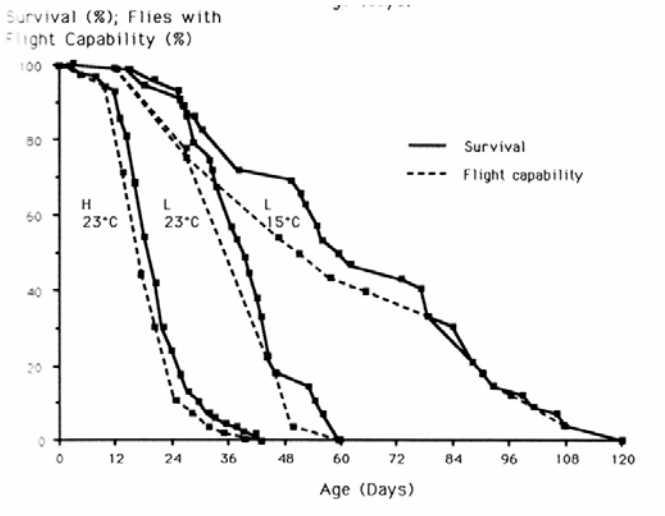
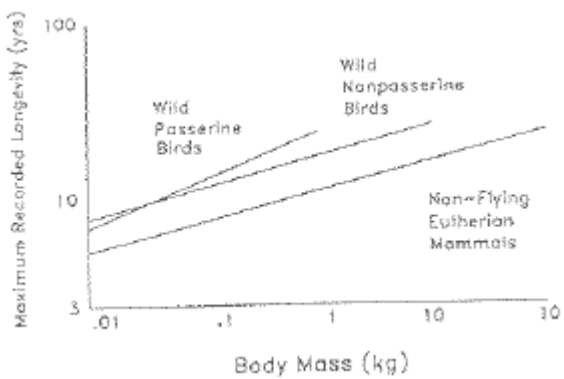
Part 7. Clock of life

Why mitochondria kill us in the end

Signaling between damaged mitochondria and the nucleus
plays a pivotal role in the cell's fate and our own

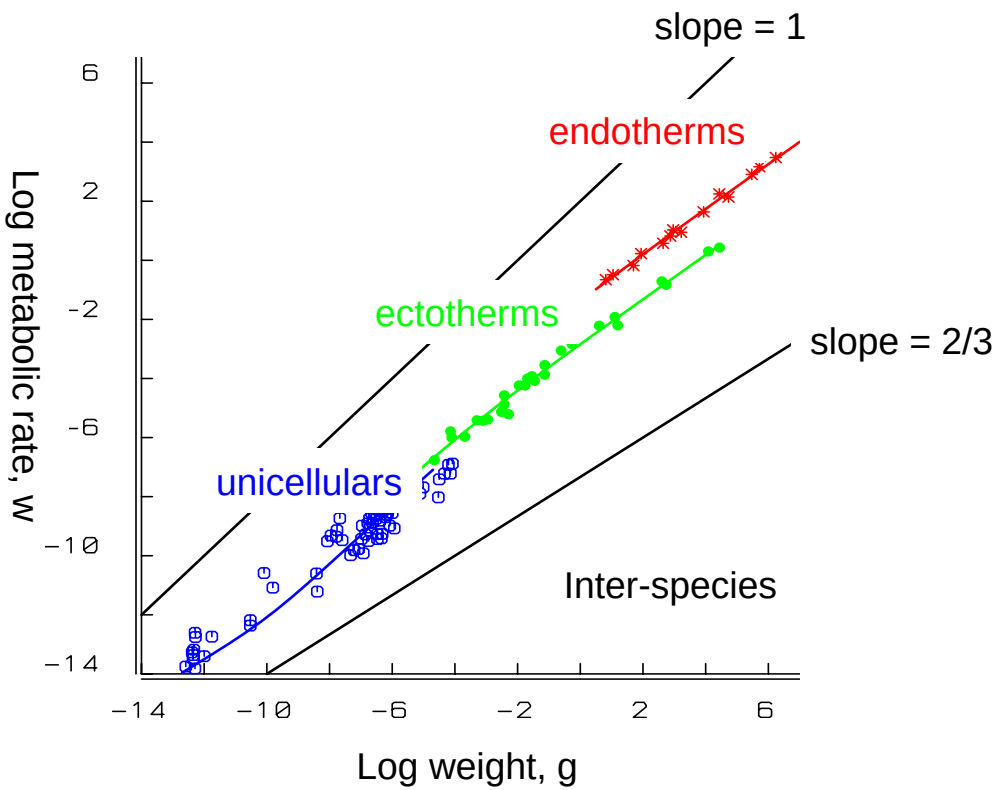
The faster the metabolic rate the shorter the lifespan
Ageing is not inevitably linked to degenerative diseases
Mitochondria are the main cause of ageing: mitochondrial theory of ageing
free radical leakage is linked to lifespan, degenerative diseases, nucleus





Austad, S.N., and K.E. Fischer. 1991. Mammalian aging, metabolism, and ecology: evidence from the bats and marsupials. J. Geront. 46: B47-53.

Metabolic rate scales with weight



The mitochondrial theory of ageing

1972, Denham Harman

Rapid metabolic rate; high oxygen consumption; increased free radical leakage

Free radical leakage is constant (depends only on metabolic rate)

An implicit prediction: protective role of antioxidants

Problems

1. Antioxidants level is higher in short living animals

    1980s Richard Cutler

    Negative correlation between antioxidant levels and lifespan

    There may be a lower risk of cell oxidation in long living cells

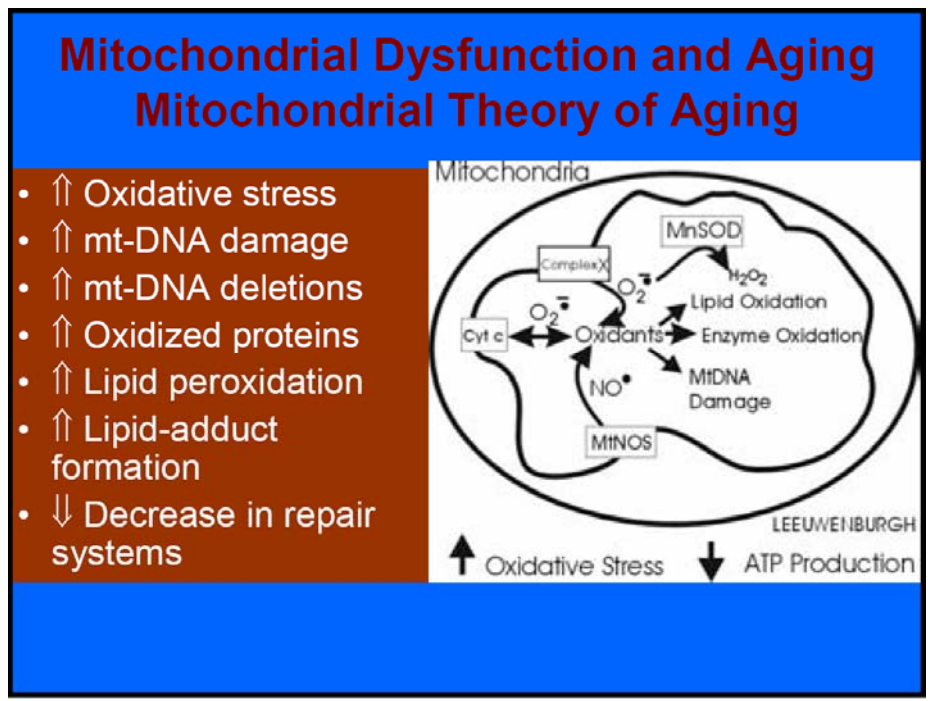
2. Free radical leakage is controllable

    Gustavo Barja's study on birds

    Leak fewer free radicals

    Then, why mouse did not?

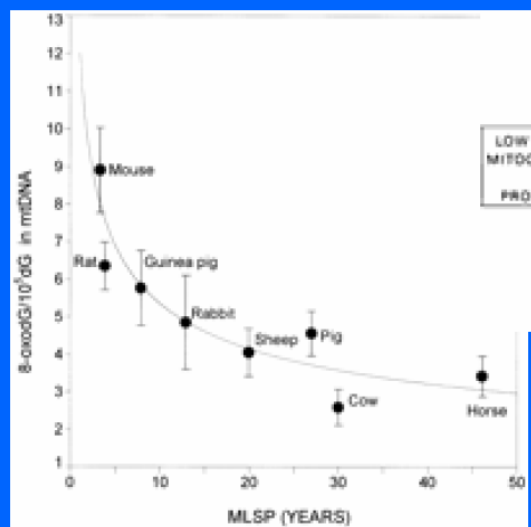
    Any hidden cost?

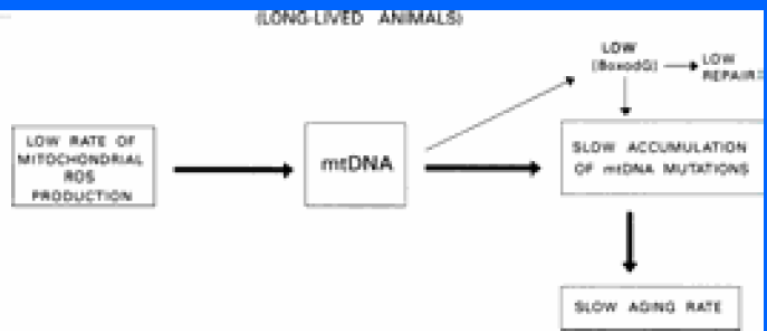


Long-lived Species; Maximum Life-span, Mean Life-span, Species-Specific Differences.

Bats (10-30 years) and Birds (30-100) have a high Metabolism, but are long lifed!!! Maybe a reduced radical production?

Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals

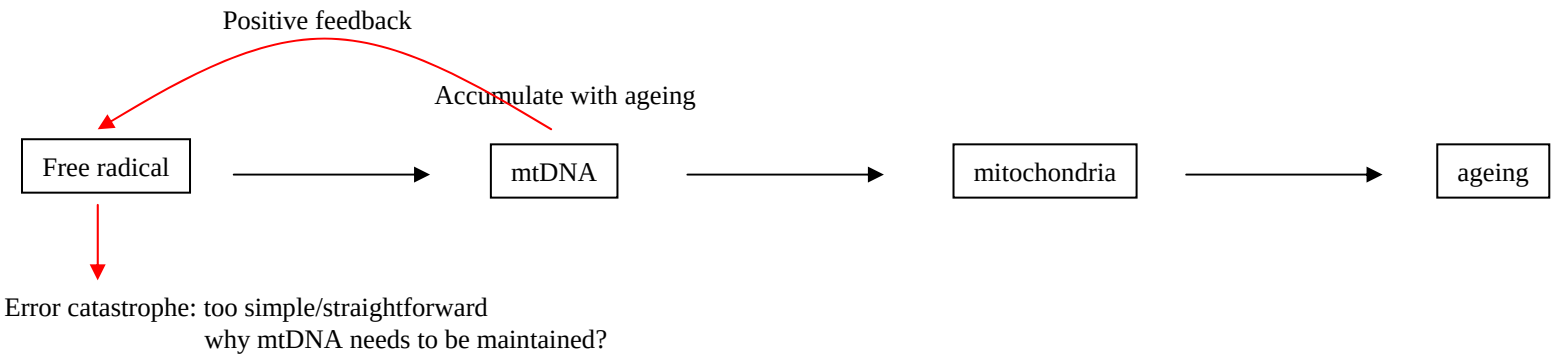




The FASEB Journal. 2000;14:312-318.) 2000 FASEB **Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals GUSTAVO BARJA[1] and ASUNCIÓN HERRERO**

Mitochondrial mutations

Mitochondrial mutations accumulate with age



Mitochondrial diseases

1959, the first reported case of mitochondrial disease
1981, mtDNA sequencing

Extreme heterogeneity of diseases
High incidence: 1/5000

If ageing is the accumulative effect of mtDNA mutations, ageing would be manifested by a variety of types
But normal ageing, which differs from degenerative diseases, is similar to all of us and even with animals
mtDNA mutations don’t seem sufficient to cause ageing

The paradox of mitochondrial mutations in ageing

1. nDNA

Haldane: ageing is little more than a dustbin of late-acting gene mutations
Natural selection can't eliminate the genes that defer their detrimental effects until later in life

How to explain the life extension induced by a single point mutation?
How can a single gene simultaneously control the many accumulated mutation?

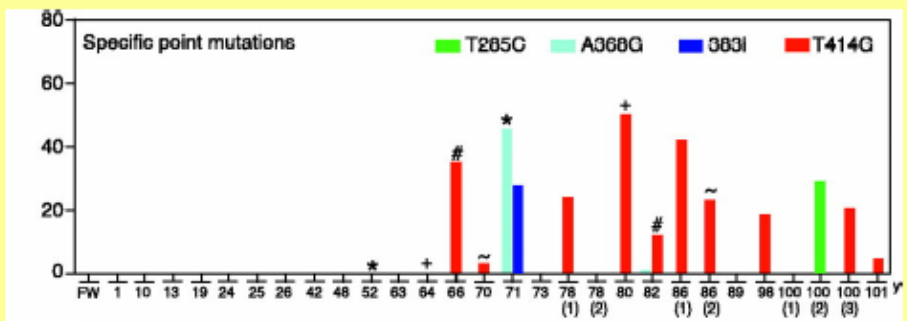
2. mtDNA

A. High mutation rate: is it true in human?
B. Mitochondria is corrosive

Yeast: 10^5 than nDNA
Human:
control region: 1999, Science, nearly absent in young age, over 50% in old age
coding region: rarely accumulate at levels about 1%
why? different mutations in different cells?
don't accumulate at the higher level

Yeast do not depend on respiration, but human does
Actually normal except control region in aged cells
removal by selection in the coding region?

Aging-Dependent Large Accumulation of Point Mutations in the Human mtDNA Control Region for Replication

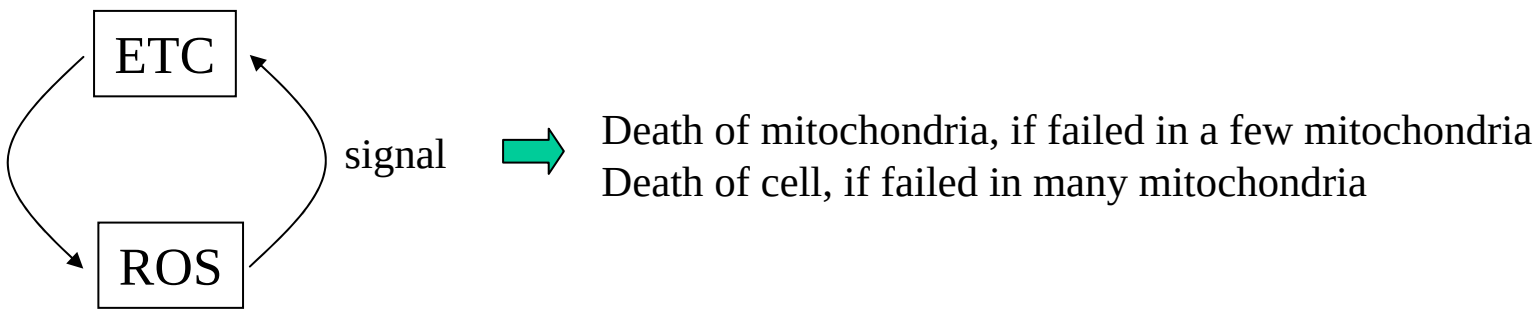


17. Demise of the self-correcting machine

The mitochondrial theory of ageing by Harman is incorrect
1. Antioxidant: disapproved
2. mtDNA mutation accumulation: only in control region
3. Dependence of the rate of free radical leakage on metabolic rate: does not explain exercise paradox
4. Mitochondria is the main place for free radical leakage generation: it is okay but not enough
5. Free radical leakage is constant

Why mouse did not evolve to reduce free radical leakage?
Allan's reasoning of the maintenance of mtDNA
advantage is more valuable than disadvantage

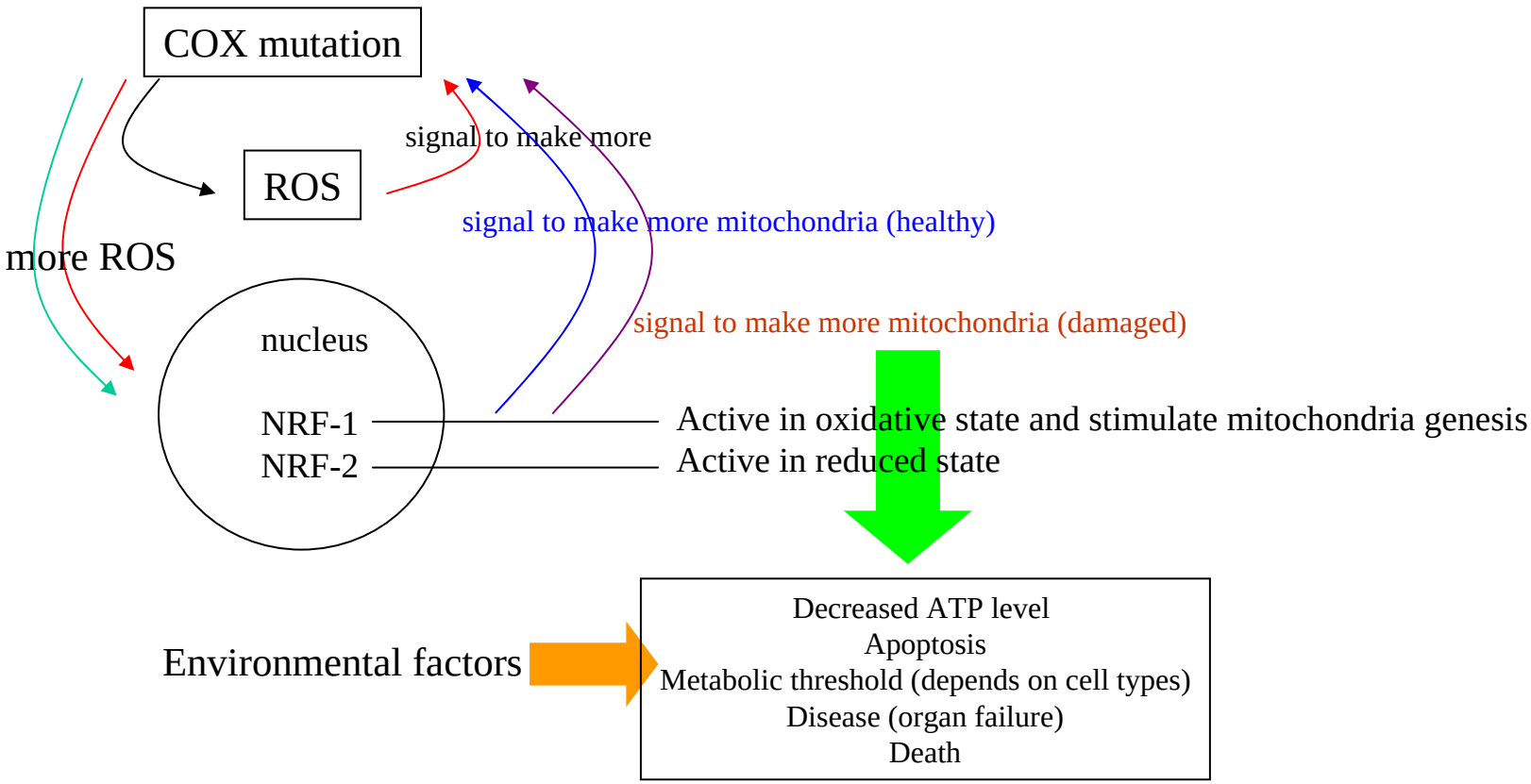
Self-correcting machine
The necessity of free radical leakage & mtDNA: a kind of thermostat



The retrograde response

Mitochondria has a sensitive feedback system

Free radical has both signal function and toxicity



mtDNA, mitochondria, cell, tissue, organ, body

Disease and death

It is not true to predict that all the diseases of old age are caused by free radicals
Ageing does not essentially mean diseases
Disease in old ages are delayed

2004, Alan Wright
10 mutations in nDNA (not related to free radical generation) causing degenerative diseases
Same diseases in mouse, rat, dog, pig, and human in the times relative to their lifespan
(why not in the same period?)

Ageing determines the onset of degenerative diseases, not the reverse

2004, Nature
Knockin mouse of abnormal mtDNA proofreading enzyme
high mtDNA mutation
reduced lifespan, but no increase in mtDNA mutation (probably eliminated by apoptosis?)

Mitochondrial mutations contribute to the progression of ageing and disease
Other genes associated with particular diseases add to the overall levels of cellular stress, leading to apoptosis
Blocking apoptosis is not a useful way to extend lifespan
Degenerative diseases of old age could be slowed down by slowing down the rate of free radical leakage

A cure for old age

The key to longer life is spare capacity, not antioxidant

Why mouse did not evolve to have a spare capacity?

The costs of evolving greater refinement could explain why mouse don't restrict free radical leakage

- The cost of elaborating a sensitive detection system
- The cost of maintaining a lot of spare capacity

mtDNA, mitochondria, cell, tissue, organ, body