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Mechanisms of ageing

Ageing

- Process of intrinsic deterioration that is reflected at the population level as an increase in the likelihood of death and a decline in the production of offspring

Ageing-related damage

- Malfunction of organelles
- Changes in extracellular matrix
- Oxidative damage
- Damage to DNA
- Necrosis, apoptosis

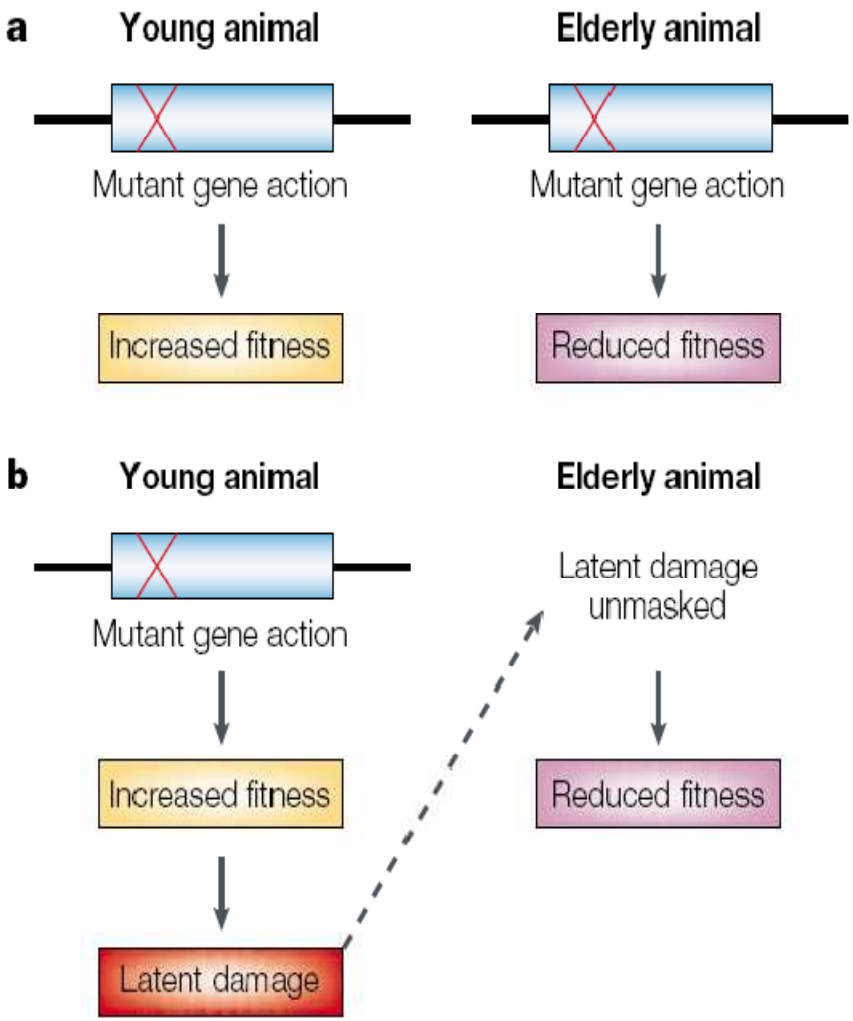
Ageing

- Public or private mechanisms?
- Is it a programmed process or not?
- Rate of ageing
  - calorific restriction
  - reproductive rate

Evolutionary theories of ageing

- Mutation-accumulation theory
- Pleiotropy/ trade-off theory

Antagonistic pleiotropy



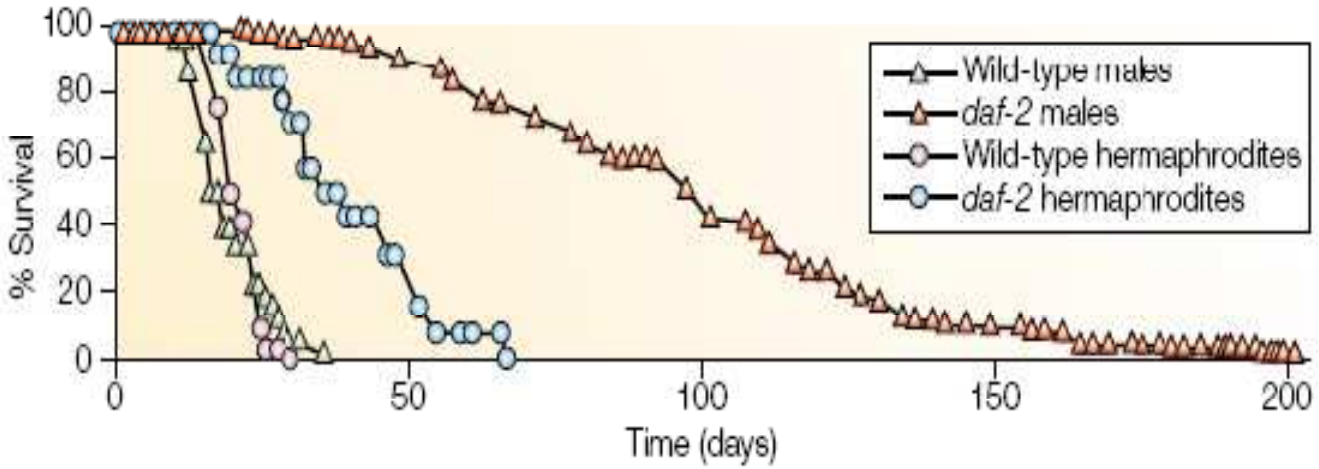
Partridge, L. and D. Gems (2002). "Mechanisms of ageing: public or private?" Nat Rev Genet 3(3): 165-75.

Model organisms

- *Saccharomyces cerevisiae*
- *Caenorhabditis elegans*
- *Drosophila melanogaster*

→ long-lived mutants

Extended lifespan in *daf-2* mutant *Caenorhabditis elegans*



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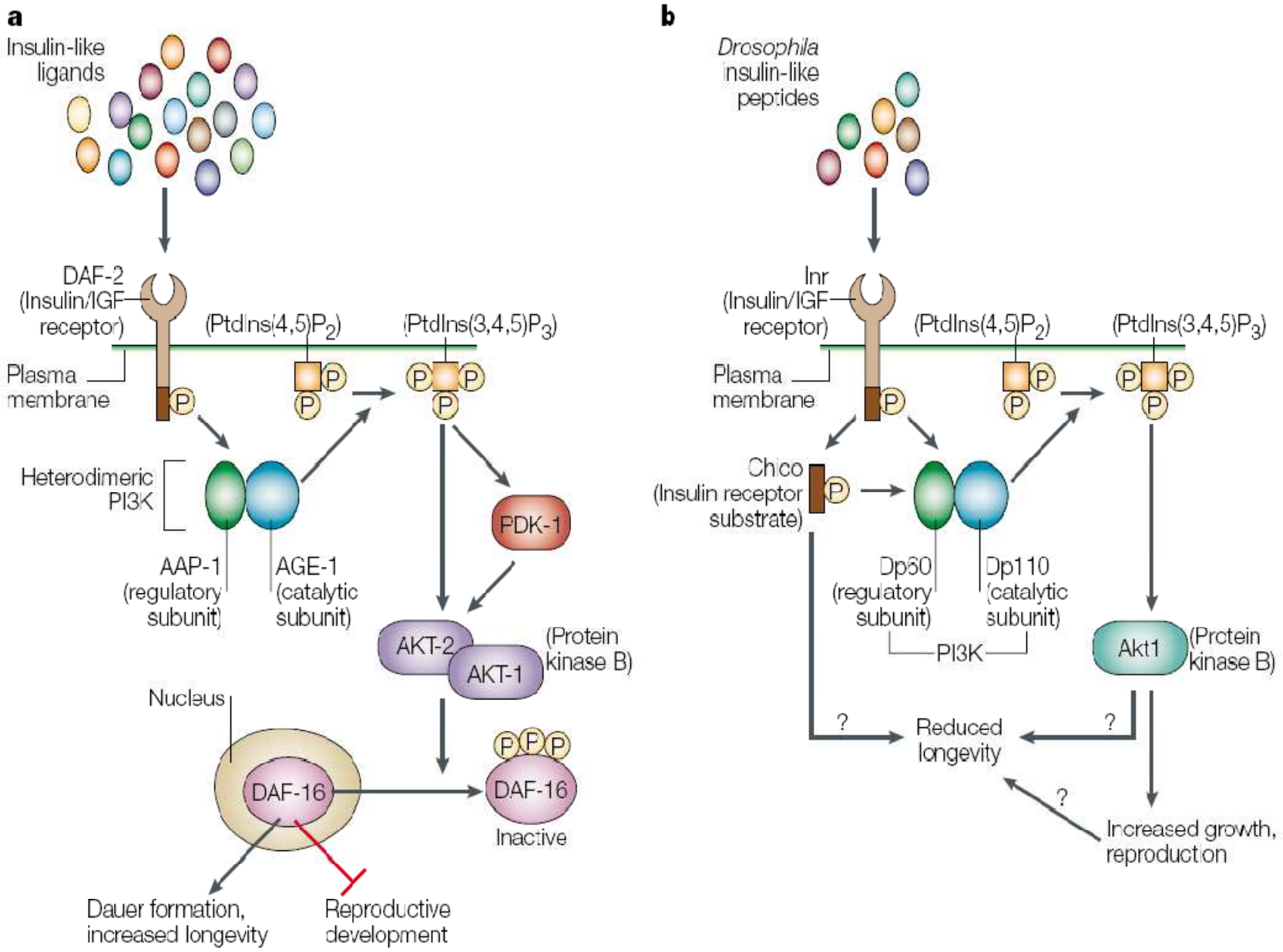
Insulin/IGF signalling

- a part of central neuroendocrine axis
- regulation of development and ageing

- 2 secretory steps:
  1. environmental stimuli/food levels → secretion of INS ligands … received by neuronal e.g. DAF-2
  2. global signal/steroid … received by receptors e.g. DAF 12

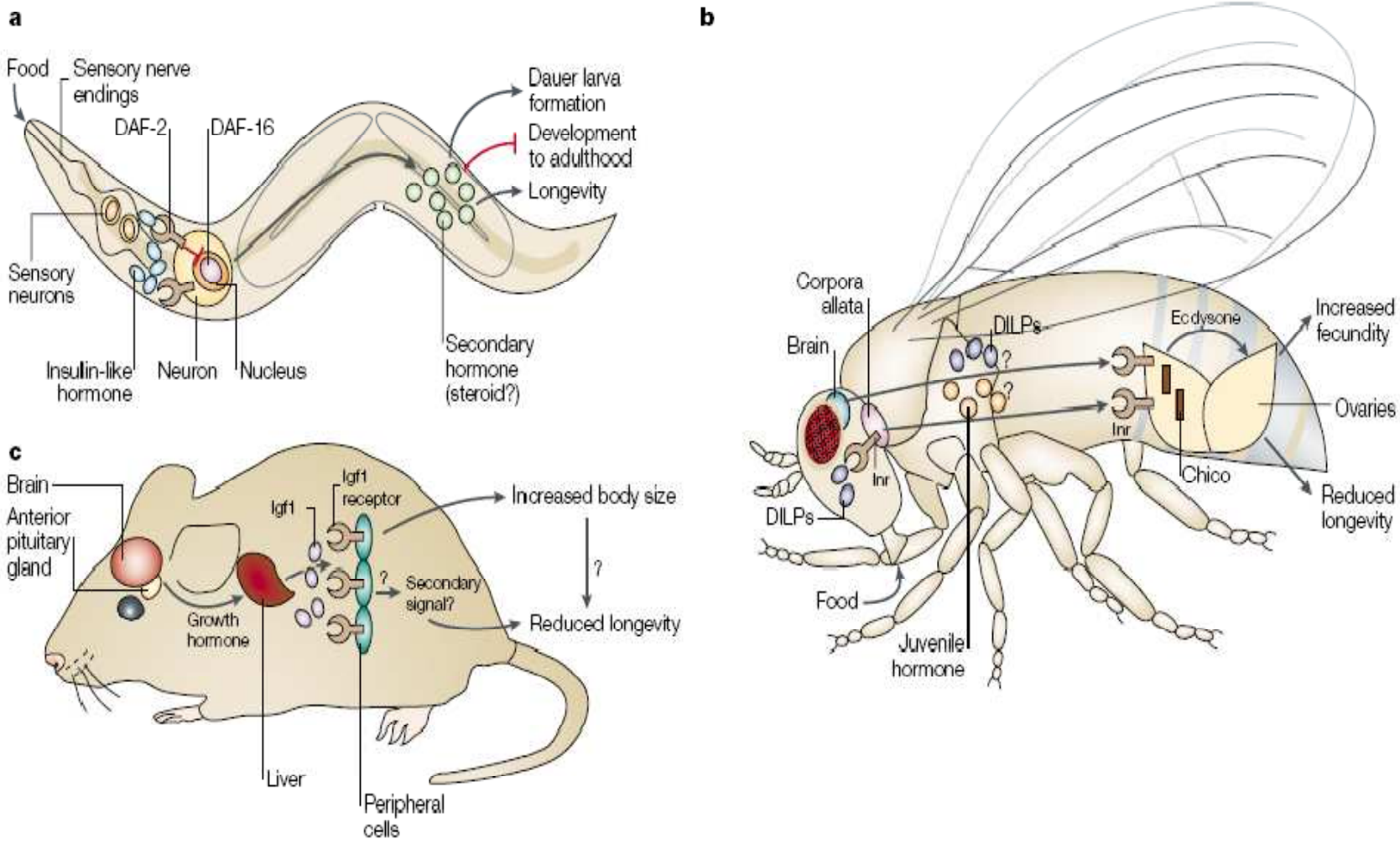
- some mutants *(age-1, daf-2)* ↑ lifespans

Insulin/IGF signalling pathways in *Caenorhabditis elegans* and *Drosophila*



Partridge, L. and D. Gems (2002). "Mechanisms of ageing: public or private?" Nat Rev Genet 3(3): 165-75.

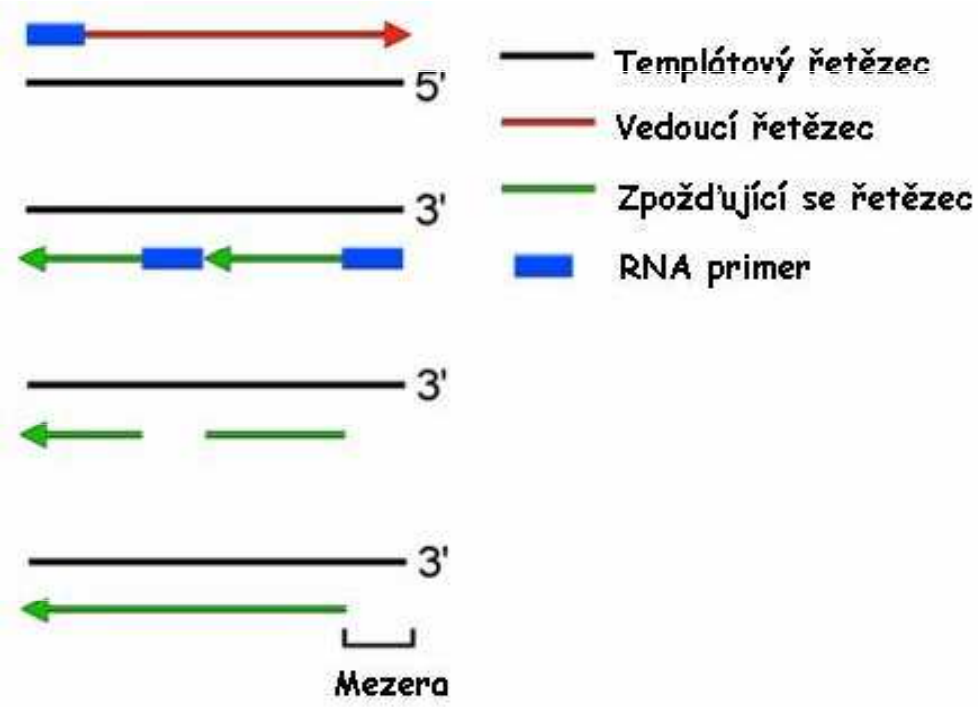
Neuroendocrine regulation of ageing



Partridge, L. and D. Gems (2002). "Mechanisms of ageing: public or private?" Nat Rev Genet 3(3): 165-75.

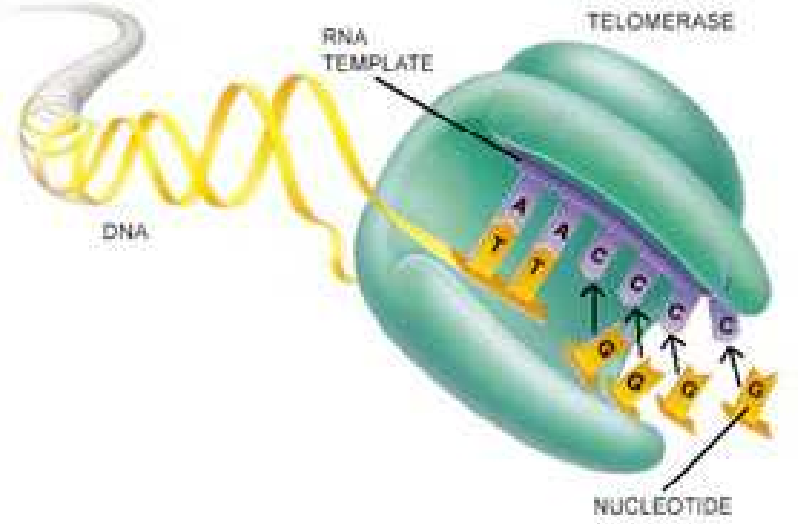
Telomery

- Repetitivní sekvence na koncích lineárních chromozomů
- Vážou proteinové komplexy
- Ochrana konců chromozomů
- Zkracují se během mitózy
- Limitující faktor pro růst buněk



Telomeráza

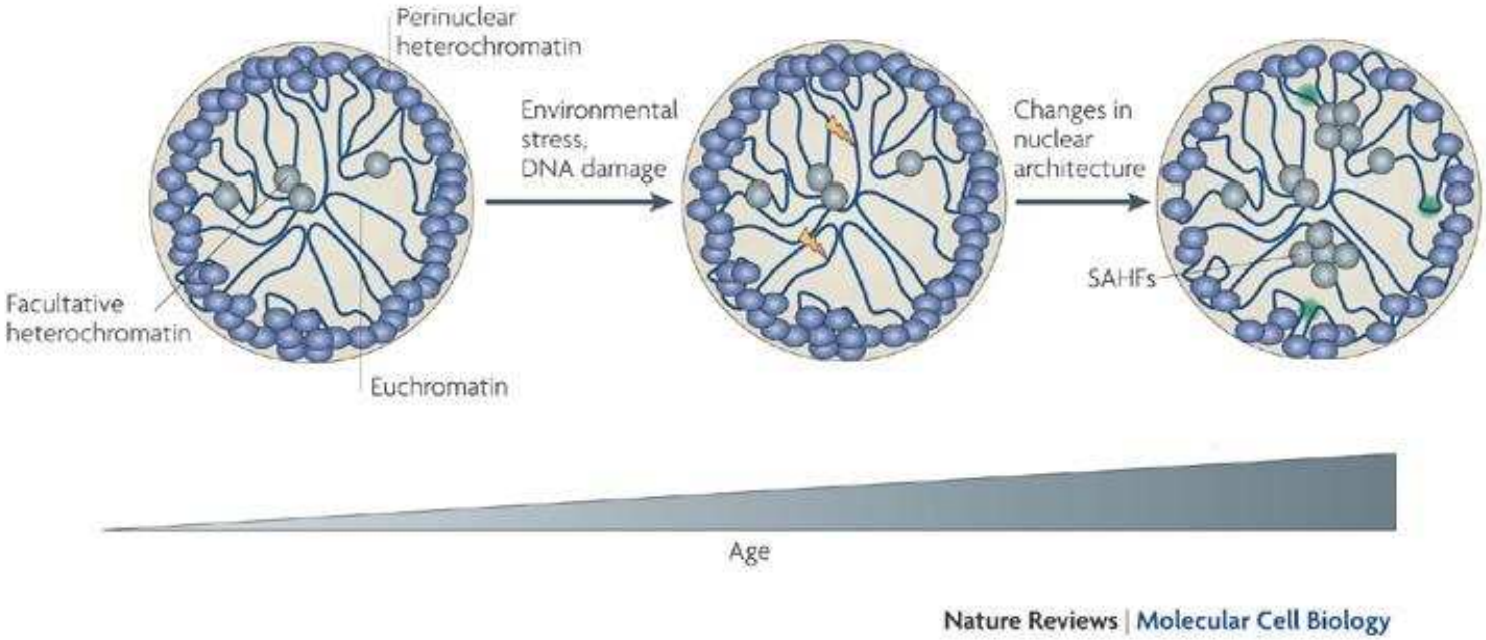
- Ribonukleoproteinový enzym, který je nutný pro kompletní replikaci konců DNA
- Rozpoznává 3‘-OH konce chromozomů
- Tert: syntéza repetic
- Terc: templát pro Tert
- Většina buněk tento enzym netvoří → replikativní senescence



http://www.postech.ac.kr/chem/sbpc/img/telomerase.jpg

Genomová nestabilita

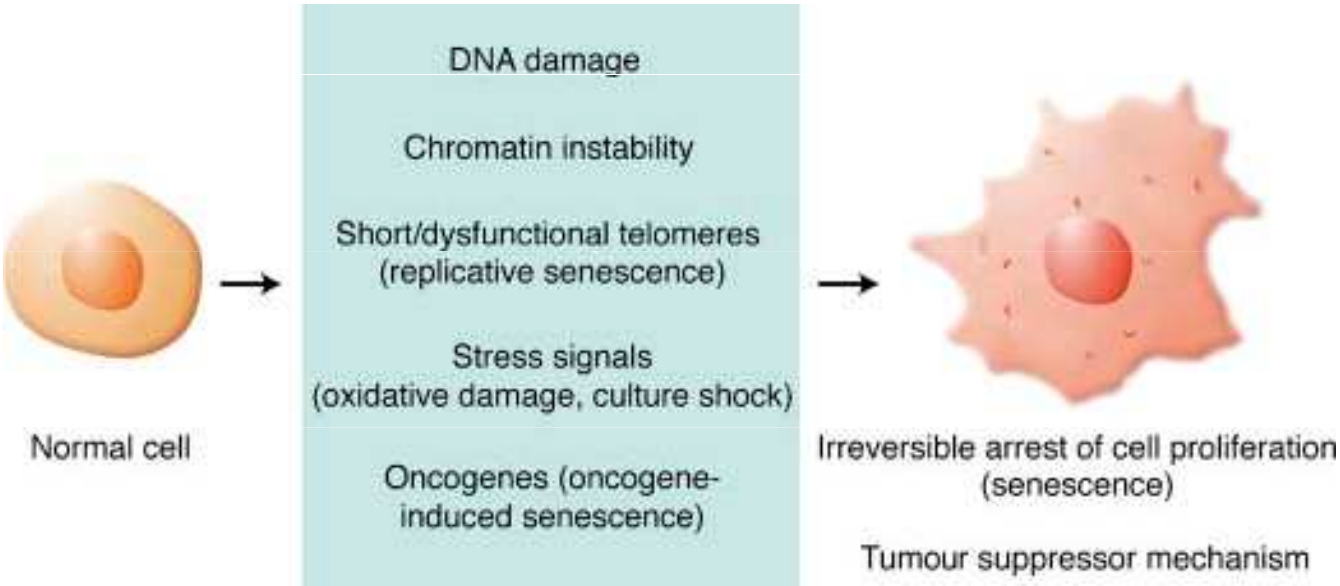
- Perinukleární konstitutivní heterochromatin
- V centru jádra – euchromatin
- Kumulace poškození v jádře během života
- Změny v distribuci histonů a jejich modifikací
- Destabilizace genové exprese
- Aktivace lokusu *INK4A/ARF* → *senescence*



http://www.nature.com/nrm/journal/v8/n9/images/nrm2238-f1.jpg; upraveno

Senescence

- Hayflickův limit
- Nezvratná zástava buněčného cyklu: *p53, p16, p21 a RB*
- Ochrana před vznikem nádorů
- Změna morfologie buněk a genové exprese



http://www3.interscience.wiley.com/cgi-bin/fulltext/114033339/nfig001

Senescence

Ztráta schopnosti kmenových buněk tkání nahrazovat poškození → stárnutí organismu

Inspiration ☺

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