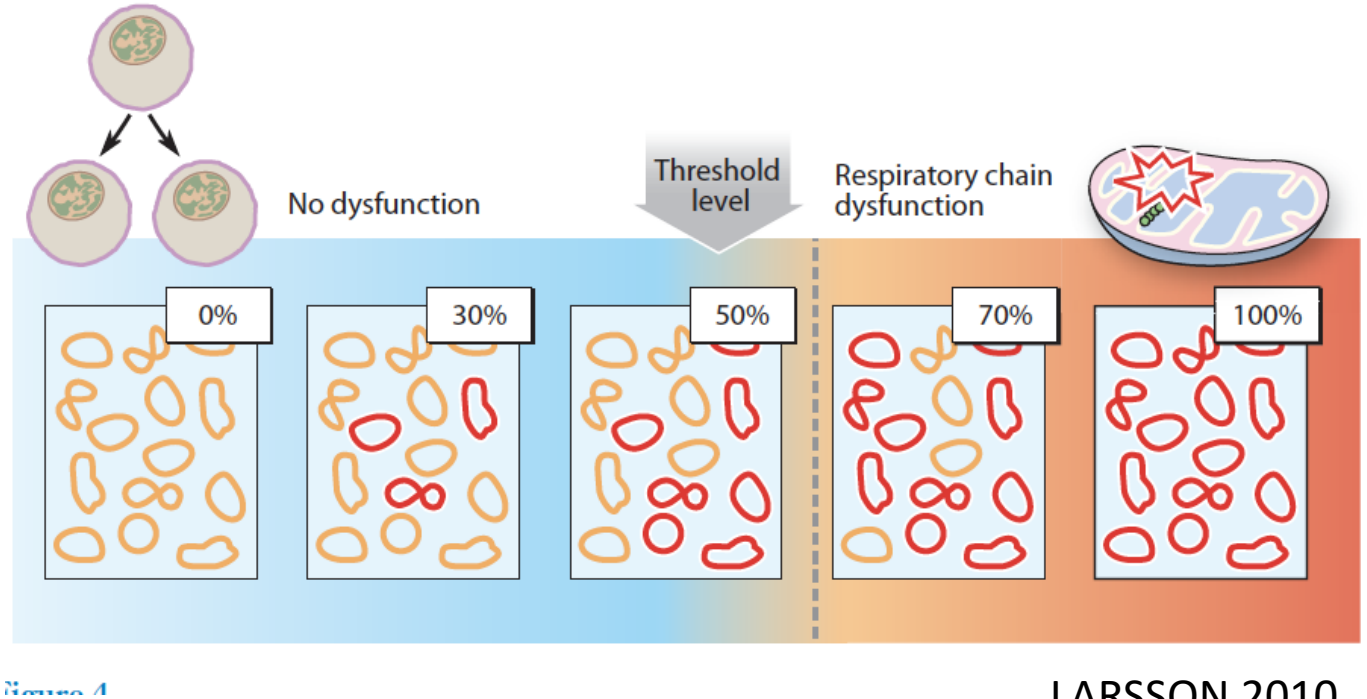
Life eternal in the face of senescence

Mutations in mtDNA

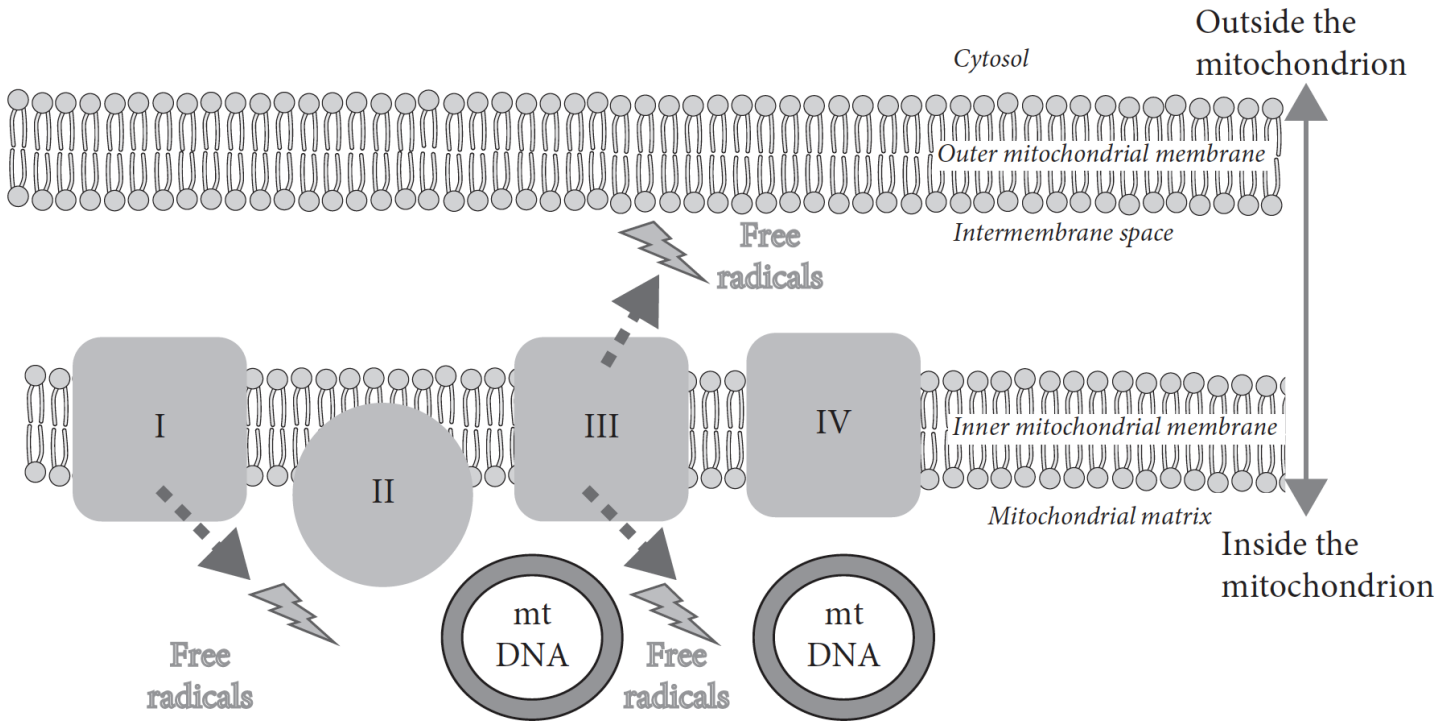
- “All main theories of aging… focus on decline in mt function and accumulations of mt mutations”
- “…there is broad consensus among aging researchers that mt dysfunction is the root cause of aging.”



LARSSON 2010

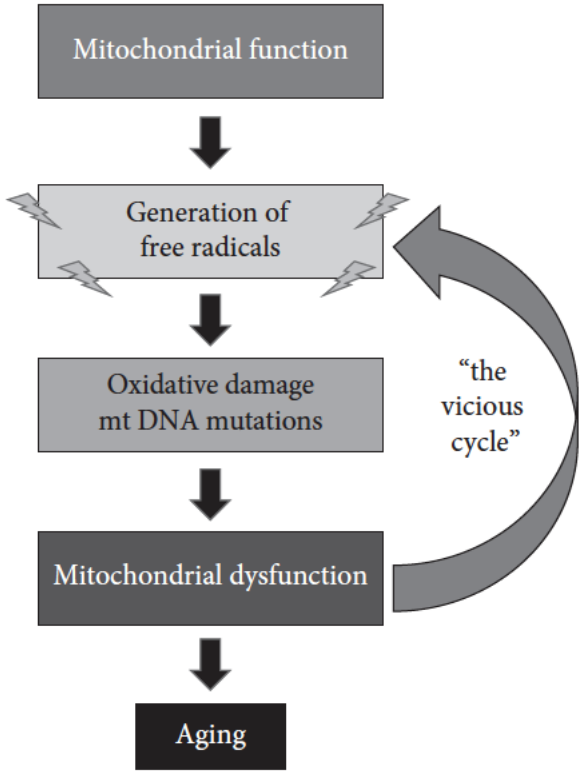
Mitochondrial theory of aging

- Aging is caused by a decrease in mt function over time
  - Free-radical theory of aging
    - Mt dysfunction caused by accumulation of mt mutations caused by ROS
  - Replication error theory of aging
    - Mt dysfunction caused by accumulation of mt mutations caused by replication errors



ROS and the mutational ”vortex” or vicious cycle

- Mitos are main sites of ROS production
- mtDNA is located right there
- “Keeping cookbook next to the fire”



COMMENTARY

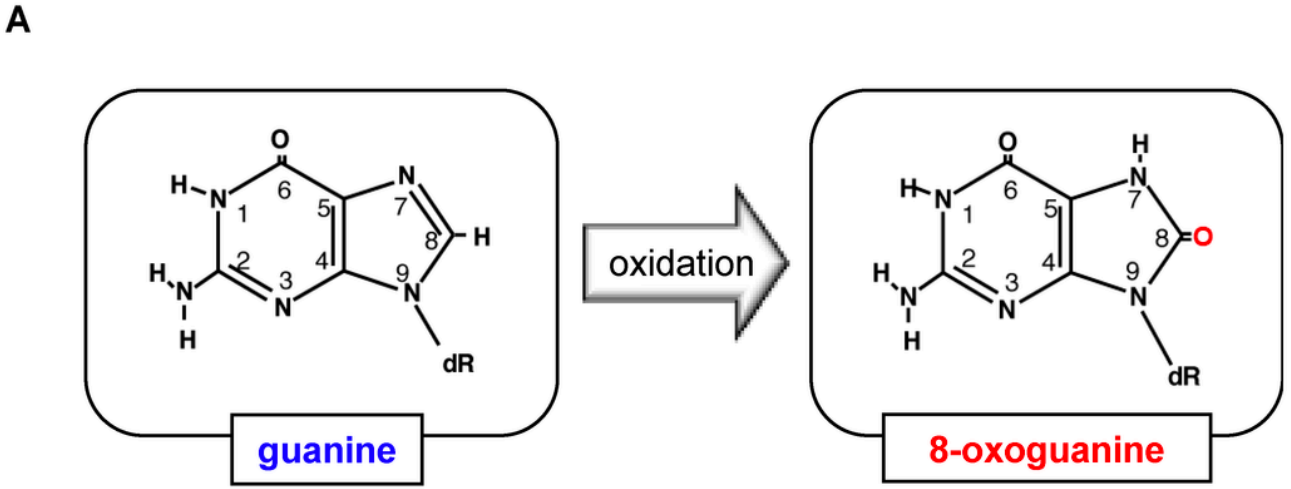
Are mitochondria the main contributor of reactive oxygen species in cells?

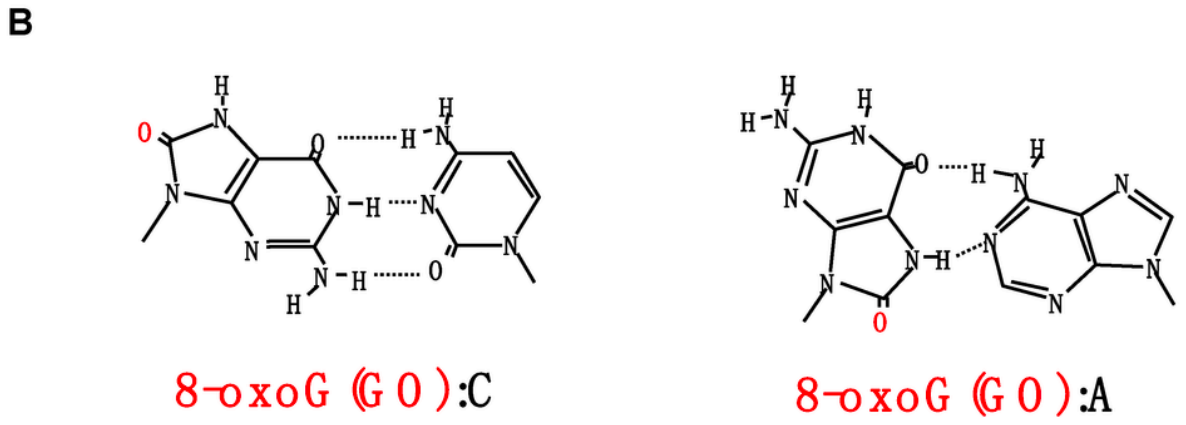
Yufeng Zhang, Hoi Shan Wong

Journal of Experimental Biology 2021 224: jeb221606 doi: 10.1242/jeb.221606 Published 11 March 2021

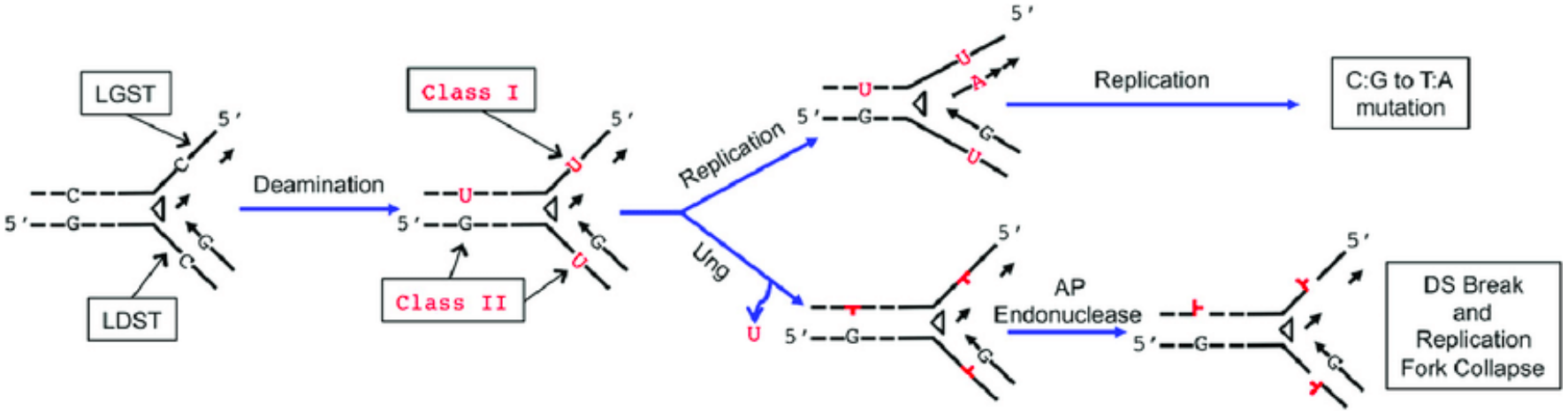
Signatures in the sequences

- G -> T = 8-oxoG
- transversion
- INDICATIVE OF ROS





Signatures in the sequences



- C->T – deamination
- transition
- Characteristic of replication error

Evidence against ROS

- Support for replication causing majority of mtDNA mutations in mammals and drosophila

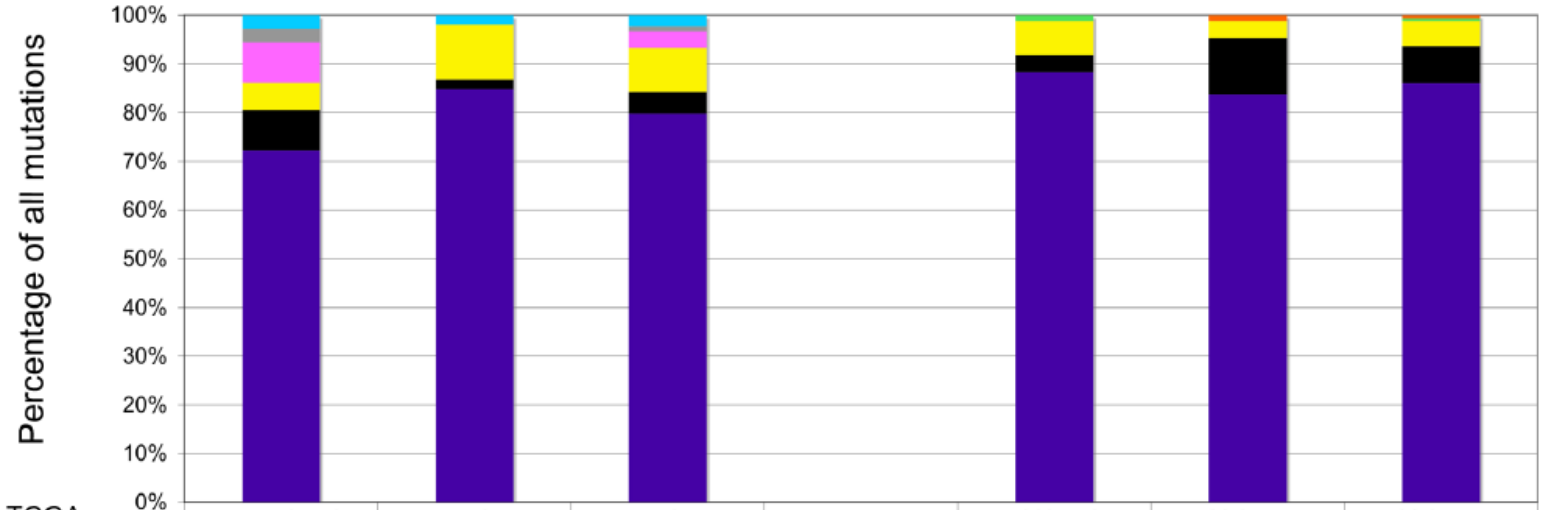
OPEN ACCESS Freely available online

PLOS | GENETICS

Oxidative Stress Is Not a Major Contributor to Somatic Mitochondrial DNA Mutations

Leslie S. Itsara[1,2], Scott R. Kennedy[3], Edward J. Fox[3], Selina Yu[1], Joshua J. Hewitt[1,4], Monica Sanchez-Contreras[5], Fernando Cardozo-Pelaez[6], Leo J. Pallanck[1]*

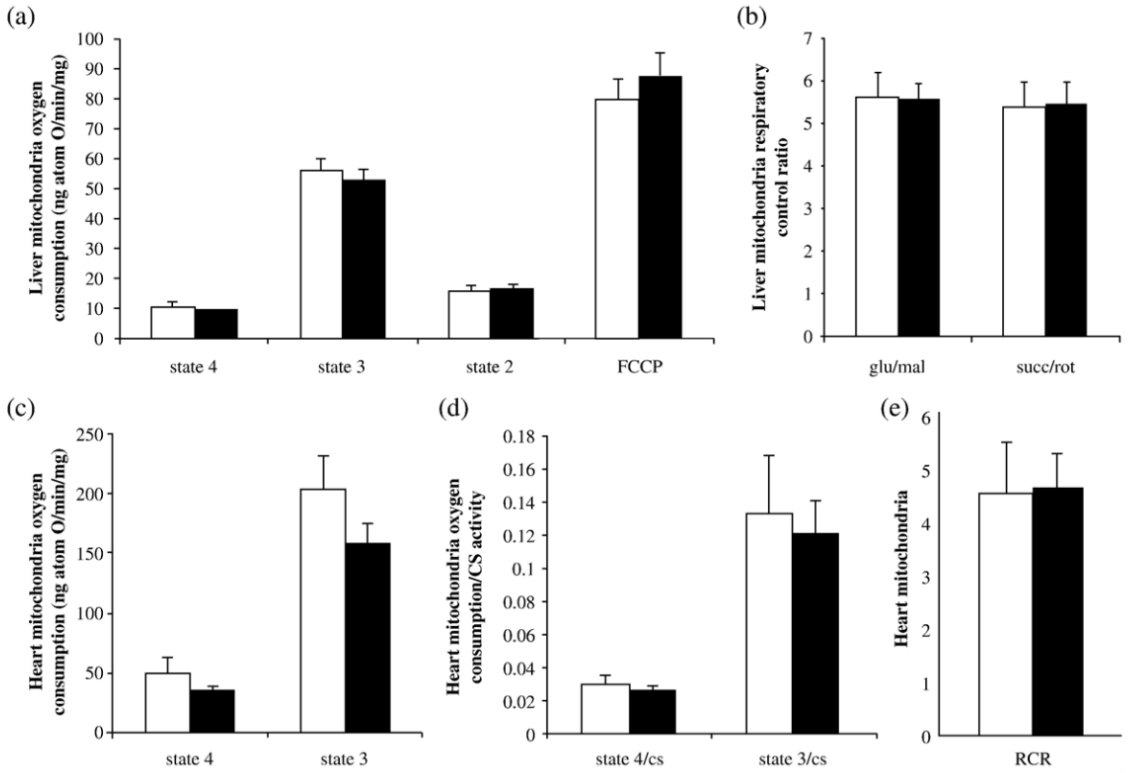
1 Department of Genome Sciences, University of Washington, Seattle, Washington, United States of America, 2 Molecular and Cellular Biology Program, University of



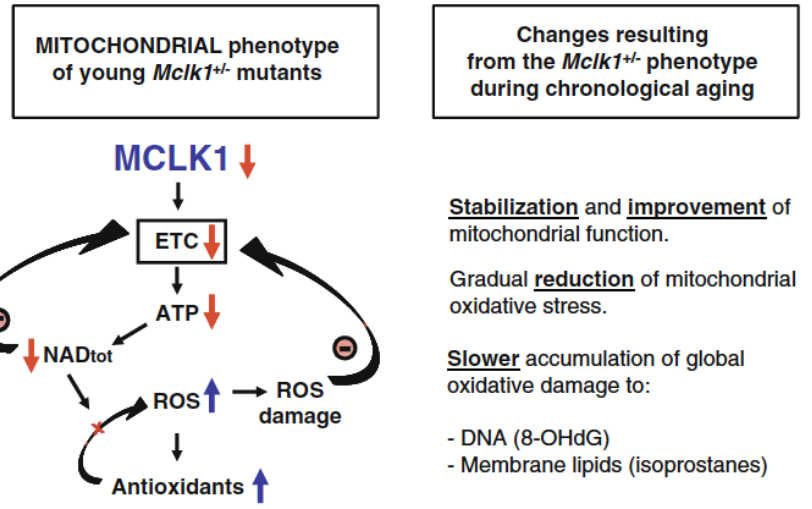
TaqI - TCGA	young head	young thorax	young tissues		old head	old thorax	old tissues
deletion	0% (0)	0% (0)	0% (0)		0% (0)	1% (1)	0.5% (1)
G:C to T:A; T:A to C:G *	0% (0)	0% (0)	0% (0)		1% (1)	0% (0)	0.5% (1)
G:C to C:G; T:A to C:G *	3% (1)	2% (1)	2% (2)		0% (0)	0% (0)	0% (0)
T:A to G:C	3% (1)	0% (0)	1% (1)		0% (0)	0% (0)	0% (0)
T:A to A:T	8% (3)	0% (0)	3% (3)		0% (0)	0% (0)	0% (0)
G:C to C:G	6% (2)	11% (6)	9% (8)		7% (6)	3% (3)	5% (9)
G:C to T:A	8% (3)	2% (1)	5% (4)		4% (3)	12% (10)	8% (13)
G:C to A:T	72% (26)	85% (45)	80% (71)		88% (76)	84% (72)	86% (148)

Other lines of evidence

- polG mice (Kendra!)
  - Increased mtDNA mutations do not cause increased ROS
- OGG1-null mice
  - Increased 8oxoG mtDNA mutations don't caused decreased mt function or aging
- MCLK1$^{-/+}$ mice
  - Increased ROS, but ages slower



Stuart et al. 2005



In general… this theory of aging is dead ☺

Cell. Mol. Life Sci. (2010) 67:1–8
DOI 10.1007/s00018-009-0138-8

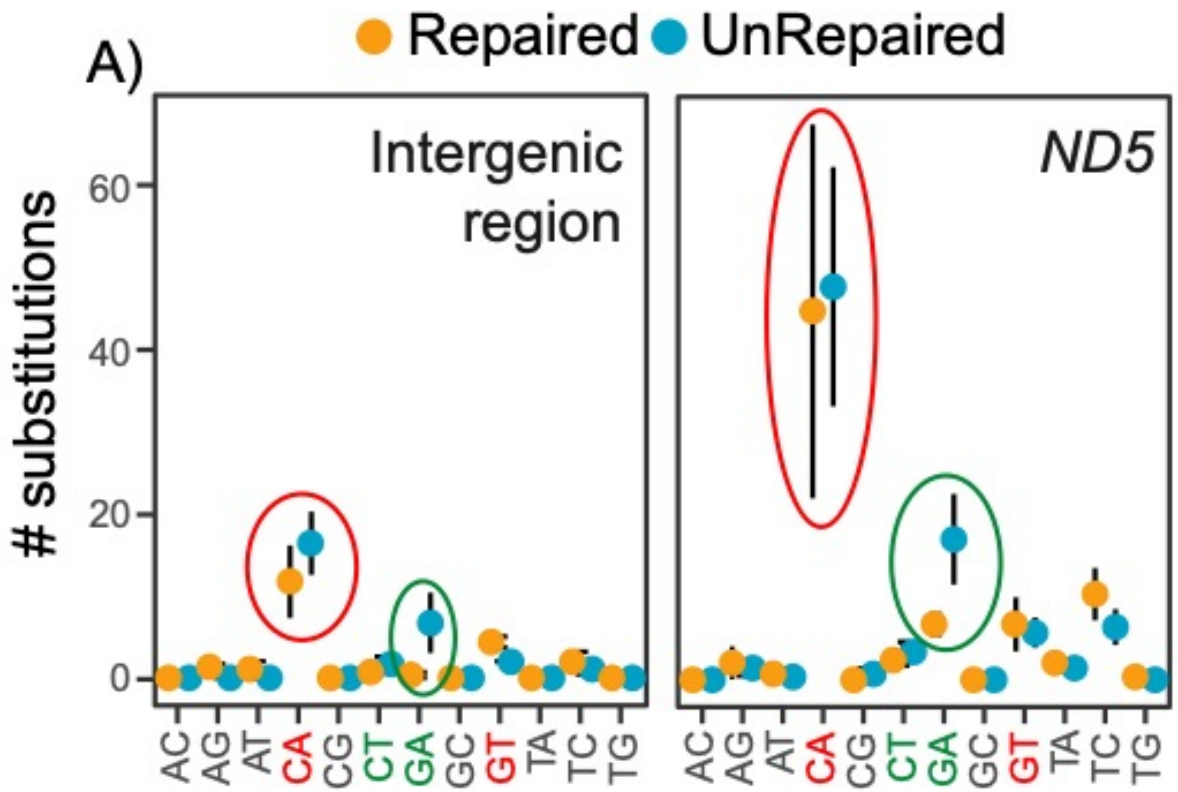
Cellular and Molecular Life Sciences

VISIONS & REFLECTIONS (MINIREVIEW)

When a theory of aging ages badly

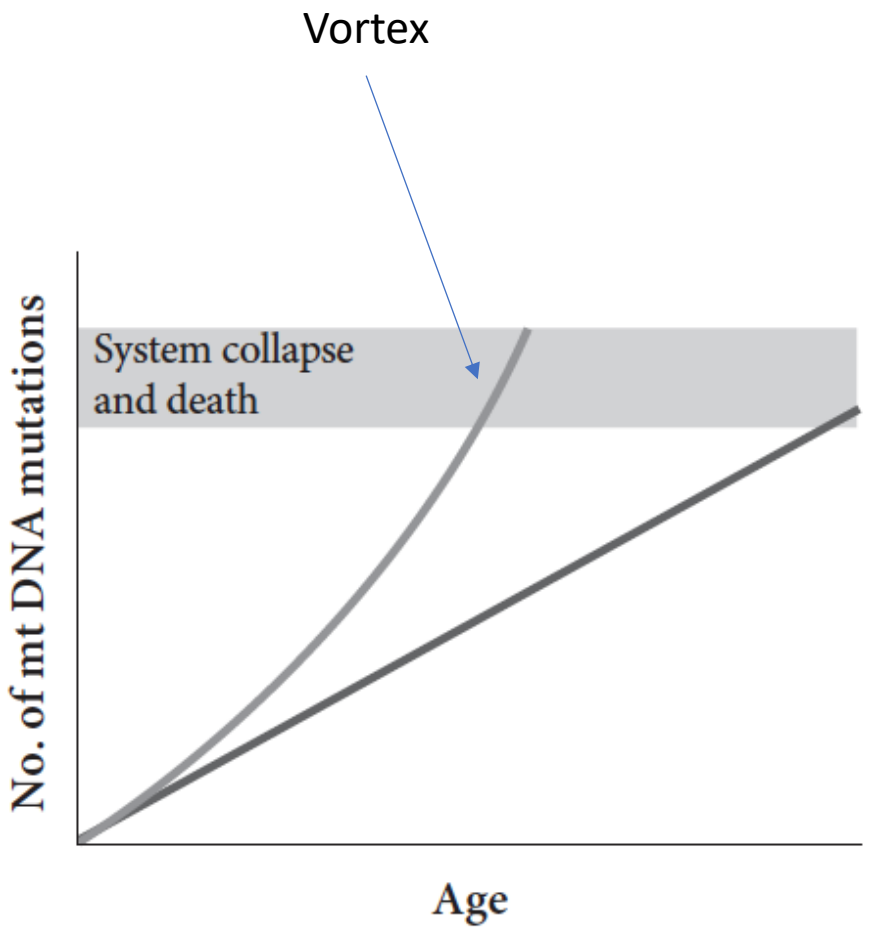
Jérôme Lapointe · Siegfried Hekimi

Long live the MFRTA



Replication error theory

- Supported by polG mice



Do mitos really cause aging?

Mutations of mitochondrial DNA are not major contributors to aging of fruit flies

Timo E. S. Kauppila[a,1], Ana Bratic[a,1,2], Martin Borch Jensen[b], Francesca Baggio[a], Linda Partridge[c], Heinrich Jasper[b], Sebastian Grönke[c], and Nils-Göran Larsson[a,d,2]

[a]Department of Mitochondrial Biology, Max Planck Institute for Biology of Ageing, D-50931 Cologne, Germany; [b]The Buck Institute for Research on Aging, Novato, CA 94945; [c]Department of Biological Mechanisms of Ageing, Max Planck Institute for Biology of Ageing, D-50931 Cologne, Germany; and [d]Department of Medical Biochemistry and Biophysics, Karolinska Institutet, SE-17177 Stockholm, Sweden

Edited by Ruth Lehmann, New York University Medical Center, New York, NY, and approved August 27, 2018 (received for review December 13, 2017)

- Antagonistic pleiotropy in nuc genes too

Can we stop aging or live forever?

- Gilgamesh and whatnot
- Hill says no: “Because aging is a fundamental property of humans, the only way humans could stop aging would be to stop being human”

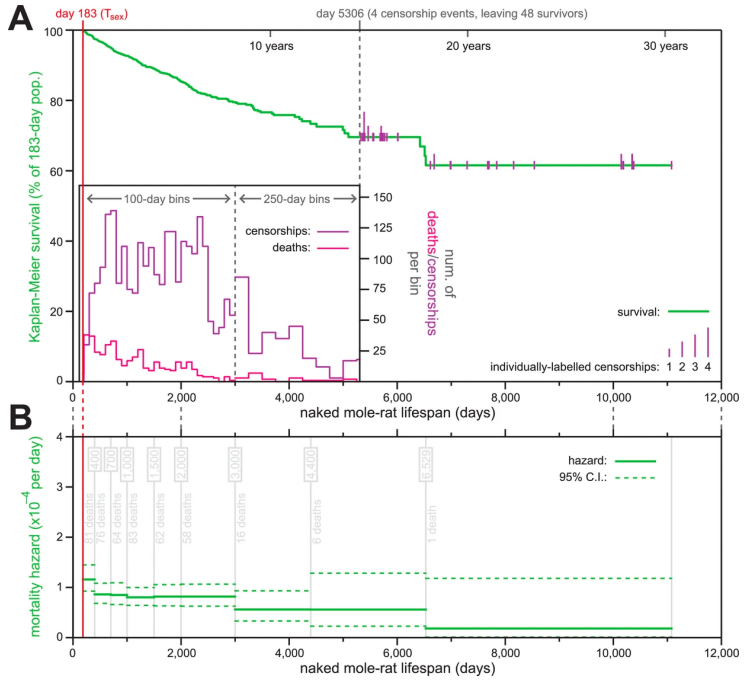
Do they though?

www.aging-us.com AGING 2018, Vol. 10, No. 6

Research Paper

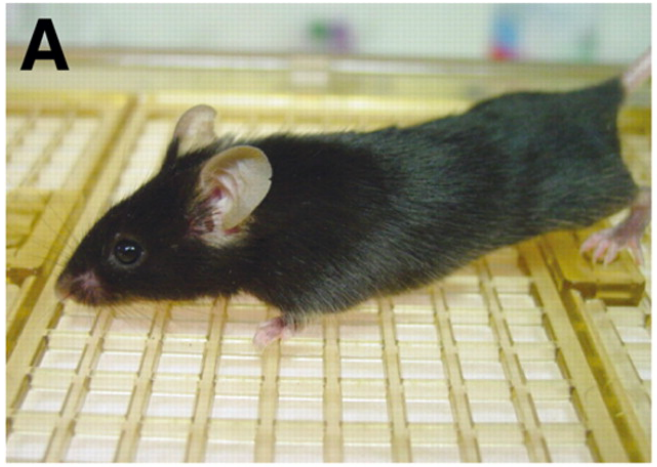
Naked mole rat cells display more efficient excision repair than mouse cells

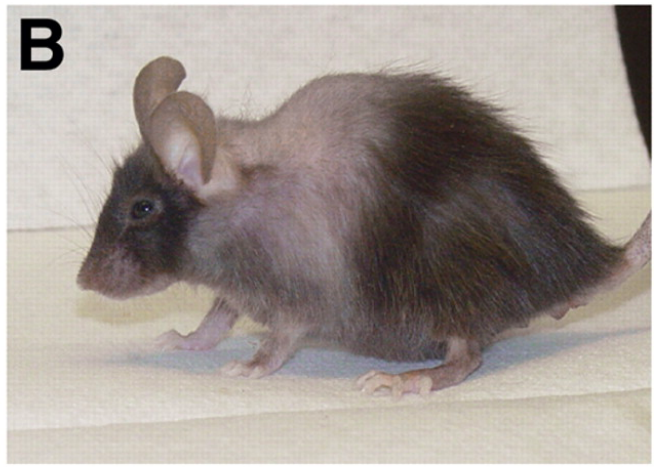
Alexei Evdokimov[1,*], Mikhail Kutuzov[1,*], Irina Petruseva[1], Natalia Lukjanchikova[1], Elena Kashina[3], Ekaterina Kolova[1], Tatyana Zemerova[1], Svetlana Romanenko[2], Polina Perelman[2], Dmitry Prokopov[2], Andrei Seluanov[4], Vera Gorbunova[4], Alexander Graphodatsky[2], Vladimir Trifonov[2], Svetlana Khodyreva[1], Olga Lavrik[1]

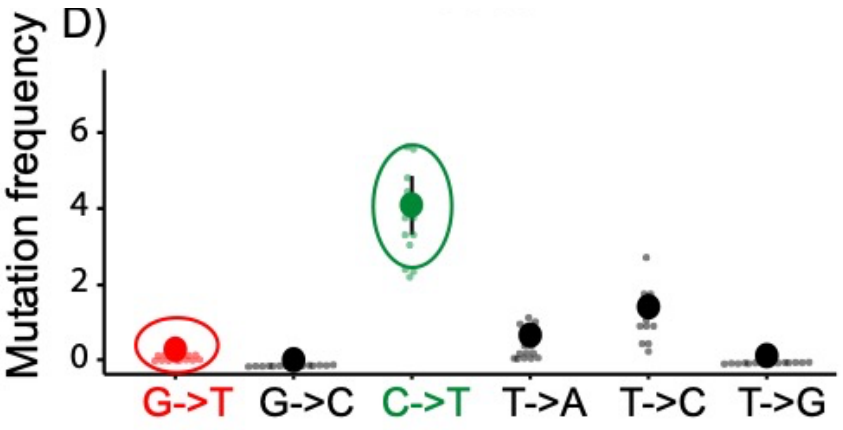


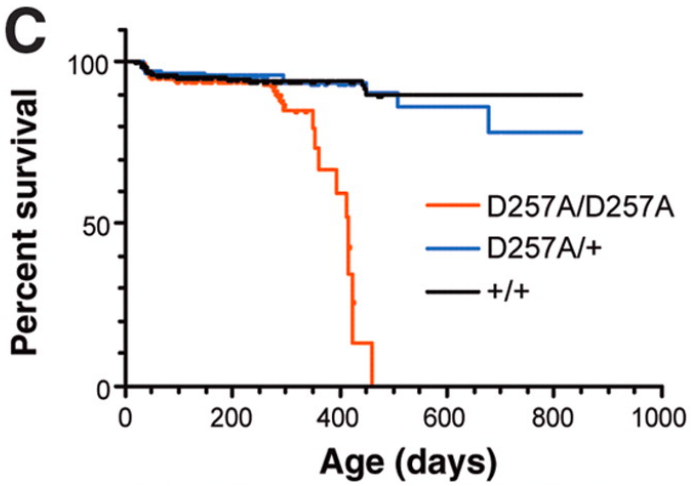
polG mice

- They accumulate mt mutations and age rapidly
- They give birth to “normal” young

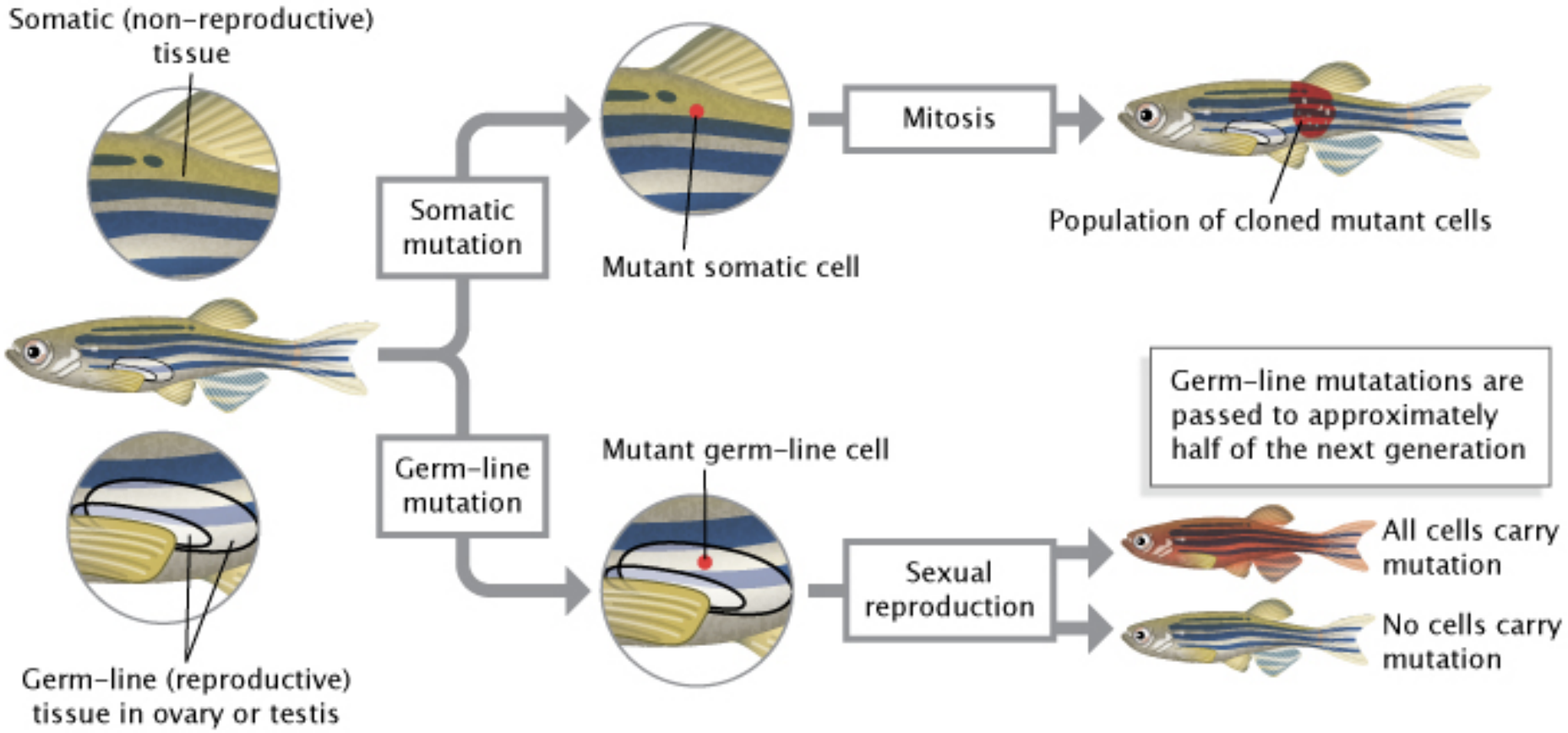








Immortal germline vs. disposable soma



Clancy 2008

Who has a germline?

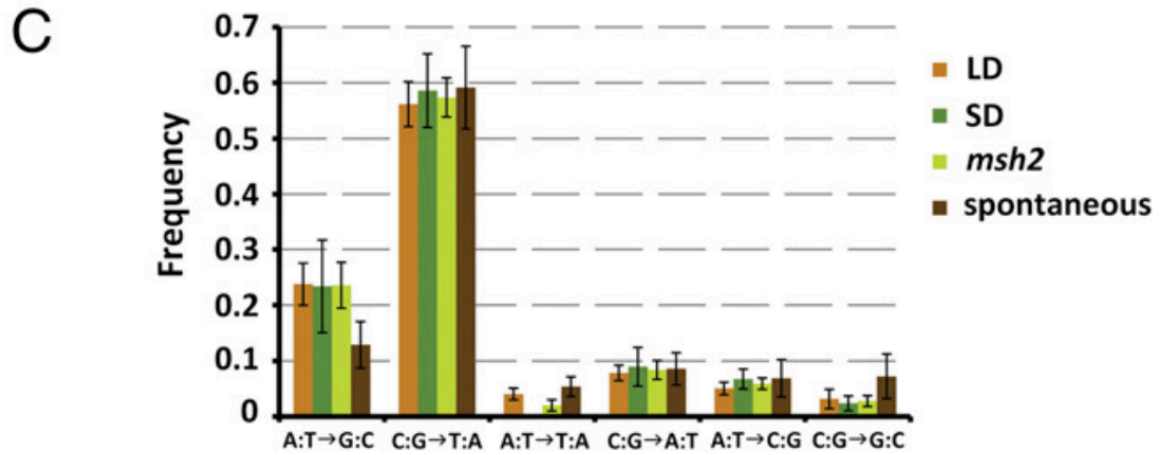
- Animals
- Plants?
  - Surprisingly, the number of cell divisions within the gamete lineage is nearly independent of both life span and vegetative growth.
  - These results suggest that stem-cell organization has independently evolved in plants and animals to minimize mutations by limiting DNA replication.
- Probably not unicellular eukaryotes

PNAS

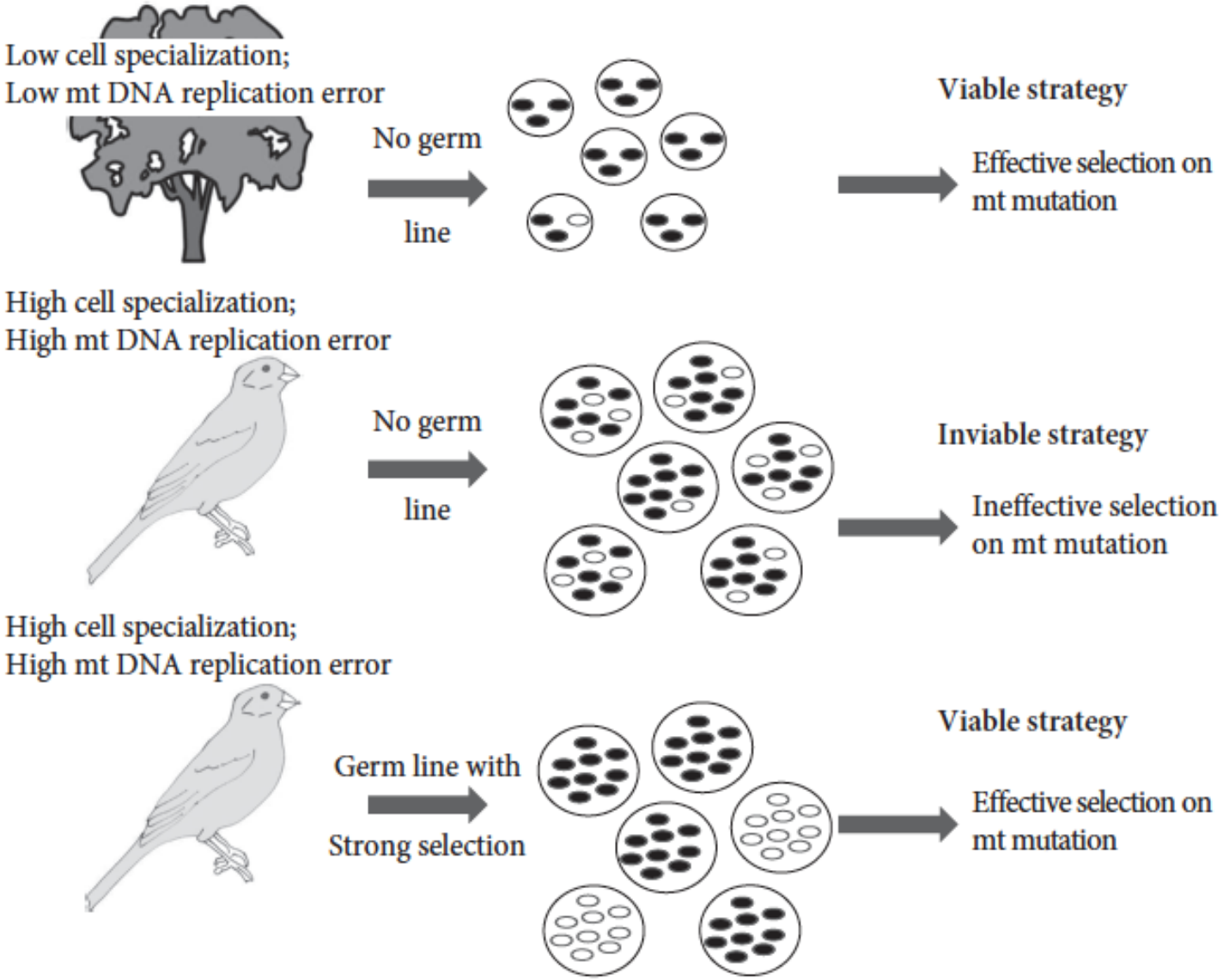
Germline replications and somatic mutation accumulation are independent of vegetative life span in *Arabidopsis*

J. Matthew Watson[a], Alexander Platzer[a], Anita Kazda[a], Svetlana Akimcheva[a], Sona Valuchova[b], Viktoria Nizhynska[a], Magnus Nordborg[a], and Karel Riha[a,b,1]

[a]Gregor Mendel Institute of Plant Molecular Biology, Austrian Academy of Sciences, Vienna Biocenter, 1030 Vienna, Austria; and [b]Central European Institute of Technology, Masaryk University, 612 65 Brno, Czech Republic



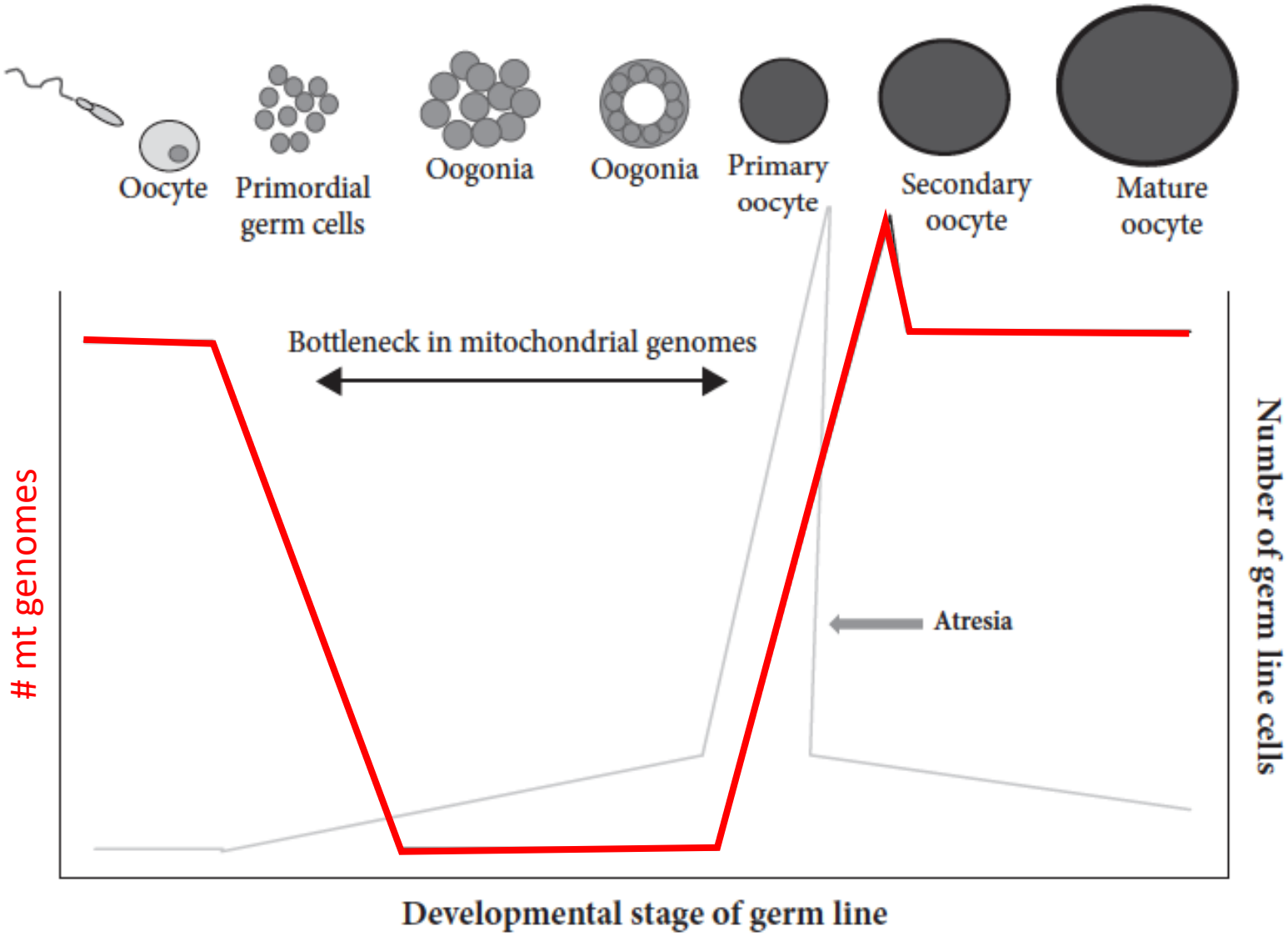
Animal-centric ideas



Selection on the germline – prior to proliferation

- Mitos are “turned off” during most of female gamete cell life
- Most female gametes do not get the chance for fertilization
- Not many cell divisions either
- “Quiescent”
- Nuc vs. mt selection

Continued selection after proliferation



Selection on mt genomes vs. mitonuclear function vs. organismal fitness

- Hard to tease these apart
- Respiration rate/mt function is screened during oogenesis
- Apoptosis
- Selection on other nuc genes?

Selection on male germ line

- Lots of mt respiration
- Selection on energetics during fertilization
- 200M sperm per ejaculate, 1 gets to fertilize = pretty intense selection
- Mt genes aren’t passed on, so selection on N-mt genes and other nuc genes
- But… sperm don’t really rely on respiration, mainly glycolysis
- So… what?

Selection on mitonuclear function throughout development

- Continued selection during early development, juveniles, adults, gametes, etc…
- All these things (bottlenecks, glycolysis, mitos turned off) are all based on mice
- How do some of these things relate to plastid-nuclear ecology?