DIAGNOSIS AND TREATMENT OF TELOMERE DISEASES

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Interphase (flow-FISH)

Metaphase

Courtesy, Peter Lansdorp
UBC, Vancouver, Canada
TELOMERES SHORTEN WITH CELL DIVISION

No telomerase

Cell division

+ Telomerase

Telomere erosion
TELOMERASE ELONGATES THE 3’ END OF TELOMEREs BY ADDING TTAGGG REPEATS

Calado & Young, NEJM 2009
TELOMERES AND HUMAN DISEASE

- Dyskeratosis congenita
- Hoyerdaal-Hreidarsson syndrome
- Revesz syndrome/Coats disease
- Coats’ plus
- Aplastic anemia/MDS/AML
- Idiopathic pulmonary fibrosis
- Liver disease (cirrhosis/NASH/non-cirrhotic portal hypertension)
TELOMERES AND HUMAN DISEASE

Nail dystrophy  Abnormal skin pigmentation  Leukoplakia

Dyskeratosis congenita
  - Inherited disorder (*DKC1, TERC, TERT, TINF2, CTC1*)
  - Triad of mucocutaneous findings
  - Marrow failure (70%), pulmonary fibrosis (20%), cirrhosis (7%)

Dokal I. Hematology Am Soc Hematol Educ Program. 2011
TELOMERES AND HUMAN DISEASE

Nail dystrophy

- Hoyeraal-Hreidarsson syndrome
  - More severe manifestation (*DKC1, TINF2, RTEL1*)
  - Triad of mucocutaneous findings
  - Cerebellar hypoplasia (ataxia)

Cerebellar hypoplasia

Savage SA. Prog Mol Biol Transl Sci. 2014
Revesz syndrome/Coats disease
- More severe manifestation (*DKC1, TINF2, RTEL1*)
- Bilateral exudative retinopathy

Nail dystrophy

Exudative retinitis

Savage SA. Prog Mol Biol Transl Sci. 2014
TELOMERES AND HUMAN DISEASE

Cranial calcification

- Coats’ plus
  - Severe manifestation (*CTC1*)
  - Bilateral exudative retinopathy
  - Asymmetric cranial calcification

Exudative retinitis

Anderson et al., Nat Genet 2012
ACQUIRED APLASTIC ANEMIA
Telomeres Are Short in Patients in with Telomerase Mutations

Yamaguchi et al., NEJM 2005
APLASTIC ANEMIA, MYELODYSPLASIA, HSCs AND TELOMERES

- Age 34: AA/hypo MDS
- Marrow cellularity <5%
- Immunosuppressive therapy with rabbit ATG + CsA
- Became transfusion independent after discharge
APLASTIC ANEMIA, MYELODYSPLASIA, HSCs AND TELOMERES

Telomere length, kb

Age, years

TERT R865H mutation
TELOMERE LENGTH MEASUREMENT

Gutierrez-Rodrigues et al., PLoS ONE, in press
TELOMERE LENGTH MEASUREMENT

Gutierrez-Rodrigues et al., PLoS ONE, in press
TELOMERE LENGTH MEASUREMENT

A. Healthy subjects

B. qPCR - Southern blot

C. Patients

D. qPCR - Southern blot

Gutierrez-Rodrigues et al., PLoS ONE, in press
TELOMERE LENGTH MEASUREMENT

Gutierrez-Rodrigues et al., PLoS ONE, in press
INDUCED PLURIPOTENT STEM (IPS) CELLS

- dermal fibroblasts
- sox2
- klf4
- oct4
- c-myc

Patient-specific disease models

Blood
Skin
Digestive

Therapies

Telomere dynamics
INDUCED PLURIPOTENT STEM (IPS) CELLS

Takahashi & Yamanaka, 2006 Cell
TELOMERE DYNAMICS IN PATIENT-DERIVED IPS CELLS

Telomere Length

Hypoxia and telomeres

Winkler et al., JCI 2013
INDUCED PLURIPOTENT STEM CELLS FROM TERT-MUTANT PATIENTS
REDUCED HEMATOPOIETIC DIFFERENTIATION

Winkler et al., JCI 2013
SEX HORMONES INCREASE TELOMERASE ACTIVITY IN CULTURED HUMAN LYMPHOCYTES

(n=10)

Telomerase Activity (TPG units)

Methyltrienolone (synthetic) 0 0.5 5 μM
Nandrolone 0 5 μM
6β-Hydroxy-Testosterone 0 5 μM
β-Estradiol 0 1 μM

Androgens

Calado et al., Blood 2009
11-H-0209: “Danazol for Genetic Bone Marrow and Lung Disorders”

Danazol, 800 mg/d x 2 yrs for patients with short telomeres +/- mutations

Phase I/II design, N=25

Primary clinical end points
- toxicity (especially hepatic)
- efficacy (blood counts and pulmonary function)

Protocol opened 19 Aug 2011; 15 patients enrolled to date

Modest drug toxicity (minimal ↑ LFTs, mild headaches)

ClinicalTrials.gov identifier: NCT01441037
11-H-RTC-0002: “Nandrolone for Genetic Marrow and Lung Disorders”

Nandrolone 15mg every 2 weeks x 2 yrs for patients with short telomeres +/- mutations

Phase I/II design, N=20

Primary clinical end points
  toxicity (especially hepatic)
  efficacy (blood counts and pulmonary function)

Protocol opened February 4, 2014; 5 patients enrolled to date

ClinicalTrials.gov identifier: NCT02055456
**Tert-DEFICIENT MICE ARE SENSITIVE TO HIGH-FAT DIET**

![Graph showing ALT (IU/L) levels with different diet conditions and genotypes.](image)

**H&E**

Alves-Paiva et al., *in preparation*
Tert-DEFCIENT MICE ARE SENSITIVE TO HIGH-FAT DIET

Alves-Paiva et al., in preparation
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Support