Molecular strategies target telomerase in cancer and aging

Fighting cancer and aging

Maria A. Blasco’s team, CNIO, Madrid
healthy cells are MORTAL

50-70 divisions

“senescent” cells

Henrietta Lacks

cancer cells are IMMORTAL

unlimited divisions
Telomeres are lost everytime that a cell divides.

“the end-replication problem”

DNA is lost from the ends
An embryonic gene known as **telomerase** is able to elongate telomeres to compensate excessive telomere loss during embryo development.

This gene, **telomerase**, is silenced after birth … however …

Cancer cells manage to reactivate **telomerase**, thus escaping the mortal fate of adult cells and becoming immortal.
Telomeres, telomerase and aging

Telomere length = **Biomarker** of aging?

Lower percentiles of telomere length =
higher risk of diseases (cardiovascular,
neurodegenerative, death by infections)

cancer
(> 95% of cancers activate telomerase)

Human pathologies due to telomerase defects

dysqueratosis congenita (DKC1, Terc)
aplastic anemia (Terc, Tert)
idiopathic pulmonary fibrosis (Terc, Tert)

loss of the regenerative capacity of the skin
lungs, bone marrow…

Telomeres, telomerase and aging

Telomere length=

Tissues and organs (including stem cells)

Mutations in telomerase

health
disease

age
Telomere length as a biomarker of biological age & health status

Telomere length decreases with age

- **men** (n = 90): $71 \pm 13$ bp/year; $r = 0.495$, $p < 0.001$
- **women** (n = 108): $72 \pm 20$ bp/year; $r = 0.336$, $p < 0.001$

Telomere length predicts age & cognitive impairment

Canela et al., PNAS (2007)
**Telomere length as a diagnosis tool**

Subject 49- Male 02/02/78 healthy  
Subject 50- Male 22/09/77 medular aplasia, TERC mut  
Subject 51- Male 17/05/78 healthy  
Subject 52- Male 06/06/78 healthy  

Canela et al., unpublished
Telomere length as a BIOMARKER of aging & health status

A very accurate technology for telomere length measurement
Telomere length measurements for individuals

Life Length’s partnership with: LABCO Quality Diagnostics
Telomere length measurements for individuals

Q1: porción de la población entre el valor mínimo y el percentil 25 (telómeros muy cortos)
Q2: porción de la población entre el percentil 25 y la mediana (telómeros cortos)
Q3: porción de la población entre la mediana y el percentil 75 (telómeros largos)
Q4: porción de la población entre el percentil 75 y el valor máximo (telómeros muy largos)
Q5: porción de la población entre el valor mínimo y el percentil 25 (muy pocos telómeros cortos)
Q6: porción de la población entre el percentil 25 y la mediana (pocos telómeros cortos)
Q7: porción de la población entre la mediana y el percentil 75 (bastantes telómeros cortos)
Q8: porción de la población entre el percentil 75 y el valor máximo (muchos telómeros cortos)
Telomere length measurements for individuals

✓% short telomeres detect more differences between individuals than average length
✓% short telomeres show higher dispersion as we age
✓% short telomeres are likely to reflect “way of living” (environment) or **biological age**
Genetic tests: genes as risk factors for disease

Telomere tests: indication of the degree of aging

INHERITED

ENVIRONMENT

# aging is the highest risk factor for all diseases

# telomere length integrates both inheritance & environmental factors

MORE POWERFUL PREDICTIONS OF RISKS AND TIME OF ONSET

DEVELOPMENT OF NEW TREATMENTS TO PREVENT DISEASE

A NEW ERA in medicine?: Personalized & preventive medicine
Breast cancer: Familial breast cancer

BRCA1/BRCA2

More powerful tools to predict risk factors and develop new treatments

Javier Benitez (CNIO)
Life Length’s impact
Life Length's impact
The role of telomerase in chromosome stability, cancer & aging

Telomerase-deficient mice (Terc−/−):

- decreased regenerative capacity due to stem cell dysfunction
- less cancer

Super-telomerase mice (K5-Tert):

- better tissue fitness
- slightly more cancer

Blasco et al., Cell (1997)
González-Suarez et al., Nat Genet (2000)
González-Suarez et al., EMBO J. (2001)
Flores et al., Science (2005)
Telomerase as an anti-cancer target (Imetelstat)

Phase II
Clinical trials
(breast, lung, prostate etc)
Can telomerase delay aging pathologies?
Mice are born with long telomeres but suffer telomere shortening with aging

HT Q-FISH in blood

Wild-type mice (n=74)
Linear regression:
Slope= -7.03 ± 1.24 kb/year
$R^2 = 0.31$
p<0.0001

Quadratic:
$R^2 = 0.34$

Mice shorten telomeres 100-fold faster than humans

Vera et al. unpublished
Telomerase is rate-limiting for mouse longevity

- **Telomere length**
  - 1 year
  - 2 years
  - 3 years

- **Telomerase**
  - *tert*

- **Genetic anticipation**
  - G3
  - G2
  - G1

- **Survival (%)**
  - Median life-span
  - Maximum life-span

La telomerasa se expresa específicamente en células madre. El exceso de telomerasa puede causar un aumento en la longevidad, mientras que el déficit de telomerasa puede causar premature aging. El super p53, super p16, super p19ARF y los inhibidores de ARF pueden prevenir el cáncer.

Gonzalez-Suarez et al., Oncogene (2004)
Increased “health span” & longevity in SUPER mice

Overall survival

Cancer-free survival

Survival at 3 years (%)

Tomás-Loba et al., Cell (2008)
**Improved health late in life in SUPER mice**

**Improved neuromuscular fitness**

- Success rate (%)
  - young (5-20 weeks)
  - old (116-160 weeks)

- **Improved glucose tolerance**
  - 30-76 weeks

- Glucose tolerance (AUC)
  - wildtype
  - SUPER

Tomás-Loba et al., *Cell* (2008)
Less skin aging in SUPER-M mice

Tomás et al., *Cell* (2008)
Defeating aging with increased telomerase + tumor suppression

The naked mole rat does it!

The longest lived rodent (>30 years old)
Size of a mouse

LETTER

Genome sequencing reveals insights into physiology and longevity of the naked mole rat

# constitutive expression of telomerase
# increased cancer resistance