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Methods in Neurobiology

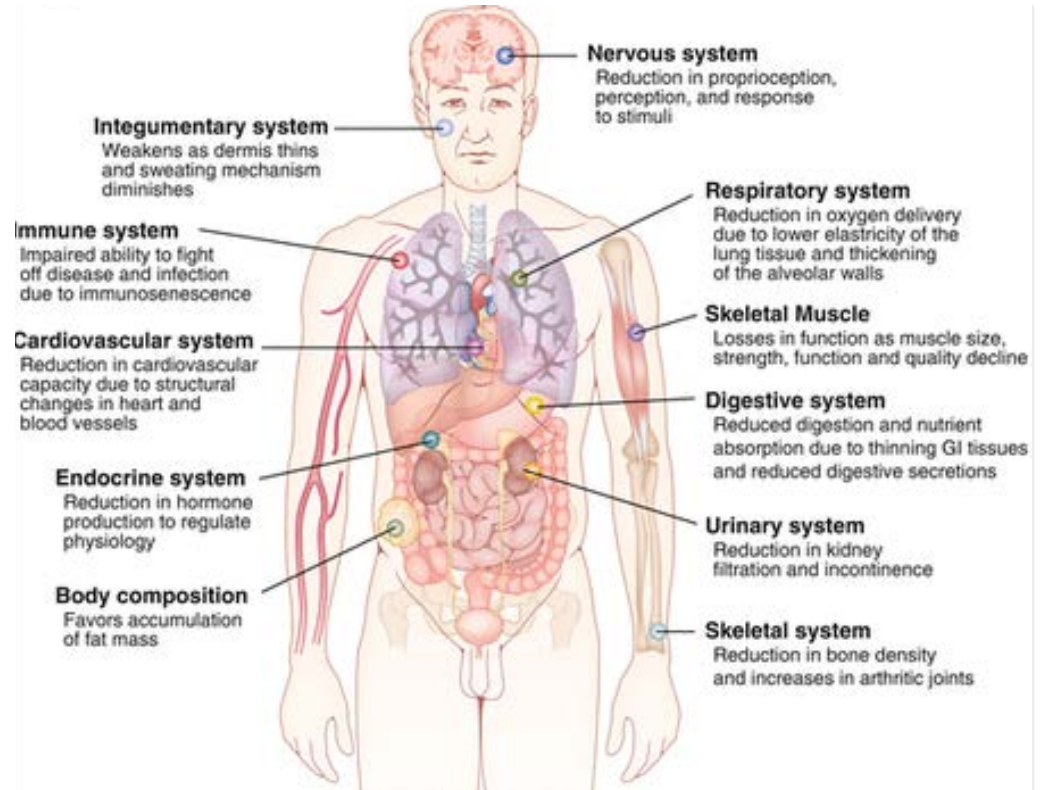
Molecular Basis of Aging



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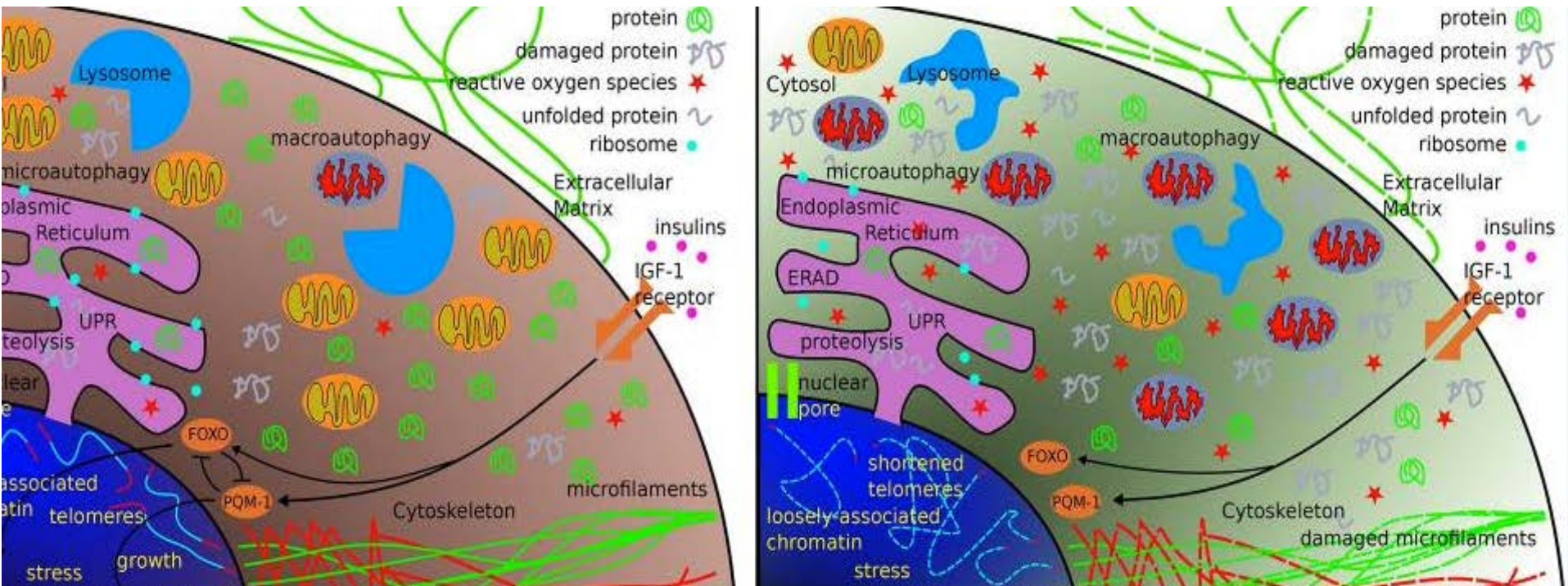
What is Aging?

Ageing: chronic, normal culmination of the loss of specific regenerative and bioprotective mechanisms that occur over time in an organism.



Cellular Aging

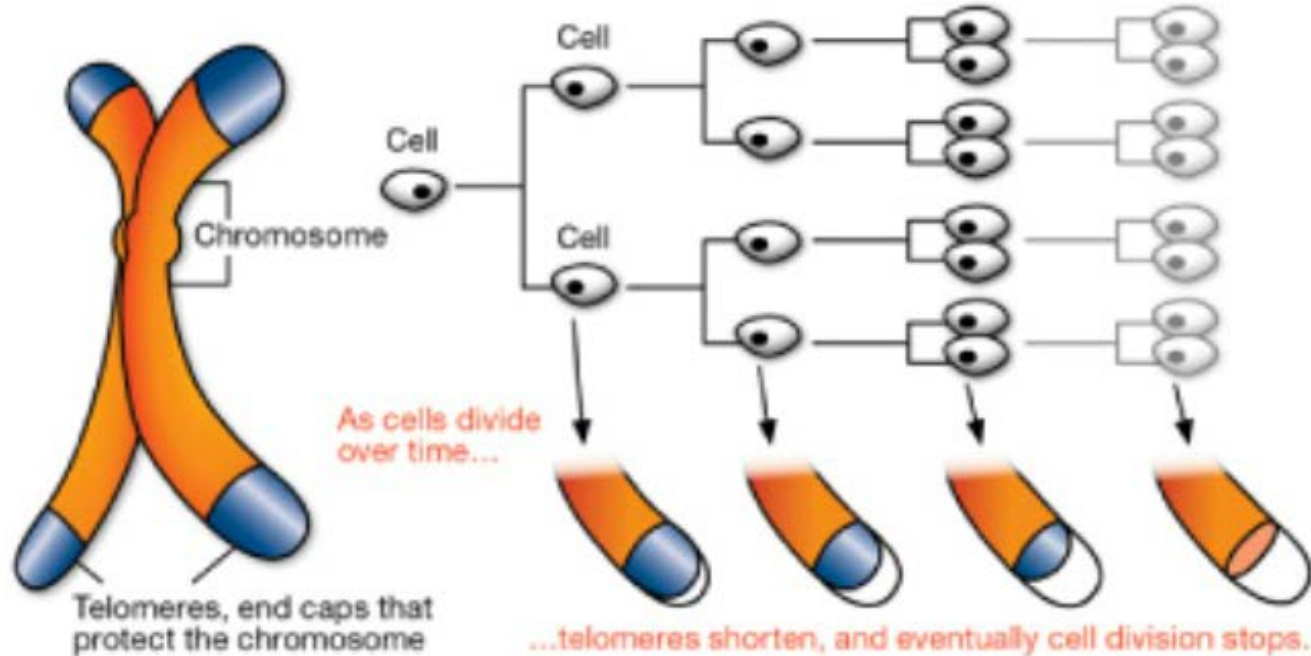
The primary aging-related cellular mechanism to occur is the cessation of cell proliferation.



Cellular Mechanisms of Aging: Genome Instability

- Telomere shortening;
- mitDNA instability;
- rDNA rearrangements.

Telomere Shortening



Cellular Mechanisms of Aging

Cellular mechanisms of aging	Cellular pathways implicated
Reduction of transcriptional regulation of genes implicated in longevity	I/IGF-1R signaling TOR pathway
Protein translation as down-regulation of translation upon reduced nutrient availability extends lifespan in many organisms	I/IGF-1R/FOXO TOR pathway
Down regulation of nuclear pore trafficking	Nucleoporins Lamins
Dysfunction in Proteostasis	Molecular chaperons Protein turnover machinery (proteasomes, ER Degradation proteins, Autophagy) Unfolded protein response
Defects in mitochondria	Respiratory chain and energy metabolism Generation of free radicals Instability of mitochondria DNA
Dysregulation of cytoskeleton integrity	Increased actin turnover
Dysregulation of extracellular matrix and cell membrane	ECM protein damage
Accumulation of iron	

Why do we age?

- Many theories:
 - Evolution-mutations
 - Oxidative stress
 - Genome instability
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- Ageing is a genetically coordinated process that includes regulation of longevity genes.



Longevity genes?

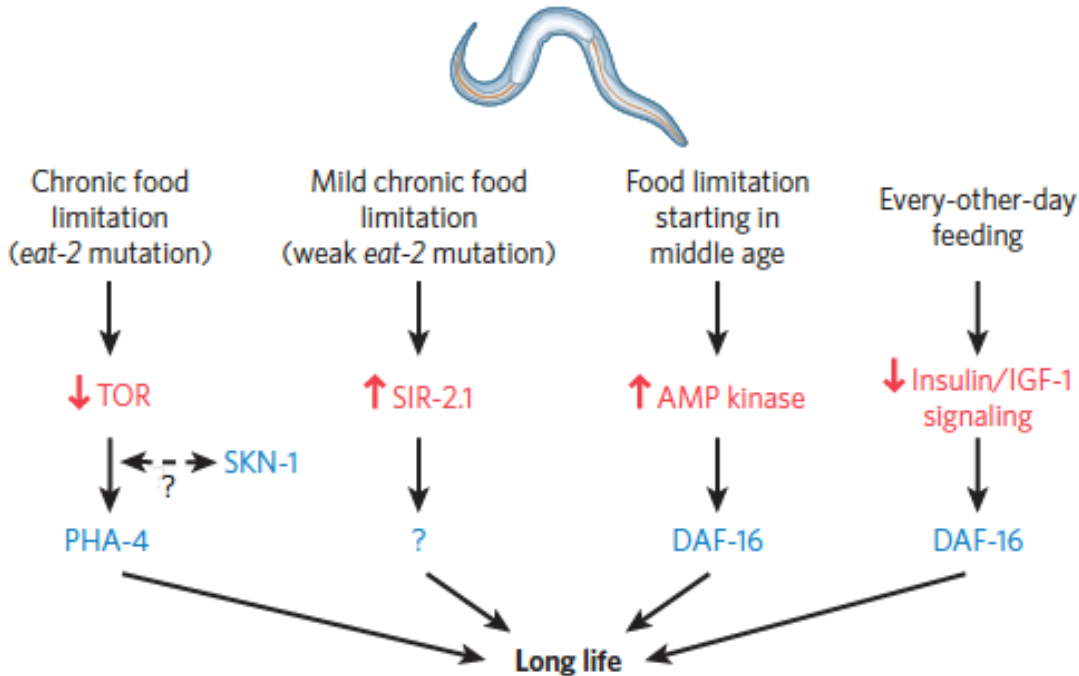
Hutchinson–Gilford Progeria Syndrome: A Premature Aging Disease

Muhammad Saad Ahmed ^{1 2}, Sana Ikram ³, Nousheen Bibi ^{4 5}, Asif Mir ⁶

A case study of “*disorganized development*” and its possible relevance to genetic determinants of aging

Richard F. Walker ^{a, b, c, d} ✉, Lawrence C. Pakula ^c, Maxine J. Sutcliffe ^{a, b}, Patricia A. Kruk ^a, Jesper Graakjaer ^d, Jerry W. Shay ^d

Longevity Genes



Other pathways associated to extend life span are:

- Linked to increased cell respiration
- Signals from reproductive system
- Telomeres.

References

Slide	Reference
2	Fragala M.S. (2015) The Physiology of Aging and Exercise. In: Sullivan G., Pomidor A. (eds) Exercise for Aging Adults. Springer, Cham.
3	DiLoreto R, Murphy CT. 2015 The cell biology of aging. <i>Mol Biol Cell</i> . 2015;26(25):4524–4531.
4	The Biology of Aging. 2013 Boston University School of Public Health. http://sphweb.bumc.bu.edu/otlt/MPH-Modules/PH/Aging/mobile_pages/Aging3.html
6	Why do we Age and can we stop it? 2014 YouTube https://www.youtube.com/watch?v=PIV_q_bpOCE
8	Kenyon, C. 2010 The genetics of ageing. <i>Nature</i> 464, 504–512.



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