Mechanisms of Aging

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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

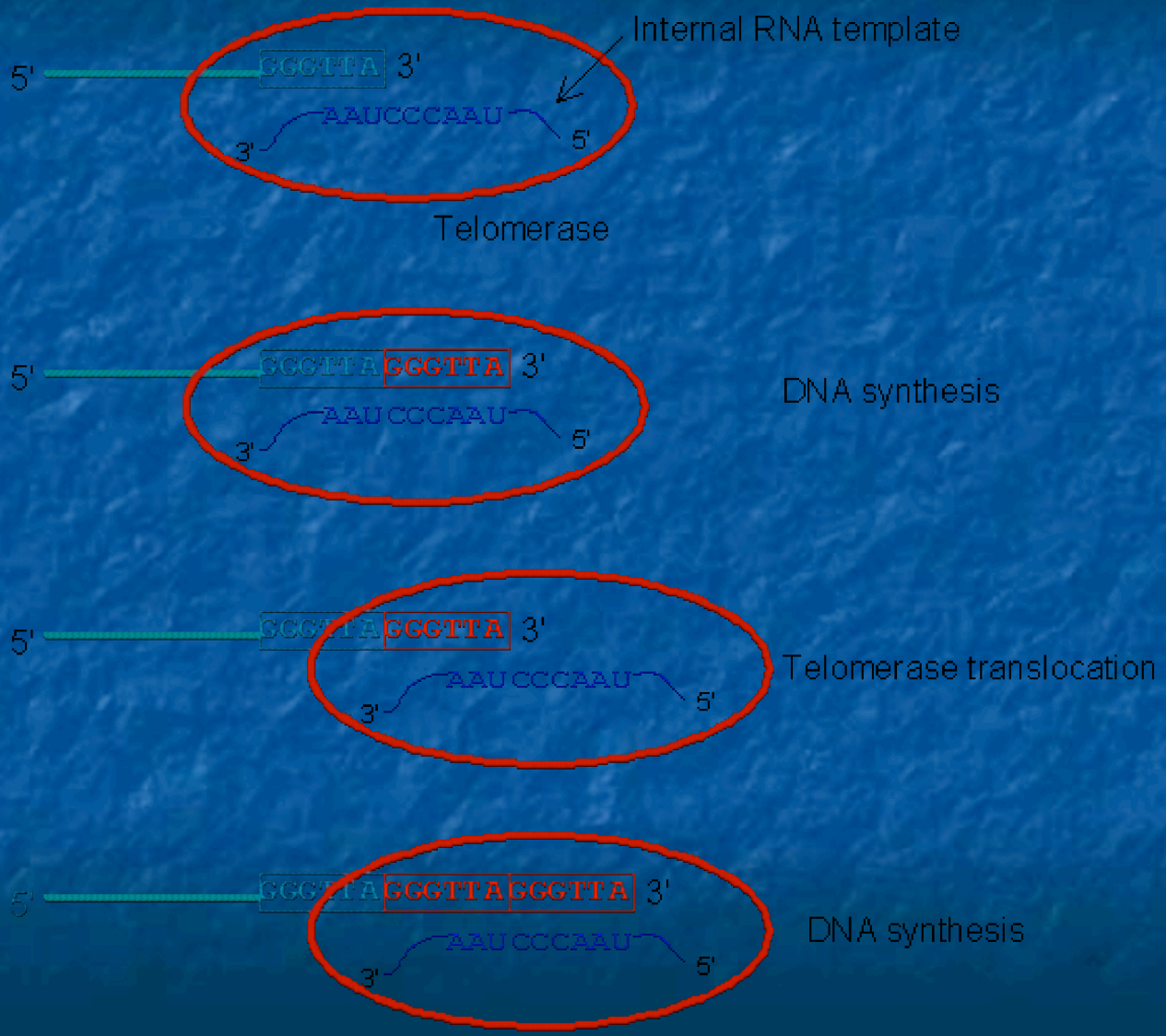
2. Genetic Programming of Aging

- Hutchinson-Gilford Progeria syndrome
- 2 examples of *C. elegans*

3. “Wear-and-Tear” Theory

- Accumulated point mutations→ Senescence
- Examples:
  - DNA & Information
  - Mitochondrial mutations
  - Telomere & Telomerase

Telomere & Telomerase



http://www.web-books.com/MoBio/Free/Ch7C.htm

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 Ageing Diseases

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 nuerogeneration, 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-AVGVAASGTIWSPAPTSW-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)

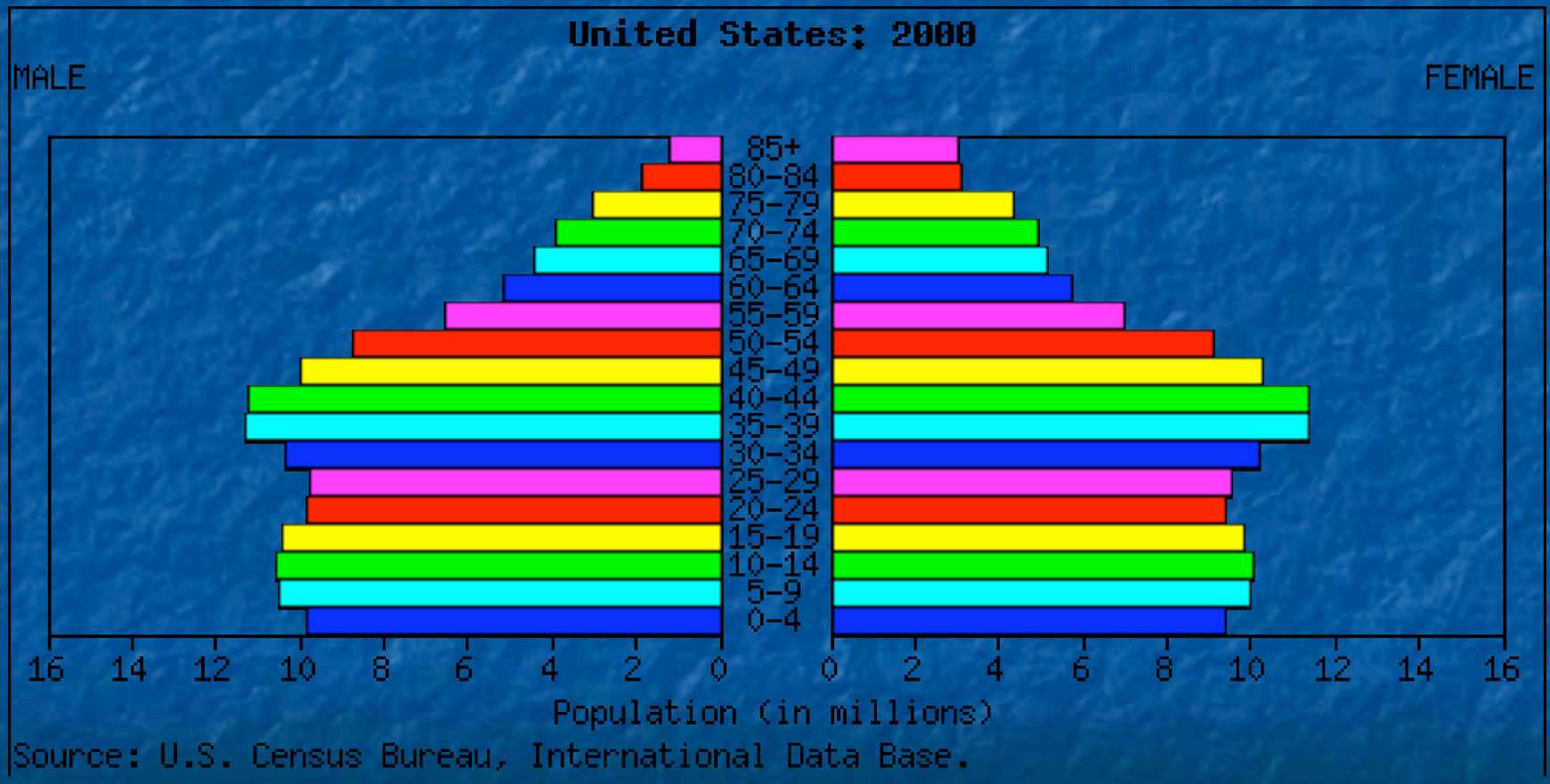
- Function: forms RNA dimers that inhibit expression of specific genes
- Blocking certain protein production may cause a change such as an increase in lifespan
- Ex: *C. elegans*

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



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

The End