TELOMERE MODULATION IN VIVO

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TELOMERE EROSION WITH AGING

Telomere length in peripheral blood leukocytes

Calado & Young, *NEJM* 2009
TELOMERES AND HUMAN DISEASE

- Mutations in TERT, TERC, TINF2, RTEL1, DKC1, TCAB1...
  - Dyskeratosis congenita is the typical telomere disease
  - Very short telomeres

**Aplastic anemia**
- Fogarty et al. Lancet, 2003
- Yamaguchi et al. NEJM, 2005

**Pulmonary fibrosis**
- Tsakiri et al. PNAS, 2007
- El-Chemaly et al. Chest, 2010

**Liver disease**
- Calado et al. Hepatology, 2011
- Hartmann et al. Hepatology, 2011
INDUCED PLURIPOTENT STEM (iPS) CELLS FROM PATIENTS WITH TELOMERASE MUTATIONS

Peripheral Blood Telomere Length

- Healthy subjects
- TERT R1084P
- TERT R889Xf
- TERT R889Xm
- TERC -58G>C
- Healthy control

Winkler et al., JCI 2013
TELOMERE DYNAMICS IN PATIENT-DERIVED iPS CELLS

TELOMERE ELONGATION DUE TO TERT AND TERC ACTIVATION

Winkler et al., JCI 2013
O₂ MODULATES TELOMERE LENGTH DURING REPROGRAMMING

O₂ ALSO MODULATES TERT AND TERC EXPRESSION

Winkler et al., JCI 2013
Anabolic Androgenic Steroids in the Treatment of Acquired Aplastic Anemia

By L. Sanchez-Medal, A. Gomez-Leal, Lorenzo Duarte and Maria Guadalupe Rico
SEX HORMONES INCREASE TELOMERASE ACTIVITY IN CULTURED HUMAN LYMPHOCYTES

Calado et al, Blood 2009
SEX HORMONES MODULATE TERT ACTIVITY

Androgens

CH₃

O

O – C – CH₂(CH₂)₇CH₃

O

O

OH

O

Estradiol

Aromatase

Estrogen

Estrogen receptors

Estrogen-estrogen receptors

TERT gene

Estrogen-response element

↑ mRNA

↑ TERT protein

↑ Telomerase activity

Calado et al, Blood 2009
**Trf1 “KNOCK OUT” MOUSE MODEL FOR APLASTIC ANEMIA**

**Androgen Therapeutic Effects**

(A) Schematic overview of the experimental design:
- 4 weeks of Flt3L treatment
- 3 injections per week
- Bone marrow transplantation
- Irradiation
- Androgen pellet implantation

(B) Survival analysis:
- Trf1\textsuperscript{lox/lox} Mx1-Cre
- 3x Flt3L injection/week, stop after 4 weeks
- + testosterone n=8
- - testosterone n=8
- P = 0.024 (Log-rank)

(C) Telomere length over time:
- Trf1\textsuperscript{lox/lox} Mx1-Cre
- 3x Flt3L injection/week, stop after 4 weeks
- No testosterone n=5
- Testosterone n=5
- P = 0.01

(D) Telomere length over time:
- Trf1\textsuperscript{lox/lox} Mx1-Cre
- No Flt3L control
- No testosterone n=5
- Testosterone n=5
- P = 0.01

(E) Blood cell counts over time:
- Granulocytes 10^9/L
- Erythrocytes 10^12/L
- Platelets 10^12/L
- No testosterone n=6
- Testosterone n=8
- P = 0.03
- P = 0.001
- P = 0.09

Bär et al. Haematologica 2015
Trf1 “KNOCK OUT” MOUSE MODEL FOR APLASTIC ANEMIA

Sex Hormone Effects on Telomere Length

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<th>MEF</th>
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<td><strong>P&lt;0.001</strong></td>
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<td>n.s.</td>
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relative telomere length (wt mean set to 1)

Tert⁺/⁺  G1 Tert⁻/⁻

D

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<tr>
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<th>MeOH</th>
<th>estradiol</th>
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<td>% of short telomeres (10th percentile of MeOH)</td>
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<td><strong>P=0.04</strong></td>
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Bär et al. Haematologica 2015
NANDROLONE FOR TELOMEROPATHIES

“Nandrolone for Genetic Marrow and Lung Disorders”

Nandrolone 5mg/kg every 2 weeks x 2 yrs for patients with short telomeres +/- mutations

Phase I/II design, N=20

Primary endpoint: telomere attrition
Secondary clinical endpoints:
  toxicity (especially hepatic)
  efficacy (blood counts and pulmonary function)

RECRUITING PATIENTS!

ClinicalTrials.gov identifier: NCT02055456
NANDROLONE FOR TELOMEROPTHIES

Clé et al. unpublished
SUMMARY

• Telomeres elongate during cell reprogramming
• $O_2$ concentration modulates telomerase expression and telomere length in iPS cells
• Expression of other genes related to DNA repair may correlate with telomere length and marrow failure in telomeropathy patients
• Sex hormones stimulate telomerase expression and telomere elongation \textit{in vitro} and \textit{in vivo}
• Androgens induce telomere elongation in telomeropathy patients
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