Aging

Time-related deterioration of the physiological functions
Outline

- Major Theories/Hypotheses on Aging
- Premature Ageing Diseases
- What’s in the Future?
Major Theories/Hypotheses of Aging
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1. Reactive Oxygen Species (ROS)
2. Genetic Programming of Aging
3. The “Wear-and-Tear” Theory
   - DNA & Information
   - Mitochondria
   - Telomere & Telomerase
1. Reactive Oxygen Species

- No mutations required
- Senescence = When oxygen atoms in the mitochondria are reduced to ROS
- ROS = molecules that oxidize and damage cell membranes/proteins/nucleic acids
Examples:

- P66shc protein in mice
- Caloric restriction
- Vitamins E & C
2. Genetic Programming of Aging

- Hutchinson-Gilford Progeria syndrome
- 2 examples of *C. elegans*
3. “Wear-and-Tear” Theory

- Accumulated point mutations $\rightarrow$ Senescence

- Examples:
  - DNA & Information
  - Mitochondrial mutations
  - Telomere & Telomerase
Telomere & Telomerase

Internal RNA template

5' CCCTTA ACCCTA
3' AAUCCCAAU

5' ACCCTA CCCTTA
3' AAUCCCAAU

DNA synthesis

Telomerase translocation

5' CCCTTA ACCCTA
3' AAUCCCAAU

5' ACCCTA CCCTTA
3' AAUCCCAAU

DNA synthesis
However, some suggested that...

- Telomere lengths are independent of life span
- There are no correlations between one’s age and one’s telomere lengths
- More research needed
Who is Geron?

- Biopharmaceutical company focusing on telomerase, human embryonic stem-cell, and nuclear transfer researches

- Feb 18th, 2003: “Effects of telomerase transduction suggest differential impairment of lytic and cytokine functions in senescent HIV-1-specific cytotoxic T lymphocytes”
Premature Aging Diseases

1. Down syndrome (Early-onset Alzheimer’s Disease)
2. Werner’s Syndrome
3. Hutchinson-Gilford Progeria syndrome
Down Syndrome (Early-onset Alzheimer’s Disease)

- Neurodegenerative disorder: loss of memory, language, & reasoning
- Autosomal-dominant genetic disease on chromosome 21
- Early onset: 30-40 years
Werner’s Syndrome

- Autosomal-recessive genetic disease on chromosome 8
- Defective DNA metabolism
- Symptoms: hair graying/loss, cataracts, atherosclerosis, osteoporosis (but NO signs of neurogeneration, hypertension)
- Average living age: 47 years
Hutchinson-Gilford Progeria Syndrome

- Single dominant mutation on exon 11 of chromosome 1 (Lamin A gene)
- Symptoms: dwarfism, arteriosclerosis, myocardial infarction
- Average living age: 13.5 years
Database Results (eMATRIX)

**Lamin A**
(Nuclear membrane structure)

- Nodavirus coat precursor endopeptidase (A6)
- Alpha-2C adrenergic receptor
- Metabotropic glutamate receptor 5

**Progeria**

[1824 C-T + 1819 – 1968del]

- EB module
- Claudin-14
Exon 11 only (eMATRIX)

Progeria
- 3.16e-02  Keratin, high sulfur B2 protein (3-MTCSITTTAPTAAARGTPLSTTCARAPCCAGPAG-36!)
- 4.54e-01  Claudin-14 signature IV (14-AAARGTPLSTTCA-26)
- 7.89e-01  EB module (21-LSTTCARAPCC-31)

Lamin A
- 7.14e-02  Nodavirus coat precursor endopeptidase (A6) aspartic protease signature VII (69-ATAVWGAVGVAASGT-83)
- 8.88e-02  Keratin, high sulfur B2 protein (3-MTCSITTTAPTAAARGTPLSTTCARAPCCAGPAG-36!)
- 1.63e-01  Alpha-2C adrenergic receptor signature I (75-AVGVAASGTIWSPTSW-92)
- 9.05e-01  Metabotropic glutamate receptor 5 sig. VII (50-RWADPSPLALLP-61)
Telomerase Connections?

- **Down syndrome:**
  Diseased cell’s telomere length no significant difference with normal cell’s

- **Werner’s syndrome:**
  Diseased fibroblast’s telomere length at senescence slightly longer than normal cell’s at senescence

- **Progeria:**
  Diseased fibroblast’s telomere length shorter than normal cell’s, but not all progeric fibroblasts have reduced telomere lengths

- **CONCLUSION:** No apparent connections → there must be other factors besides telomerase!
Other Premature Aging Diseases

Generalized
- **ROTHMAN-THOMSON SYNDROME**: cataracts, thinning hair
- **COCKAYNE SYNDROME**: degeneration of the brain, cataracts

Neurodegeneration
- **HUNTINGTON’S CHOREA**

Eye
- **RETINITIS PIGMENTOSA**
- **MACULAR DEGENERATION**
- **CATARACTS**

Skin
- **CUTIS LAXA**: early degeneration of elastin in the skin
- **PSEUDOXANTHOMA ELASTICUM**: disorder of elastic tissues affecting skin, eyes (retinal tears), and vasculature.
What is in the Future?
Technology: RNA interference (RNAi)

- Function: forms RNA dimers that inhibit expression of specific genes
- Blocking certain protein production may cause a change such as an increase in lifespan
- Ex: *C. elegans*
Main Social Issue:

As more and more people are living longer...

How do we better life quality of the elderly?
Population Pyramid of the US

United States: 2000

Source: U.S. Census Bureau, International Data Base.

http://www.census.gov/cgi-bin/ipc/idbpyrs.pl?cty=US&out=s&ymax=250
The End