some COMMON variations in genes known to maintain telomeres - that can cause telomere shortness - raise risks for common diseases of aging.

COMMON variation in telomere/telomerase genes

Codd et al, 2013

GENETICS tells us:

- Pulmonary fibrosis
- Coronary artery disease
Lessons learned 3: 

Other COMMON variations of genes known to maintain telomeres are especially likely to be in centenarians.

(Better maintenance of telomeres?)

COMMON variant SNPS – eg TERT, TERC, others

Deelen et al, 2011
Telomere shortness in White Blood Cells Predicts Future Cancer incidence and Cancer Mortality

Telomere length measured at this time

Willeit, P. et al. JAMA 2010;304:69-75
Short Telomere Length Predicts CVD

Telomere Length at Baseline by Tertiles

CVD

Stroke

MI

Vasc. Death

Shortest

Mid

Longest

Lessons learned 4: GENETICS tells us:

Just 2x too little telomerase causes cancers

BUT

ALSO

Just 2x too much telomerase gene expression causes cancers

We live balanced on a knife-edge
Disease impact

Telomere shortness in the general population is associated with diseases of aging.

GENETICS tells us:

Too-short Telomeres → Disease impact
WHAT CAN INFLUENCE TELOMERE MAINTENANCE IN HUMANS?

CAUSALITY – Part 2
A story from 2500 years ago:
how stress accelerates aging
Chronic psychological stress

Disease Impact
eg, heart disease
Stressors and Shortened Telomeres in Adults

• Perceived stress (Epel et al, 2004, Parks et al, 2009; Puterman 2010)

• Caregiver stress (Damjanovic, 2006; O’ Donovan, 2011, Wolkowitz et al, 2011)
  - mothers of ill child
  - dementia caregivers

• Major Depression (Simon, 2006; Wolkowitz, 2011)

• Former Domestic Abuse victim (length of abuse) (Humphreys et al, 2011)
Cynical hostility level is associated with telomere shortness in the UK Whitehall Civil Servants Cohort.

Brydon et al, 2011
Factors in Earlier Life/Childhood are Associated with Persistent Effects on Telomere Shortness into Late Adult Life

1. Intrauterine maternal stress exposure

2. Cumulative exposure to childhood traumas

3. Cumulative exposure to childhood traumatic events – in adults with PTSD

4. Low educational attainment
Chronic psychological stress is associated with telomere shortening.

NON-GENETIC INFLUENCES
Shorter telomeres are associated with disease
Connecting Chronic Psychological Stress, Telomeres and Disease Impact
Combined factors contribute to aging-related diseases. NON-GENETIC and GENETIC factors are involved:

- Environmental
- Life events/behavior

Risks for aging-related diseases and mortality:
- Poor immune function
- Cancers
- Cardiovascular disease
- Diabetes
- Mental/cognitive disorders/depression
Telomere attrition: a stress-related, malleable biomarker for, and contributor to, aging-related diseases

NON-GENETIC and GENETIC

Environmental Life events/behavior

Telomere attrition

Risks for aging-related diseases and mortality:
- Poor immune function
- Cancers
- Cardiovascular disease
- Diabetes
- Mental/cognitive disorders/depression
The Future of Medicine: Prevent, preempt and intercept Diseases. Why Now?

Pre-disease

Preempt

Pre-disease

Preempt

Advanced

Treat

Advances in understanding disease etiology and biology and in clinical options are giving us the ability to think about preventing and intercepting more diseases.
Genes

Telomere loss

Adverse Childhood Events

Chronic Stress

Pessimism Hostility

Disease risks

Telomere upkeep

Education

Exercise

Stress reduction

Health