Biological embedding of life stress?
Telomeres and Telomerase

Elissa Epel, UCSF
“Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older.”

-Hans Selye
Cell Aging: Telomere Length

**Telomeres**
non-coding sequences capping ends
A “senescence clock” (Blackburn, 1978)
Stops proliferation

**Telomerase:**
enzyme that prevents telomere shortening
Promotes cell resilience.
Publications on telomeres and telomerase

Discovery of telomerase

Courtesy of Elizabeth Blackburn
Telomere Length predicts healthspan and mortality (8 studies)

**Longer telomeres:**
- increased years of healthy life \((Njajou, 2009)\)

**Shorter telomeres:**
- Lower 17-year survival from aggregate of all causes (infectious, CVD) \((Cawthon, 2003)\)
- Lower 10 year survival \((Erlenbach, 2009)\)
- Lower 12 year survival in women \((Epel, 2009)\)
- CAD patients (4.4 years) \((Farzaneh-Far, 2008)\)
- Alzheimers patients \((Honig, 2006)\)
- Twin studies \((Baykasa, 2007; Kimura, 2008)\)
WHR still leads to shortening

Table 3. Independent predictors of leukocyte telomere shortening as a dichotomous variable (multivariable logistic regression with backward selection of candidates in table 1 retained at p<0.1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio for Telomere Shortening</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline T/S (per SD)</td>
<td>7.6</td>
<td>5.5, 10.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (per 10 yrs)</td>
<td>1.6</td>
<td>1.3, 2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>2.4</td>
<td>1.3, 4.7</td>
<td>0.007</td>
</tr>
<tr>
<td>Waist-to-hip ratio (per 0.1 increase)</td>
<td>1.4</td>
<td>1.0, 2.0</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Low Telomerase is associated with major risk factors for CVD

In the largest epidemiological study of risk factors for cardiovascular disease, the top six prominent factors were shown to be:

- smoking
- poor lipid profile
- high blood pressure
- diabetes
- abdominal obesity
- psychological stress

(Yusef et al, Lancet 2004:304)

Lower telomerase activity

- smoking
- cholesterol/blood lipids
- resting cardiovascular activity
- Fasting glucose
- adiposity
- psychological stress

(Epel et al, 2006, Psychoneuroendocrinology)
Biological embedding??

1) Relations with stress, early life stress
2) What makes cell aging unique?
3) Developmental course: Little Data!
4) Future directions
Telomeres: A new psychobiomarker? (Epel, 2009)
I think it's stress!!
Telomere Length covaries with exposure to a chronic stressor

Epel, Blackburn et al, 2004, PNAS
Indices of ‘stress’ and Telomere Length

Low SES (Cherkas et al, 2006)

Psychological Stress (Epel et al, 2004; Damjanovic et al, 2006; Parks et al, 2009)

Stressed female mice (Kortschral, 2006)

Depression (Simon et al, 2006; Lung et al, 2007)

Mental Health (SF-36) (Huzen et al, 2010)

Early Trauma (Tyrkas et al, 2010)
Telomeres are shorter in those with childhood maltreatment

Tyrka et al, 2010
Unique biomarker?
Telomere maintenance: a master integrator?

Infectious exposures
- Nutrition
- Mental states
- Exercise

Biochemical Stressors

Genes

Risks for aging-related diseases/Poor immune function
- Psychiatric disorders
- Cardiovascular disease
- Cancer
- Metabolic disease
- Fibrosis
Pathways to cell aging

Stress perception

Hypothalamus

Biochemical Stressors

↑ CORTISOL

↓ Adiposity

↑ Cytokines (fat, immune cells)

↑ Oxidative Stress (tissue, blood cells)

Teleomere Telomerase Maintenance System

Epel, Hormones, 2009
DEVELOPMENTAL FRAMEWORK: CRITICAL PERIODS VS. LIFECOURSE LOAD?
Telomere length: Large variance across the lifespan

Average human leukocyte telomere length is 11kb at birth, and drops to 6 kb at age 90. (Yamaguchi, NEJM, 2005)
Telomere Attrition by Age

Fig. 3. Phases of telomere shortening in normal PBLs. The point shown for age 5 is taken from the oldest child shown in Fig. 2. The initial phase is characterized by rapid loss of telomeric repeats. An apparent stabilization then occurs between age 5 and young adulthood. Telomere loss resumes at a slower rate later as adults grow older. See text for further discussion.

Frenck et al., 1998; PNAS
Development of immune system

“Pruning” in early years
Dramatic decrease in telomere length
Unknown mechanisms
Fetal environment
Stem cell status
No longitudinal studies from early life to adult!
Telomere Attrition in Infants

ZEICHNER ET AL

270 bp/year, 4x higher than adults
Telomeres and Infant Growth

Jennings, 1999

Rat pups studied with protein restriction prenatally or postnatally, vs. controls

Telomere attrition mirrored growth (shortened most during early growth, and then at end of life)

Postnatal growth restriction ⇧ longer TL, longevity

Prenatal growth restriction ⇪ shorter TL, earlier mortality (due to catch up growth?)
Implications?

Prenatal development and Infancy appear to be critical periods for telomere attrition.
Set up for life long (but malleable) “trajectory” for disease?
CHALLENGES
Challenges

Make few assumptions
- Dogma is vast, data is scarce

Whole blood vs. specific cell types
- Need mechanistic studies

Cross sectional vs. longitudinal

Telomerase is reactive! *(Epel et al, 2010, BBI)*

(need resting baselines)
Some next steps

Methodological:
TL in other cells / assay types / effects on behavior
(Puterman, Lin, Blackburn, Schamarek)

Clinical studies
Trajectories & functional significance of immune senescence in caregivers & controls
Interventions (Hecht, Kemeny, Moran, Daubenmier, Blackburn, Lin)
Telomeres in caloric restriction (Tomiyama)

Populations
TL: SES/ethnicity, predicting mortality in NHANES
Acknowledgments to some key collaborators:
Elizabeth Blackburn, UCSF
Jue Lin, UCSF
Firdaus Dhabhar, Stanford
Richard Cawthon, U. Utah
Owen Wolkowitz, UCSF
Teresa Seeman, UCLA

FUNDING
NIA Behavioral & Social Research (R56, R01)
NIMH (K08)