



# WHY DO WE AGE?

Never Stand Still

Medicine

Psychiatry

**Perminder Sachdev**

**Co-Director, Centre for Healthy Brain Ageing**

**Director, Neuropsychiatric Institute, POWH**

**[p.sachdev@unsw.edu.au](mailto:p.sachdev@unsw.edu.au)**



# TWO CERTAINTIES OF LIFE



# A THIRD CERTAINTY



Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death.

# **ARE AGEING AND DEATH INEVITABLE?**

## HOW OLD CAN ONE GET?



**A Great Basin Bristlecone Pine forest**  
*Pinus longaeva*



# Long-lived aquatic animals



**White sturgeon**

>100 years



**Black coral colony**

around 4,000 years old



***Turritopsis dohrnii***

the immortal jellyfish





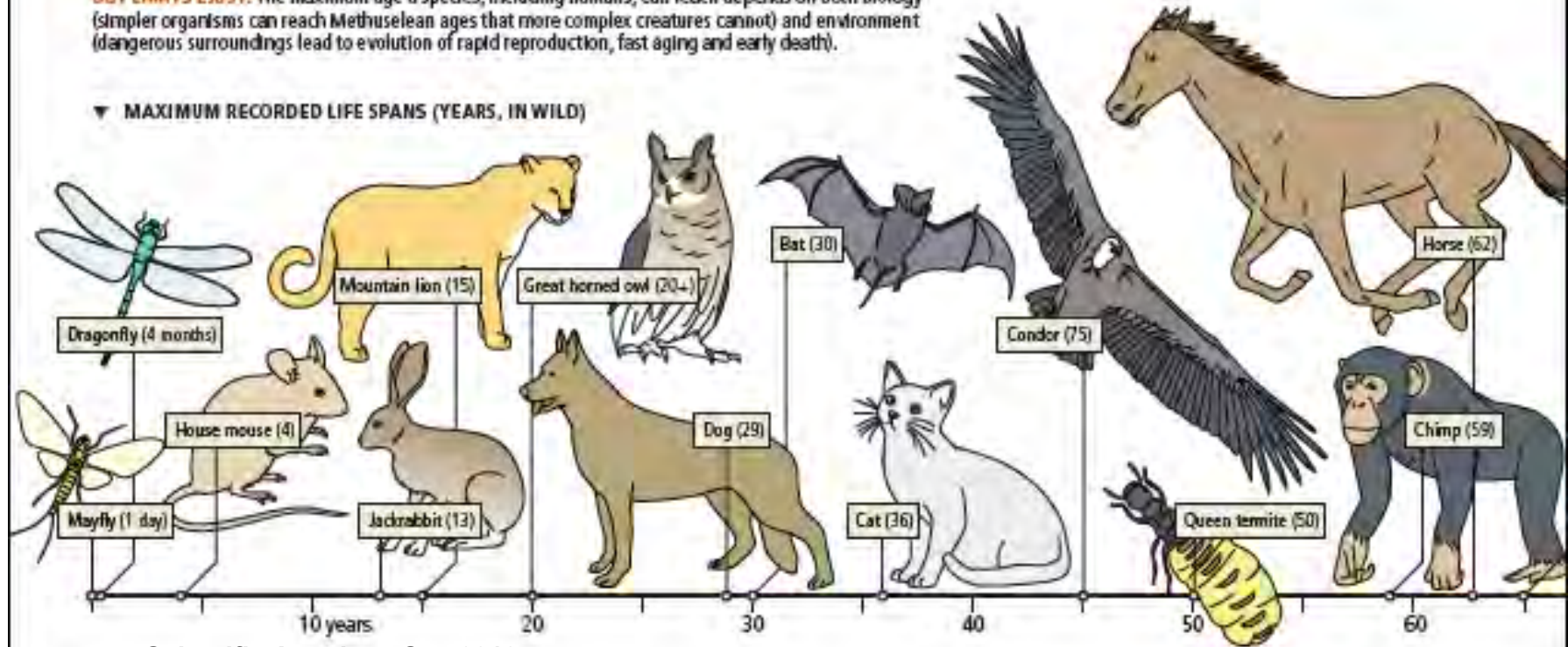
**Highest recorded life  
span of 255 years**

**Aldabra Giant Tortoise**  
*Geochelone gigantea*

# Terrestrial animals

**BUT LIMITS EXIST:** The maximum age a species, including humans, can reach depends on both biology (simpler organisms can reach Methuselean ages that more complex creatures cannot) and environment (dangerous surroundings lead to evolution of rapid reproduction, fast aging and early death).

▼ MAXIMUM RECORDED LIFE SPANS (YEARS, IN WILD)



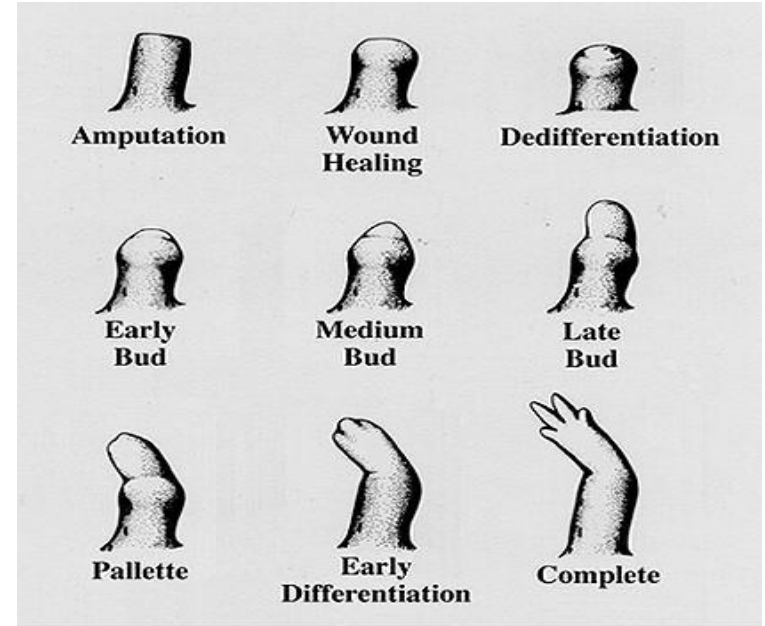
Scientific American Sep 2010

BA  
Ageing

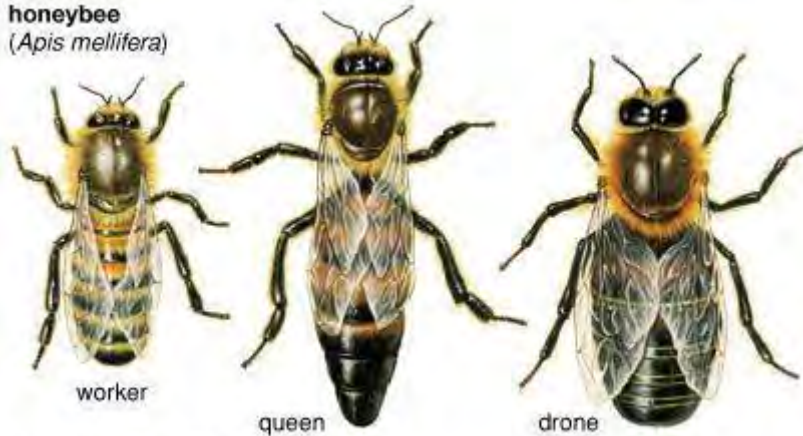




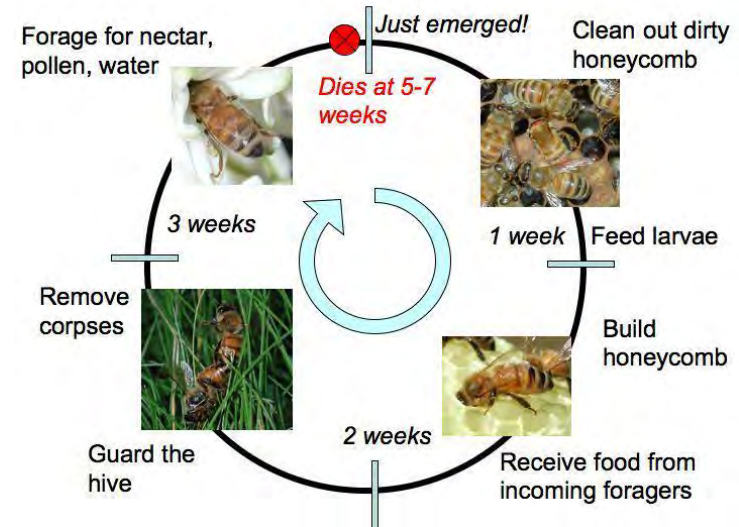
An adult salamander  
*Msx1* to the Rescue



honeybee  
(*Apis mellifera*)



© 2006 Encyclopædia Britannica, Inc.



**Honey bee castes have different lifespans even though a queen or a worker can be formed from the same egg**

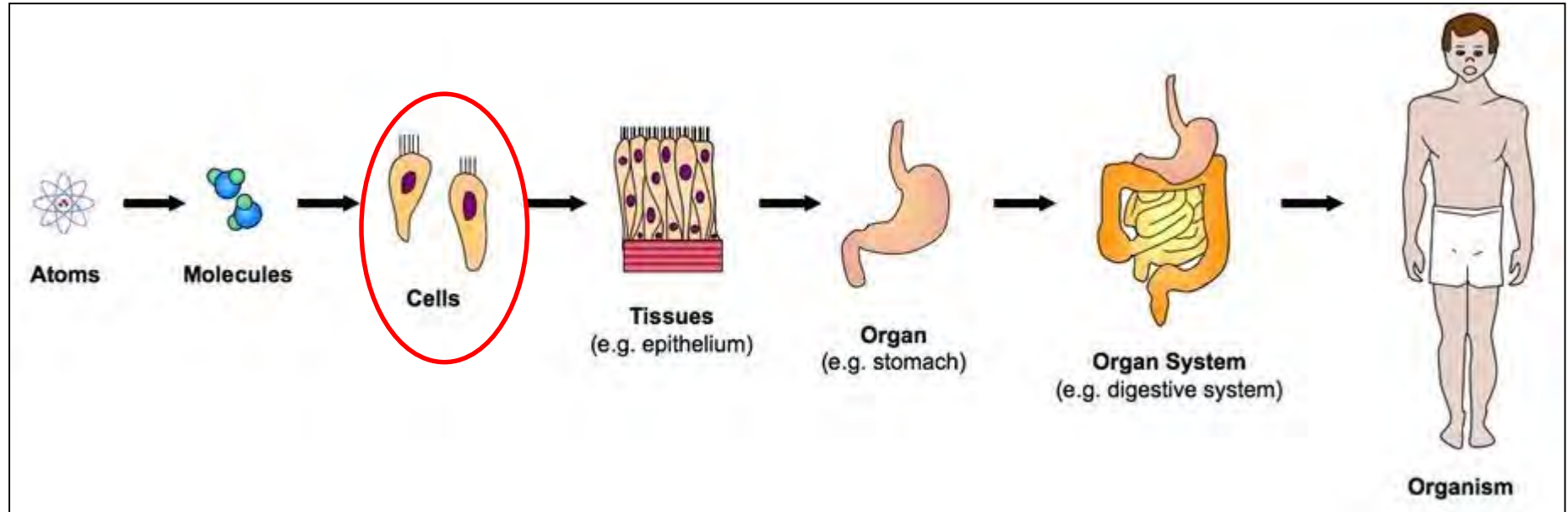


Madame Jeanne Calment of Arles, France, photographed in 1994 at the age of 119. She died in 1997, aged 122, of 'natural causes'.

“Living independently until the age of 110..... Despite visual and hearing loss, she maintained autonomy in the face of the dependence imposed by the regulations of a nursing home - refusing care and visitors she did not want, smoking in a public place, and insisting on her daily glass of port..”

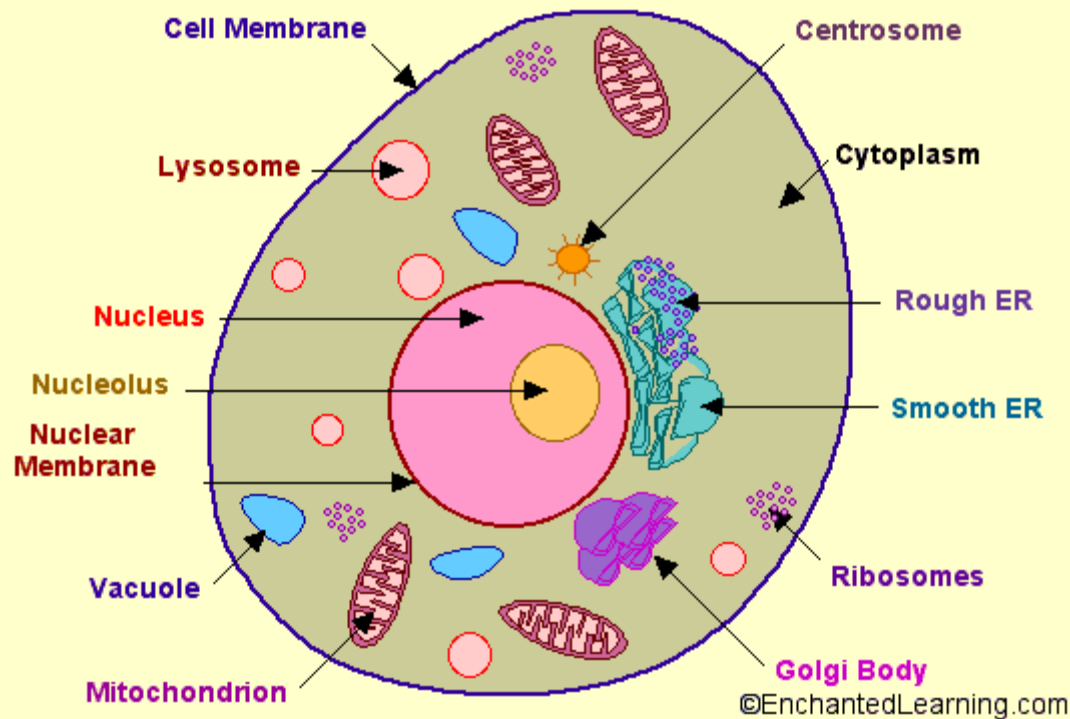
Ritchie, 1997

# Levels of organisation





## Cross-Section of an Animal Cell



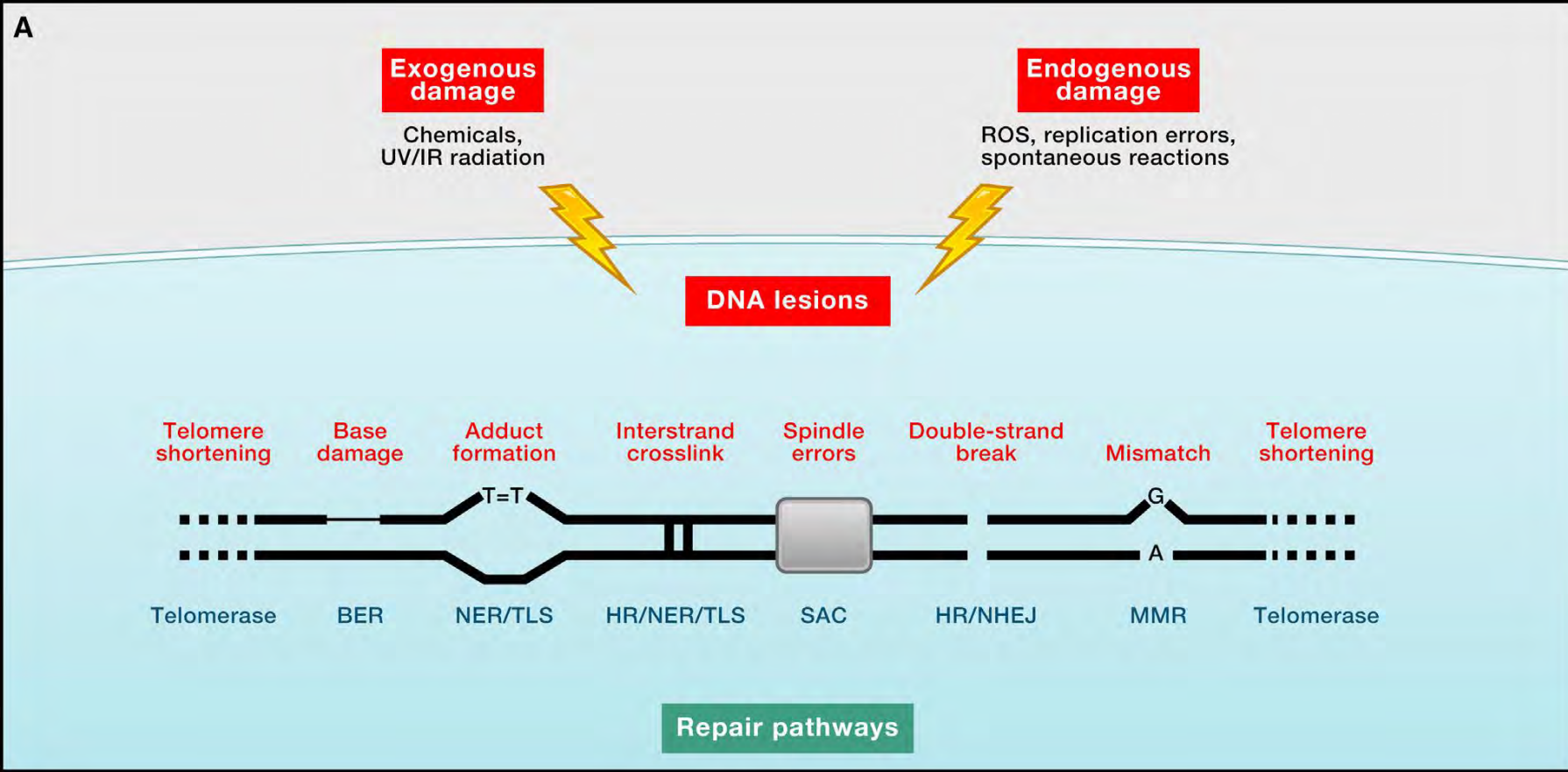
# THE CELLULAR BALANCE





# Hallmarks of Ageing

Cell 153, June 6, 2013



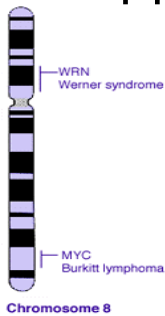
# 1. Genomic Instability





14

48



# Progeria

Hutchinson-Gilford  
Syndrome



## Accelerated ageing diseases

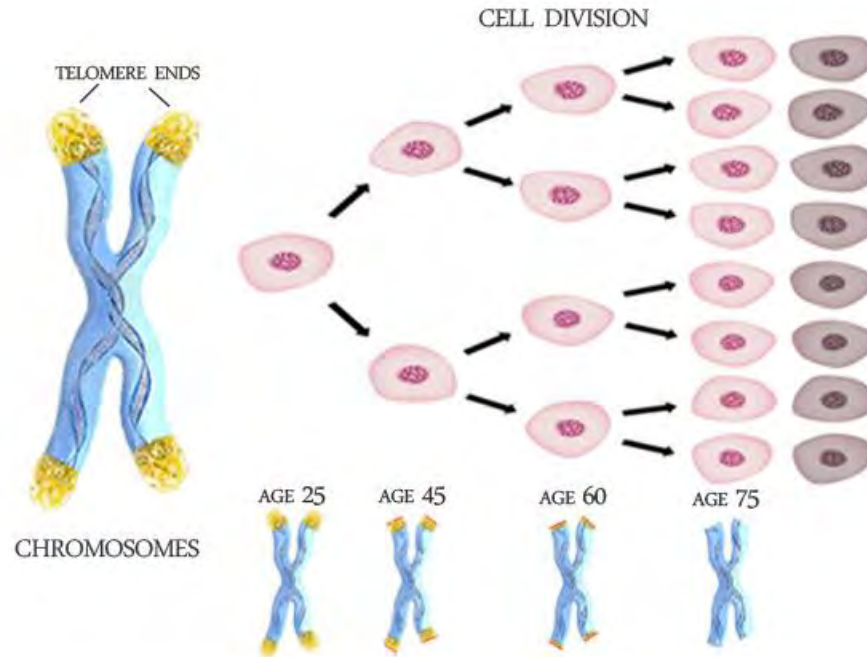
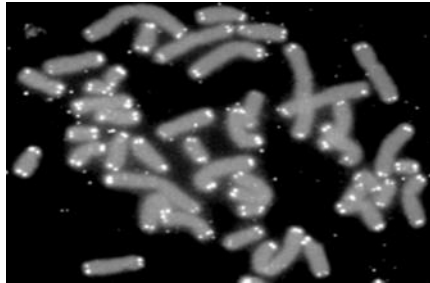
← Werner Syndrome  
Cockayne's syndrome  
Xeroderma pigmentosa



In HGPS patients, the cell nucleus has dramatically aberrant morphology (bottom, right) rather than the uniform shape typically found in healthy individuals (top, right)



## 2. Telomere attrition



# Replicative Senescence

- Cellular senescence – Hayflick Limit 52 (40-60)



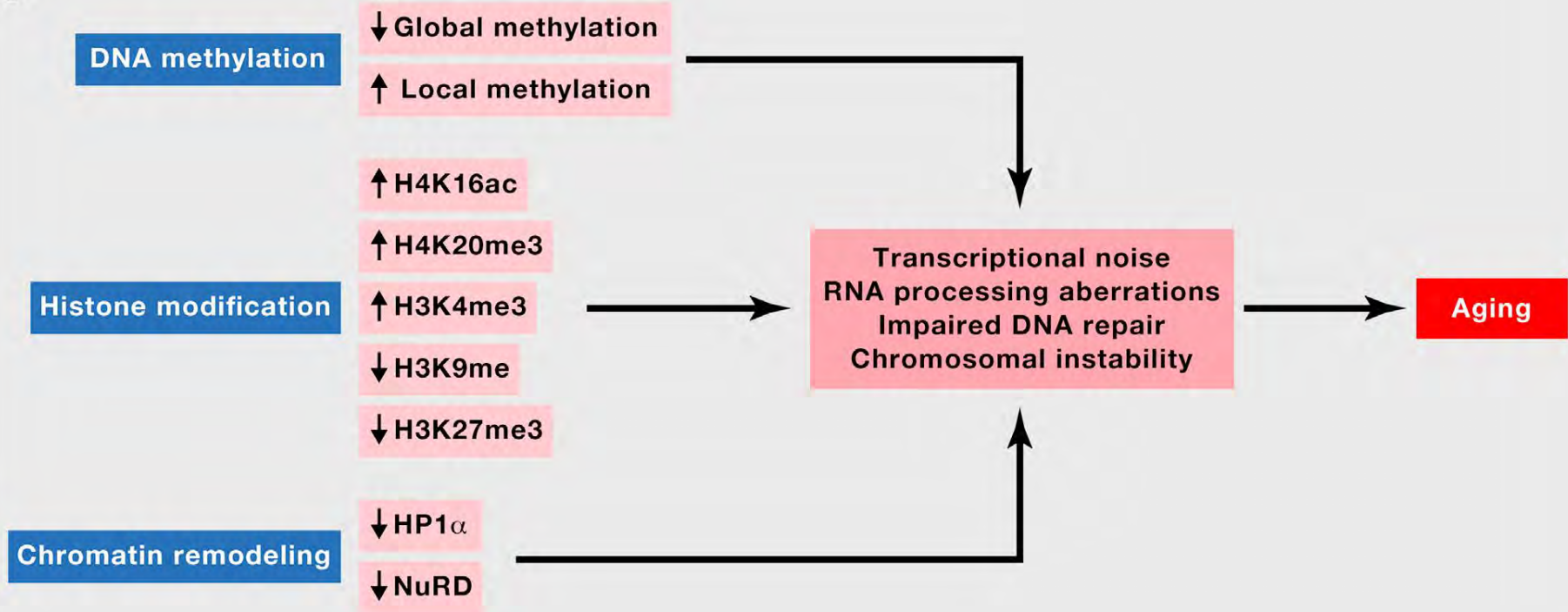
Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exp Cell Res* 1965;37:614-36.

- Mouse 14-28



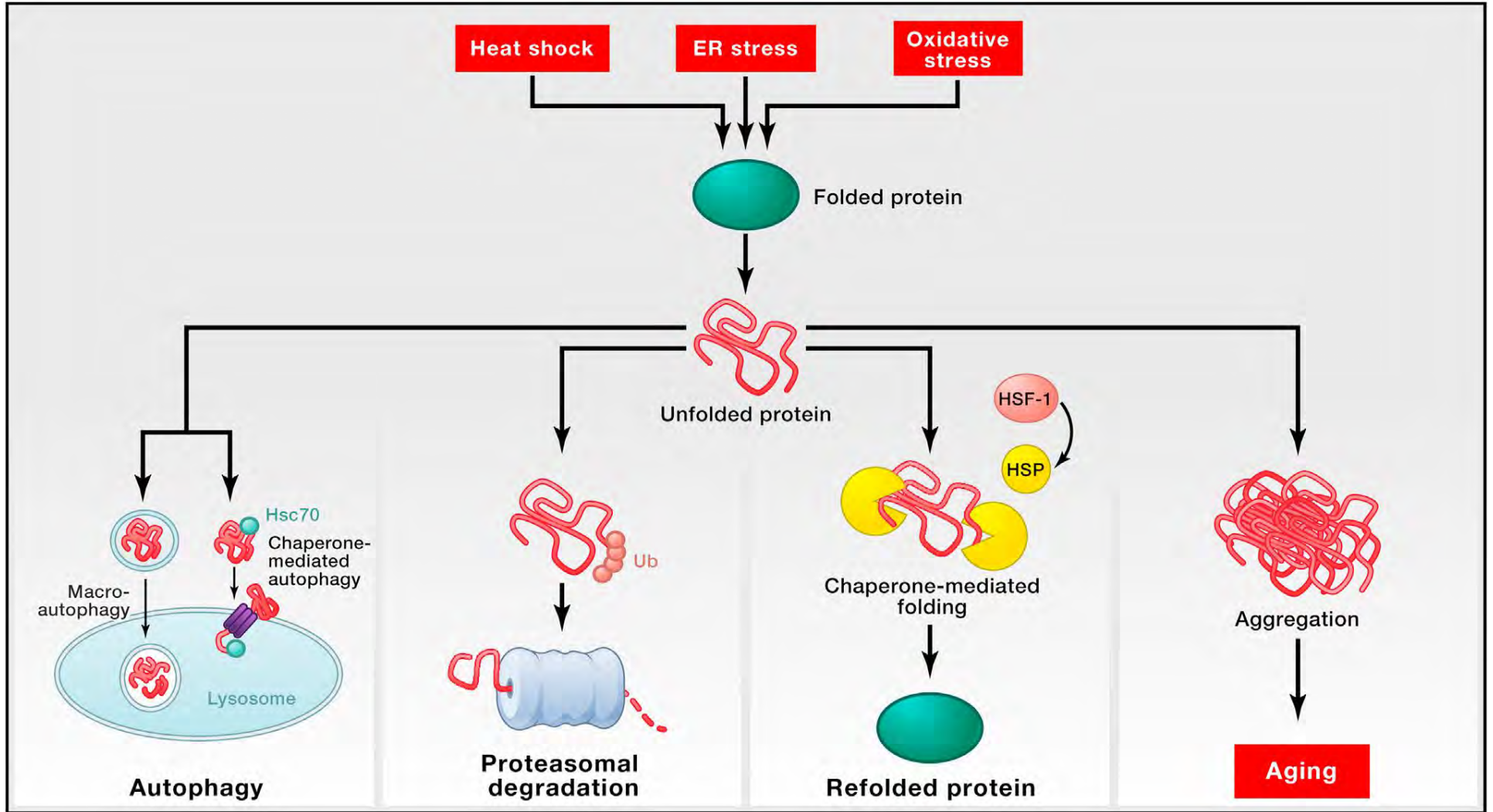
- Tortoise 100



**B**

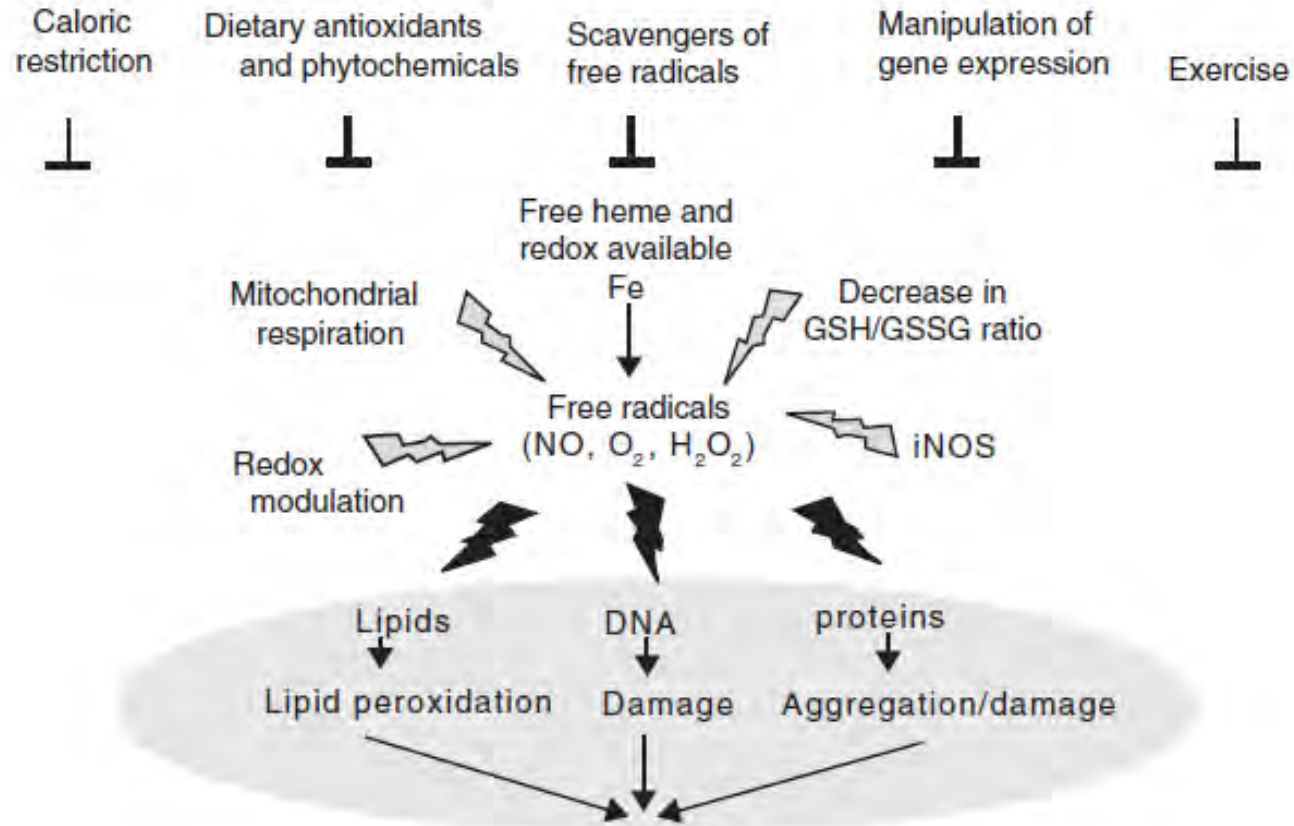
**3. Epigenetic alterations.** Alterations in the methylation of DNA or acetylation and methylation of histones, as well as of other chromatin-associated proteins, can induce epigenetic changes that contribute to the aging process.

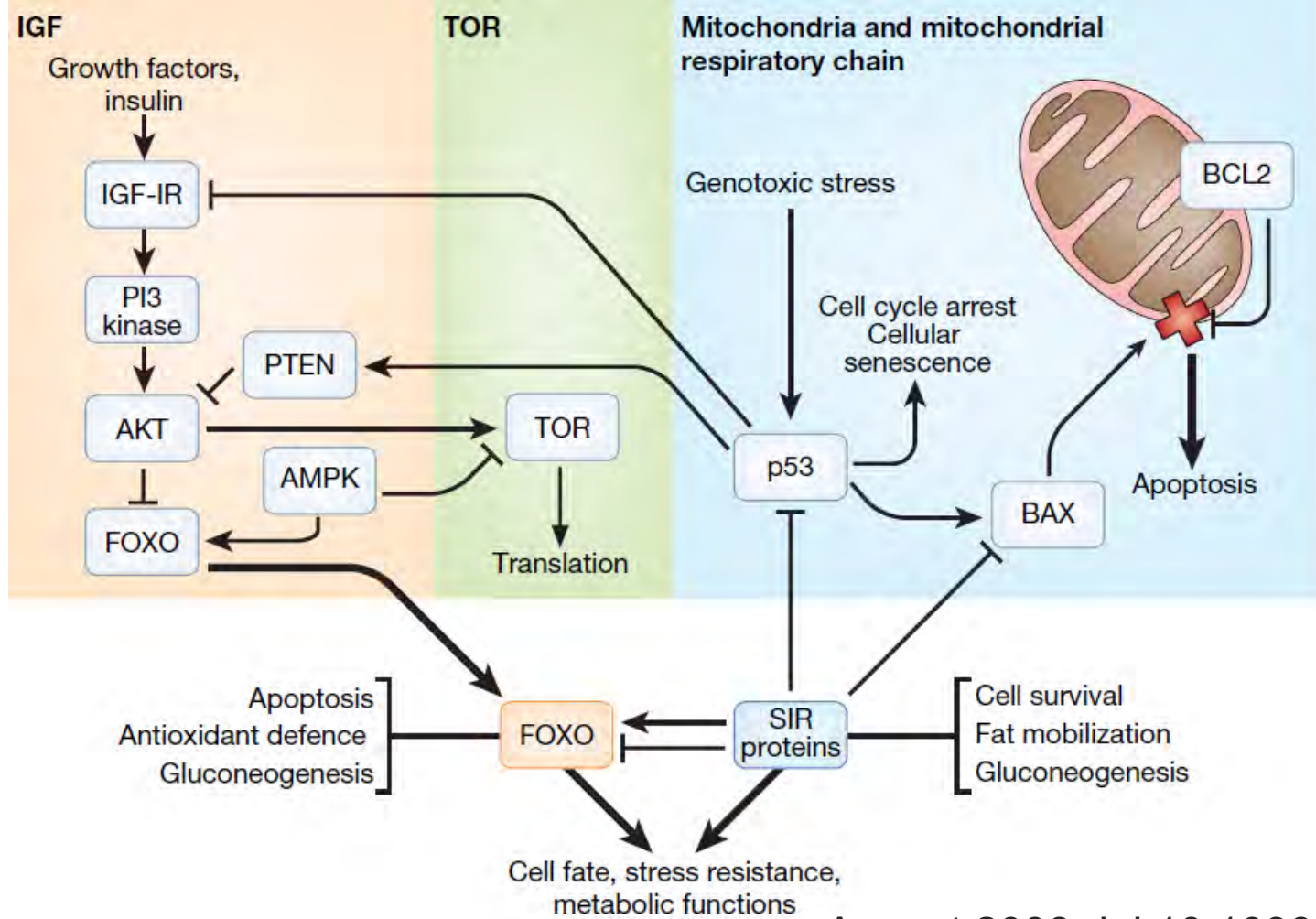




## 4. Loss of Proteostasis

# Oxidative stress (free radical) theory of ageing

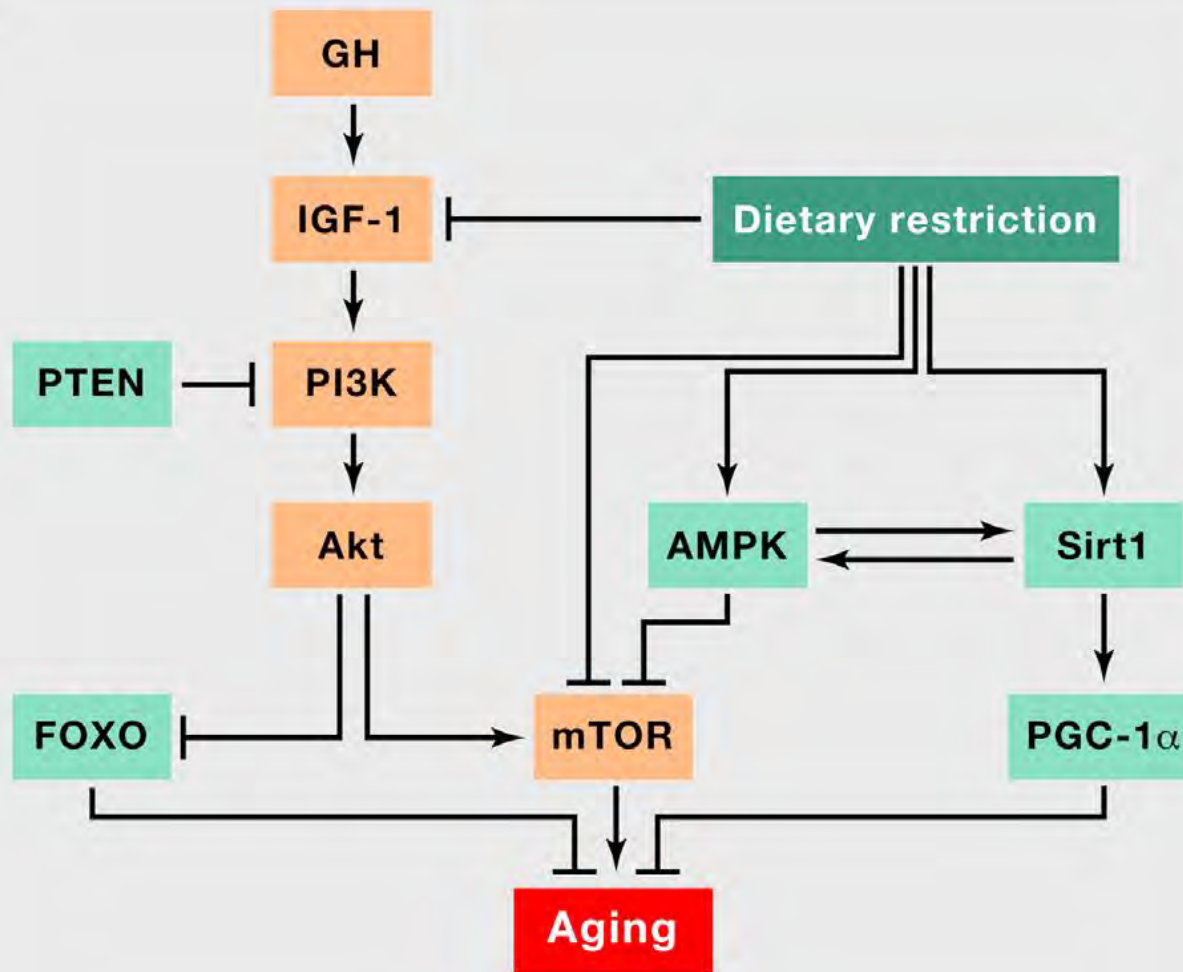




## 5. Nutrient Sensing

**Potentially conserved pro-ageing pathways**

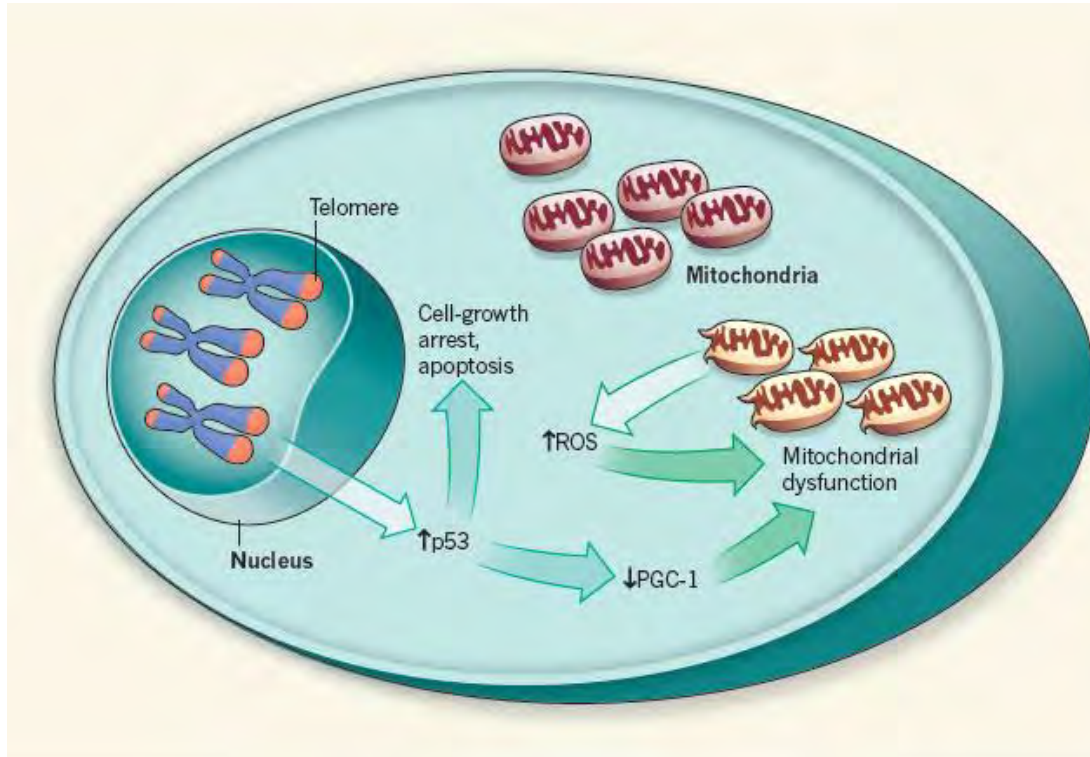
A



## Caloric restriction

Available evidence strongly supports the idea that anabolic signalling accelerates ageing and decreased nutrient signalling extends longevity. Further, a pharmacological manipulation that mimics a state of limited nutrient availability, such as rapamycin, can extend longevity in mice





**The nucleus, mitochondria and ageing.**

**Mitochondrial function has a profound impact on the ageing process. Mitochondrial dysfunction can accelerate aging in mammals, but it is less clear whether improving mitochondrial function, for example through mitohormesis, can extend lifespan in mammals, though suggestive evidence in this sense already exists.**

Visceral obesity

## Key points

- High levels of pro- inflammatory markers in the blood and other tissues are often detected in older individuals and predict the risk of cardiovascular diseases, frailty, multimorbidity, and decline of physical and cognitive function.
- In individuals with obesity, visceral fat produces pro-inflammatory and chemotactic compounds and is infiltrated by macrophages, lymphocytes, and senescent cells with a senescence- associated secretory phenotype that contributes to inflammageing.
- Clinical trials suggest that modulating inflammation prevents cardiovascular diseases, but studies to explore the effects on other chronic diseases, frailty, and disability are scarce and controversial.

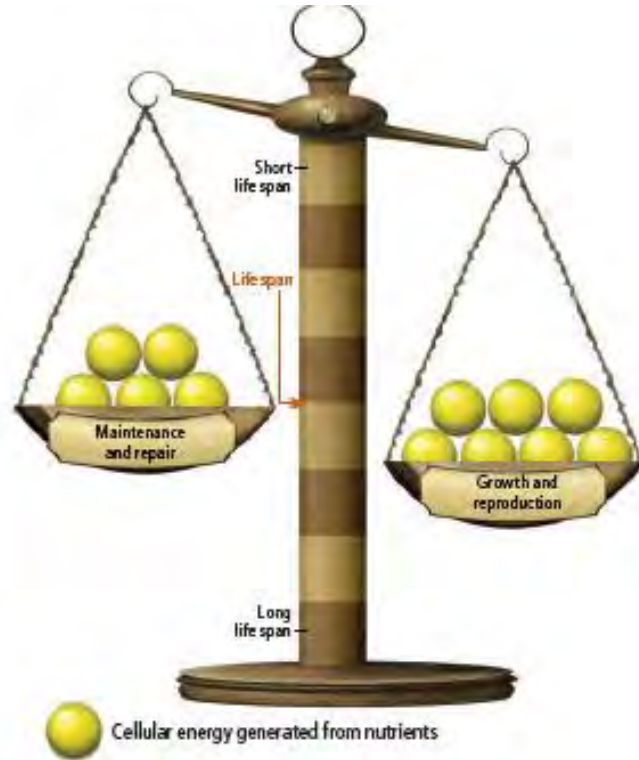
Genetic predisposition  
(IL1RN, IL6R,  
and IL6)

Inflammageing

Intrinsic immune  
cell defects

Potential causes of inflammageing.

# HOW ENERGY IS ALLOCATED IN THE BODY



Ageing has to be understood in the context of evolution

Scientific American Sep 2010

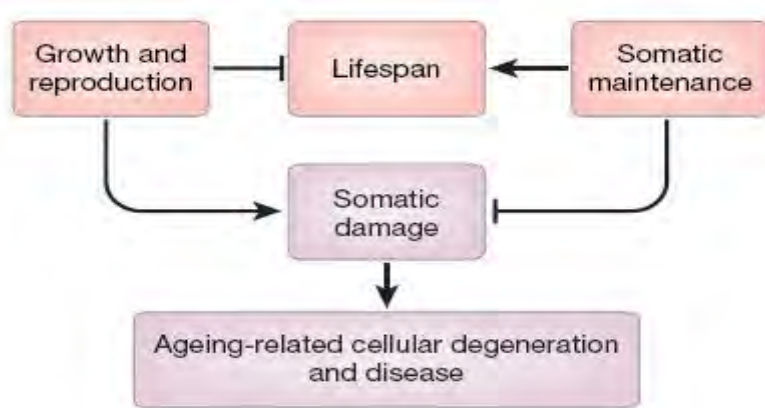
**CHeBA**  
Healthy Brains Positive Ageing



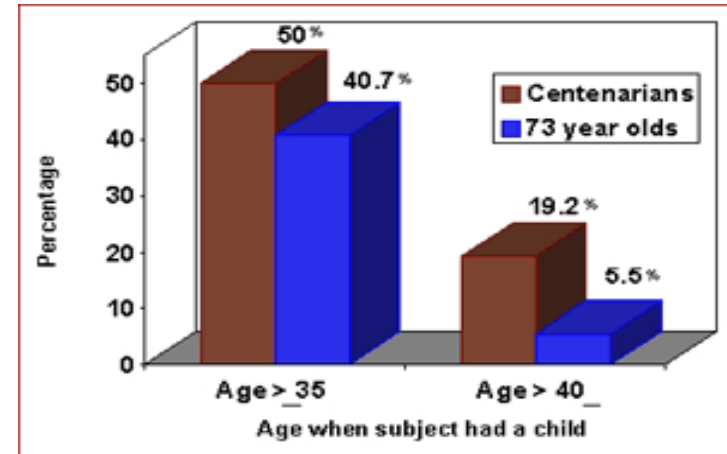
**UNSW**  
AUSTRALIA

# Evolutionary theory of ageing

## Disposable Soma



According to the '**disposable soma theory**', organisms must compromise between energy allocation to growth and reproduction or somatic maintenance and repair.



Centenarian women's reproductive systems age slowly

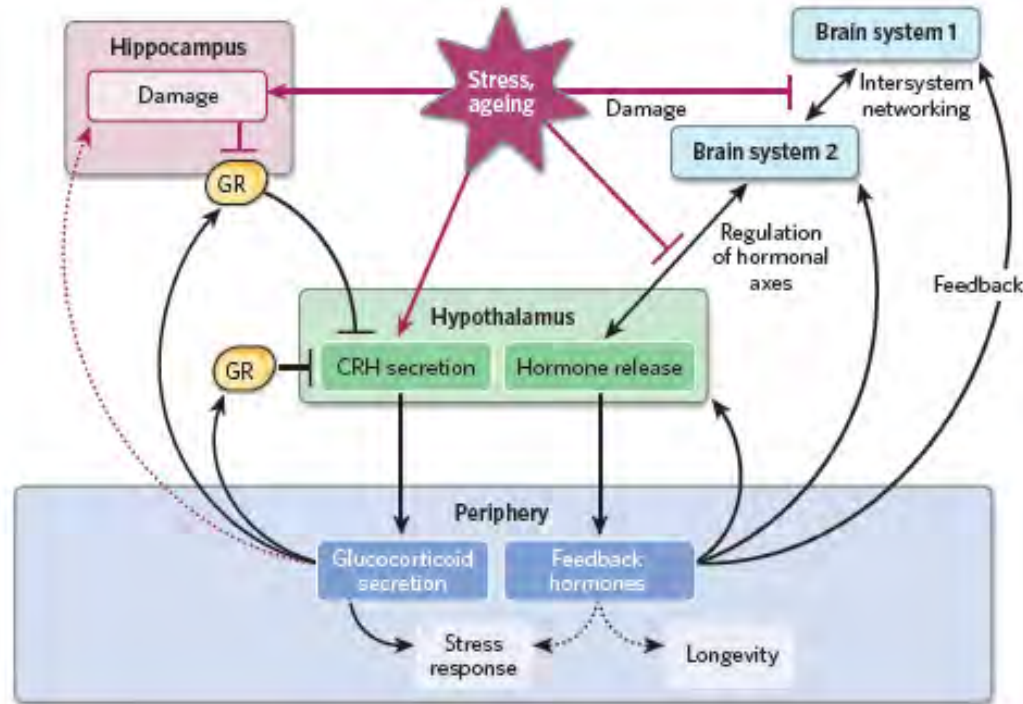


**Experiments on dietary restriction and genetic or chemical alteration of nutrient-sensing pathways**

Fontana et al, 2010. Science

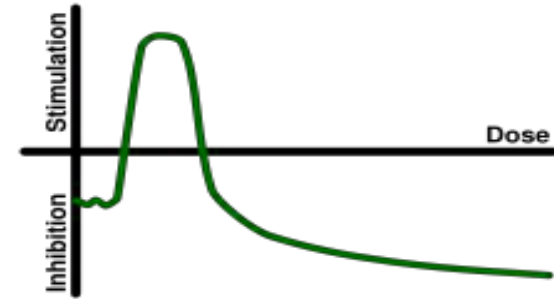
|                                                                                   |         | Life-span increase  |                                                       | Beneficial health effects                                                                                                                     |                                                                                                                                                          |
|-----------------------------------------------------------------------------------|---------|---------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                   |         | Dietary restriction | Mutations/ drugs                                      | Dietary restriction                                                                                                                           | Mutations/ drugs                                                                                                                                         |
|  | Yeast   | 3-fold              | 10-fold (with starvation/ DR)                         | Extended reproductive period                                                                                                                  | Extended reproductive period, decreased DNA damage/mutations                                                                                             |
|  | Worms   | 2- to 3-fold        | 10-fold                                               | Resistance to misexpressed toxic proteins                                                                                                     | Extended motility<br>Resistance to mis-expressed toxic proteins and germ-line cancer                                                                     |
|  | Flies   | 2-fold              | 60–70%                                                | None reported                                                                                                                                 | Resistance to bacterial infection, extended ability to fly                                                                                               |
|  | Mice    | 30–50%              | 30–50% (~100% in combination with DR)                 | Protection against cancer, diabetes, atherosclerosis, cardiomyopathy, autoimmune, kidney, and respiratory diseases; reduced neurodegeneration | Reduced tumor incidence; protection against age-dependent cognitive decline, cardiomyopathy, fatty liver and renal lesions. Extended insulin sensitivity |
|  | Monkeys | Trend noted         | Not tested                                            | Prevention of obesity; protection against diabetes, cancer, and cardiovascular disease                                                        | Not tested                                                                                                                                               |
|  | Humans  | Not determined      | Not determined (GHR-deficient subjects reach old age) | Prevention of obesity, diabetes, hypertension. Reduced risk factors for cancer and cardiovascular disease                                     | Possible reduction in cancer and diabetes                                                                                                                |

# The brain as a potential regulator of organismal ageing



NATURE|Vol 464|25 March 2010

**Hormesis** (from Greek *hormæin*, meaning “to excite”) is the term for generally-favourable biological responses to low exposures to toxins and other stressors.



**A non-monotonic curve**

A very low dose of a chemical agent may trigger from an organism the opposite response to a very high dose

**Repetitive mild stress exposure has anti-aging effects**

- Exercise is a paradigm for hormesis in this respect
- Others are heat shock, irradiation, pro-oxidants, hypergravity and food restriction
- Some natural and synthetic molecules, such as celasterols from medicinal herbs and curcumin from a spice turmeric have also shown to have hormetic beneficial effects - "hormetins"
- Psychological Stress as a hormetin

# Genetics

- Demographic selection
  - Evidence in medflies, nematode and humans
  - Apo E4 ↓ and E2 ↑ (Rebeck et al, 1994)
  - Apo B locus (Italian Centenarian Study)
  - HLA – DRw9 ↓ and DR1 ↑ (Okinawa Study)
  - Chr 4 D4S1654
  - Chr 11 11.p15.5





# The Blue Zones

Loma Linda,  
California

Nicoya,  
Costa Rica

Ogliastra Region,  
Sardinia

Ikaria,  
Greece

Okinawa,  
Japan

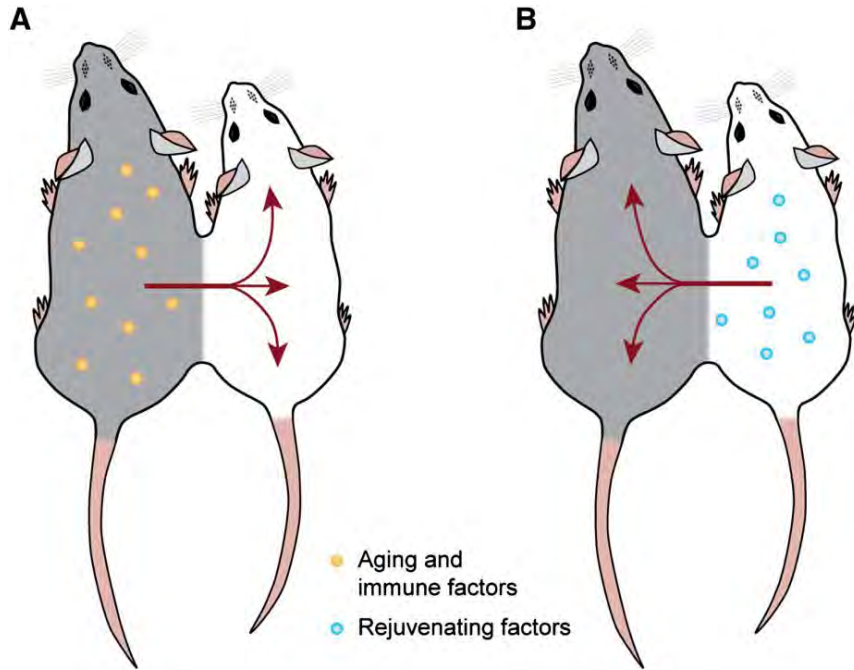
HUFF  
POST  
LIVE





# Parabiosis

**Oxytocin**  
**Blood borne chemokines – including CCL2/  
MCP-1 and CCL11/Eotaxin**



## Aging

- Decreased neurogenesis
- Impaired synaptic plasticity
- Impaired cognition

## Rejuvenation

- Increased neurogenesis
- Unknown effect on synaptic plasticity?
- Unknown effect on cognition?

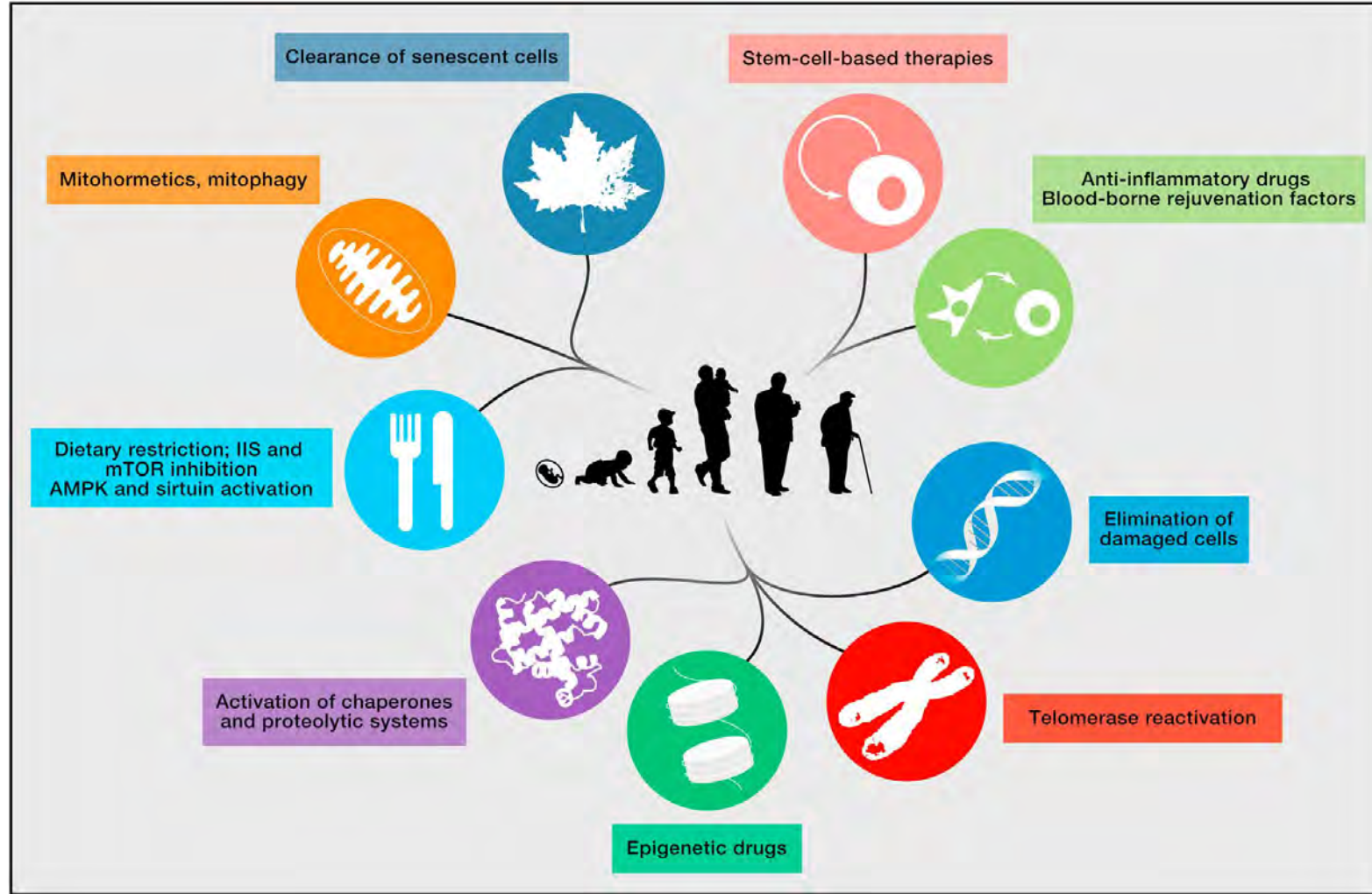
S.A. Villeda, T. Wyss-Coray / *Autoimmunity Reviews* 12 (2013) 674–677

Wagers, A. et al. *Science* 297, 2256–2259 (2002).



## Why Do Women Live Longer?

**Not only is she likely to live longer than he does, but she will help him live longer, too**



**Interventions  
that might  
extend  
human  
healthspan**