Telomere Dysfunction-Induced Senescence in Aging and Disease

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Cellular Senescence

DNA Replication (Telomere Shortening)
Oncogenic Stress
DNA Damage
Oxidative Stress
Cytokines
Chromatin Changes
Developmental Cues
Mitochondrial Disturbances
Cell Reprograming
Cell-Cell Fusion

Human Diploid Fibroblasts
Biological Role of Cellular Senescence

Tumor Suppression
2005

Wound Healing
2008

Aging
2011

Embryonic Development
2013
Biological Role of Telomere Dysfunction-Induced Senescence - TDIS

Aging
Herbig et al., 2006, Science

Tumor Suppression
Suram et al., 2012, EMBO J

Wound Healing
Razdan et al., 2018, Aging Cell
Cells Age and Undergo Replicative Senescence

[Diagram showing the process of cell division and senescence, with healthy and senescent cells indicated.]
Telomere Dysfunction-Induced Senescence

Fibroblasts
In
Dermal Tissue

Cells With Dysfunctional Telomeres Increase With Age

Skin (2-21%)
Liver (4-7%)
Heart
Kidney
Lung (fibroblasts, 12-17%)
Adrenal Cortex (2-6%)
Colon (epithelium)
Pancreas (1-6%)
Brain (Frontal Cortex; 2-20%)

J. Kaplunov; unpublished
Mice Accumulate p16\textsuperscript{INK4a}-Senescent Cells With Advancing Age

Clearance of $p16^{\text{Ink4a}}$-positive senescent cells delays ageing-associated disorders

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Senescence Associated Secretory Phenotype (SASP) Causes Telomere Dysfunction

Razdan et al., 2018 Aging Cell
Senescence and Aging

Formation of senescent cells
- Healthy cell
- Senescent cell
- SASP

Restricted immune response
- Elimination
- Immune cell

Tissue homeostasis

Acute stress
- Radiation
- Chemicals
- Oncogene activation

Young

Ageing
- Genomic instability
- Telomere attrition
- Epigenetic aberrations
- Loss of proteostasis

Persistance of senescent cells
- Dysfunctional immune cell
- Pre-malignant cell

Degeneration & malignancies
- Tumor cell
- Tissue degeneration

Old

Chronic stress

Degeneration & malignancies
Age-related diseases

from Y. Ovadya & V. Krizhanovski; Biogerontology (2014) 15:627-642
The Accumulation of Senescent Cells Causes Aging and Age-Related Diseases

Universal aging traits:
- Impaired wound healing
- Weak immune system
- Reduced hearing
- Osteoporosis
- Sarcopenia
- Hair graying
- Skin wrinkling
- Poor vision

Age-related diseases:
- Alzheimer’s disease
- Parkinson’s disease
- Cataracts
- Macular degeneration
- Glaucoma
- Atherosclerosis
- Hypertension
- IPF
- COPD
- Osteoarthritis
- Type 2 diabetes (obesity, fat dysfunction)
- Cancer
- Treatment-related disability
Senotherapeutic Strategies to Improve Healthy Aging
Our Current Research Efforts to Improve Healthy Aging

1. **Improving the detection and characterization of senescent human cells in tissue**
   Current techniques (*TIF, SA-βGal, DDR-foci, SudanBlack, p16, p21, LaminB1, macroH2A...*) are expensive, laborious, and time consuming. Separation of senescent cells from non-senescent cells is challenging.

2. **Rejuvenation of aged cells through pharmacological activation of hTERT expression**
   *In mice, hTERT gene therapy and TA-65 expression improves health-span and extends lifespan.*

3. **Inducing cellular plasticity by SASP factors**
   *In mice, SASP factors induce cellular plasticity and promote “stemness” of keratinocytes in a paracrine manner.*
1. Improving the detection and characterization of senescent human cells in tissue
2. Rejuvenating Aging Cells

- Telomeres shorten with each cell division.
- Telomere Dysfunction leads to Replicative Senescence.
- Aging is associated with shortened telomeres.
- Introduction of hTERT (telomerase) can reverse telomere shortening.

Human Chromosome 5:
- 5p and 5q regions.
- Repressed hTERT promoter.
- Active hTERT promoter.

Aged cell → "young" cell with hTERT gene locus.

Aging? → Replicative Senescence → Telomere Dysfunction → Shortened Telomeres
3. Inducing Cellular Plasticity

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"young" cell

stress

Early Senescence
TGFβ, SASP 1

4-6 days

"Deep" Senescence
IL6, IL8, MMPs

Fibroblast

Pluripotency?

Wound Healing
Tissue Repair
Cellular Plasticity

Pro-Inflammatory
Aging
Cancer

SASP 2
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