Cellular Biology of Aging

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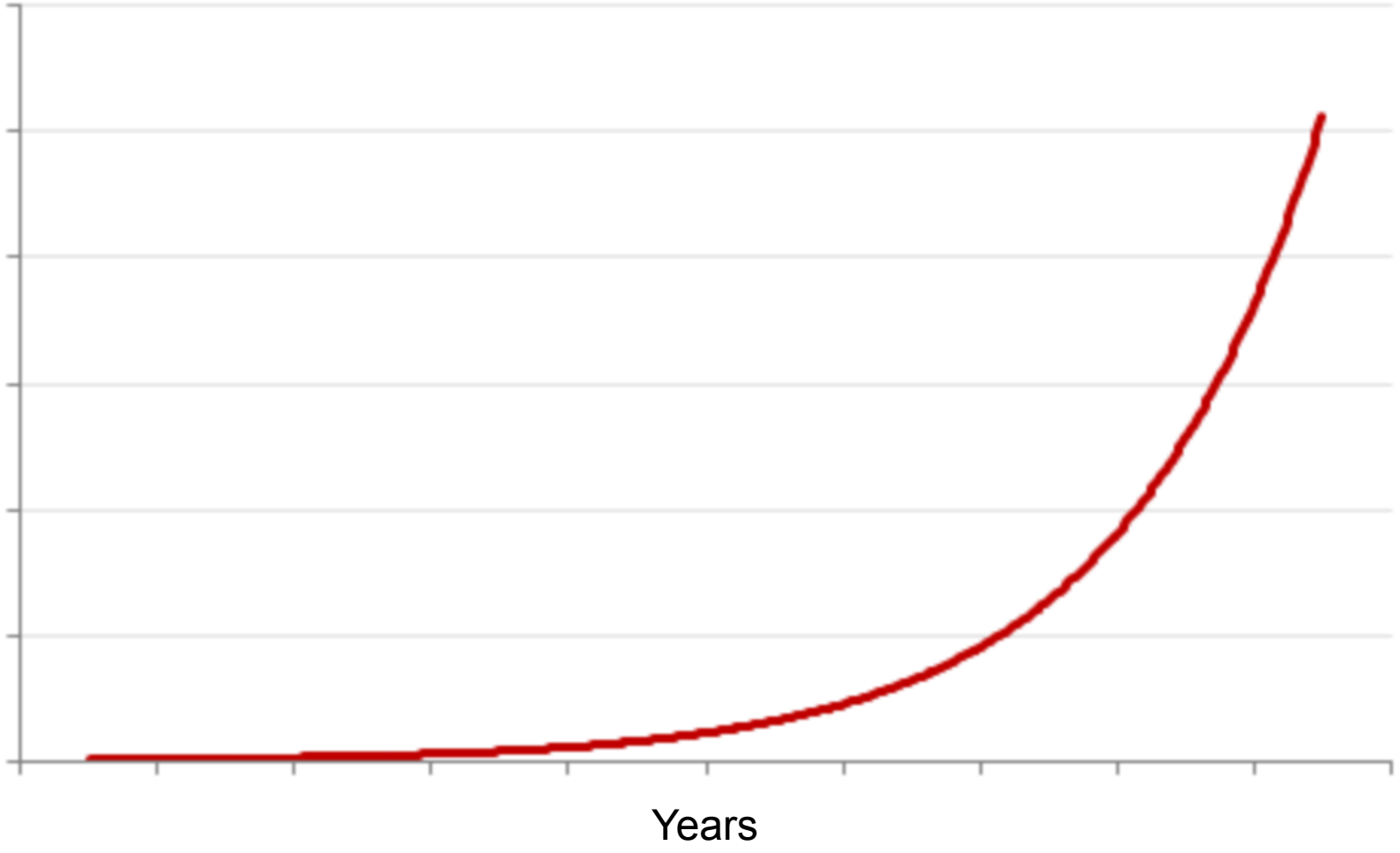
Outline

- Major cellular processes of aging
  - Energy and mitochondria
  - Damage
  - Clearance of damage and autophagy
  - Replacement from stem cells
  - Cell senescence
- Treatments
  - Exercise
  - Caloric restriction
  - Senolytics

The Epidemiology of Aging Biology in 1 slide: Aging causes exponential failure with time

Risk of aging-related Conditions:
Death
Dementia
Disability
Stroke
M.I.
Hip fracture
etc.



Exponential failure

Requires the interaction of at least two processes

The most likely cellular processes that give rise to failure:

- Accumulation of damage
- Clearance of the damage
- Capacity to generate energy

Interactions that lead to exponential failure of tissue function

- Accumulation of damage exceeds it’s clearance
  - By very little at the start then increasing with age
- Decreasing capacity to generate energy
  - A consequence of damage that also contributes to failure

Classical hallmarks of aging

These define domains of research

Arrows denote topics for today

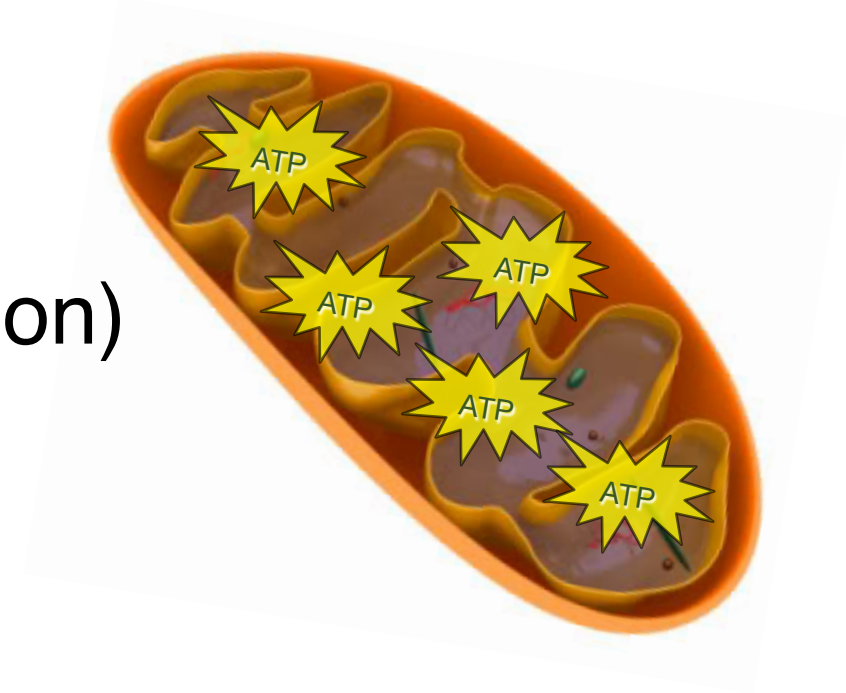
Hallmarks of aging

These are based almost entirely on research in short-lived model systems, usually mice and works

Capacity to generate energy

Mitochondria

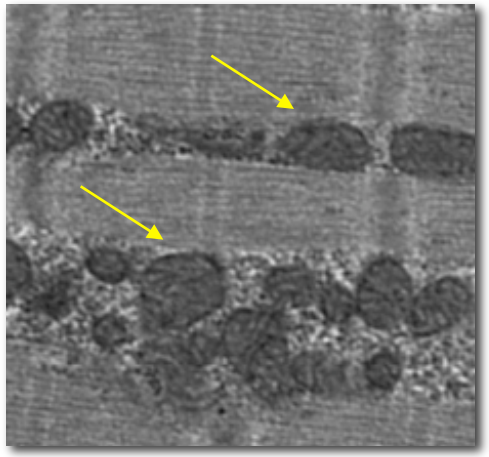
- Produce ATP to supply 90% of energy
- From reactions of oxygen with glucose and fatty acids (oxidative phosphorylation)



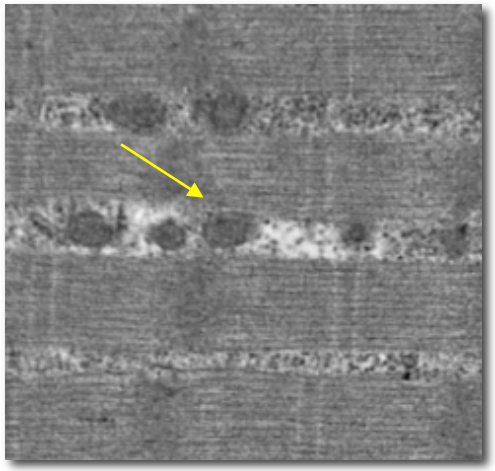
Mitochondria decrease with aging

- Decreased quantity
- Accumulate damage
- Decreased function

Young



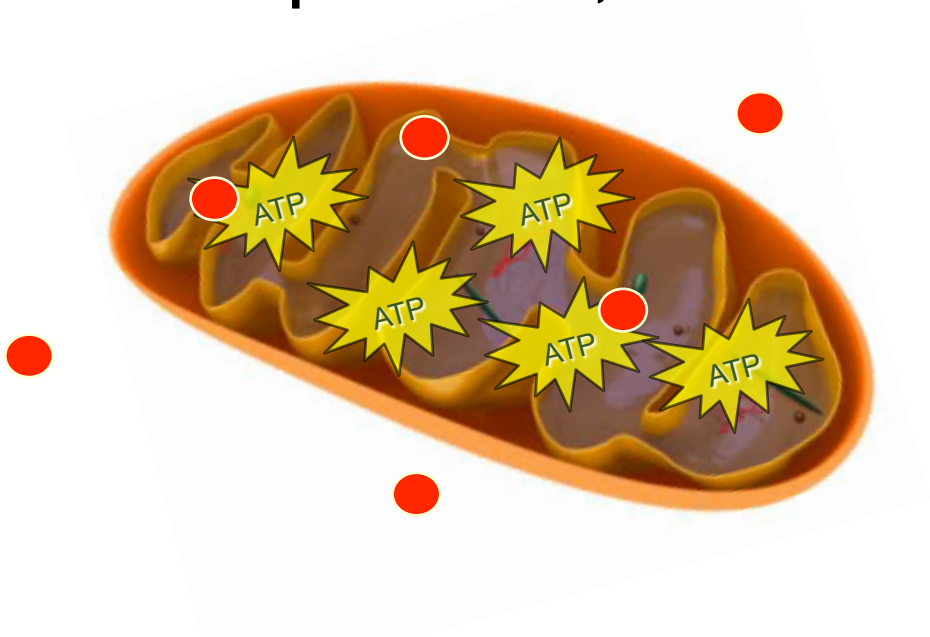
Old



Damage

Oxidative damage

- Oxidative phosphorylation generates ‘reactive oxygen species’ (ROS) ROS
- About 2 ROS per 1,000 molecules of ATP
- Bind to proteins, membranes, DNA, and mitochondria



Oxygen	Superoxide anion	Peroxide
O_2	$\cdot O_2^-$	$\cdot O_2^{-2}$
Hydrogen Peroxide	Hydroxyl radical	Hydroxyl ion
H_2O_2	$\cdot OH$	OH^-

We rust…

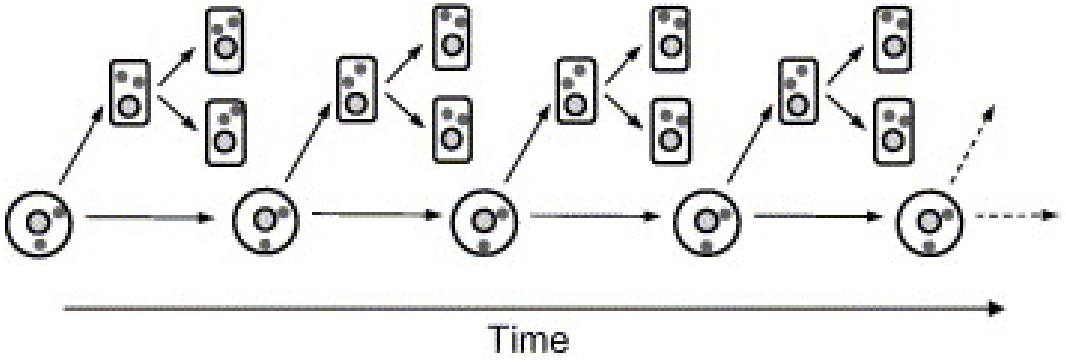
Other types of damage

- Entropy – ’random’ rearrangements of molecules
- Glucose binds irreversibly – glycosylation
- Nitrogen ’radicals’ also bind – nitrosylation
- Many other types of damage
- Very little research; an opportunity to find new markers

Clearance of damage

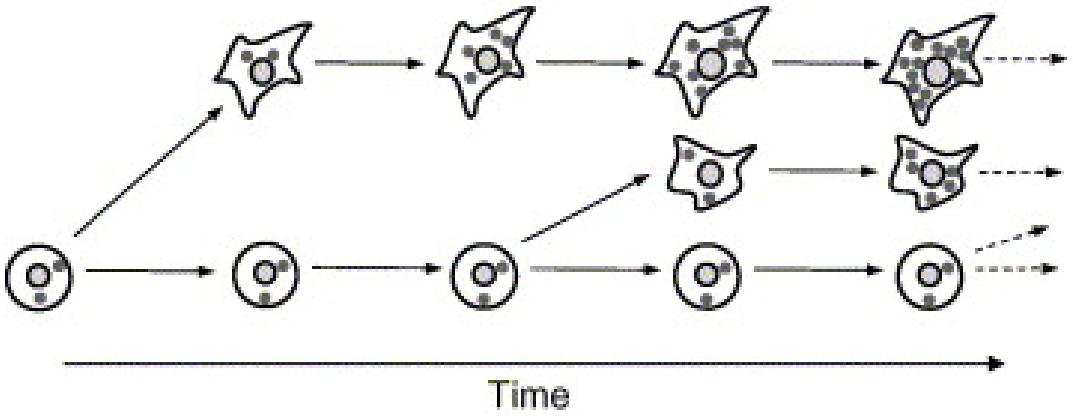
Strategies for clearing damage depends on the general type of cell

Renewable, shorter lived cells



White blood cells
Cells lining the G.I. tract

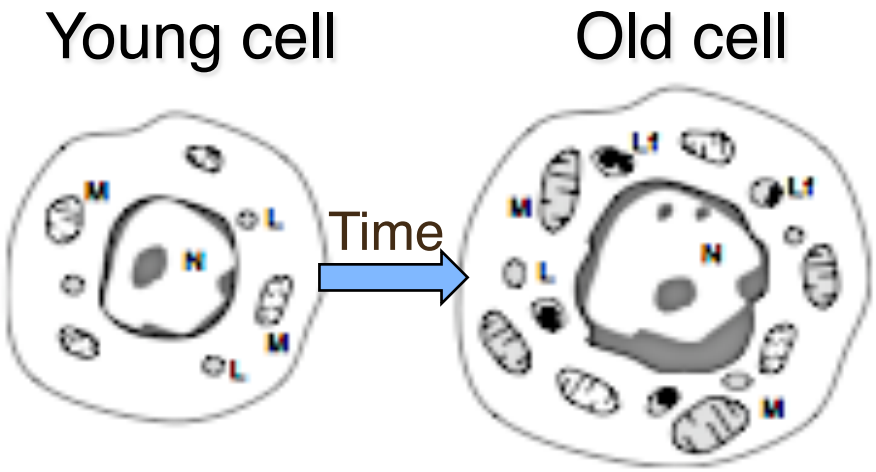
Postmitotic, longer lived cells



Cardiac myocytes
Neurons

Alexi Terman, et al. Mol Aspects Med 2006;471

Postmitotic, long-lived cells that no longer divide and reproduce

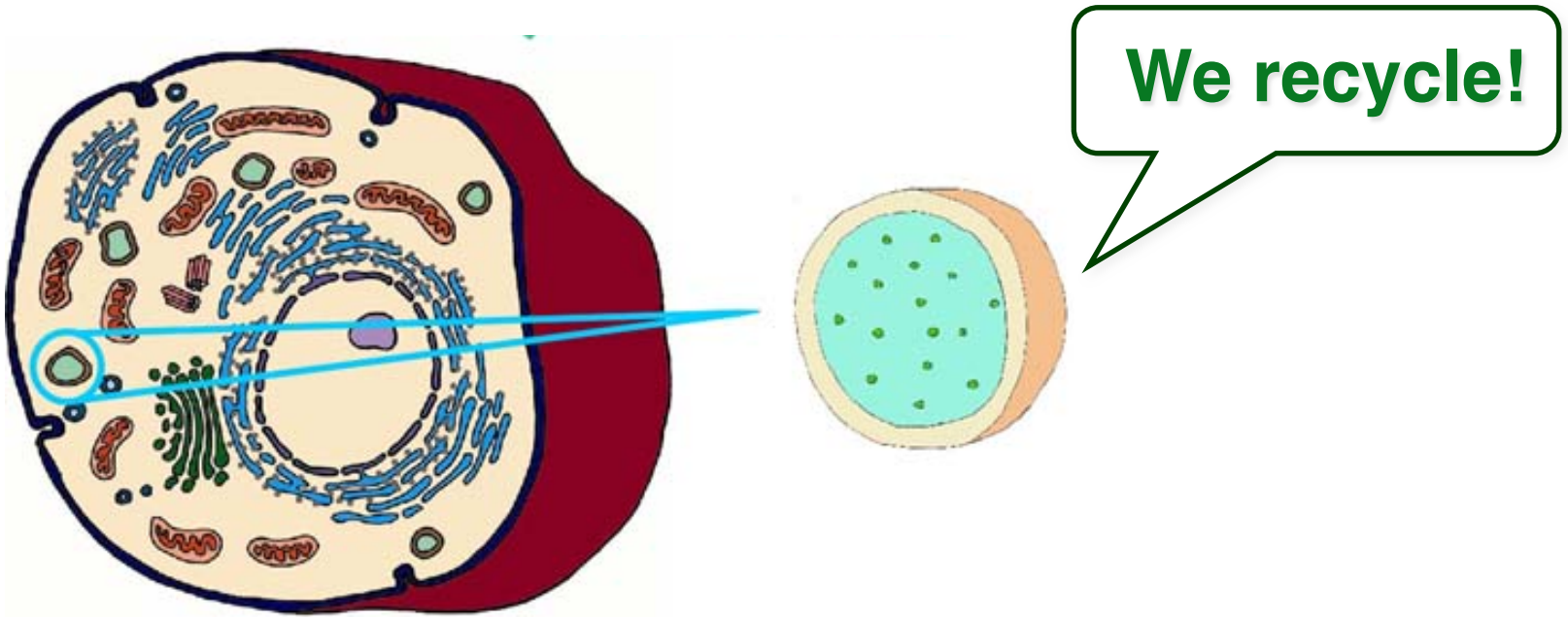


They are not replaced
Garbage accumulates:
damaged proteins, enzymes,
DNA, mitochondria,

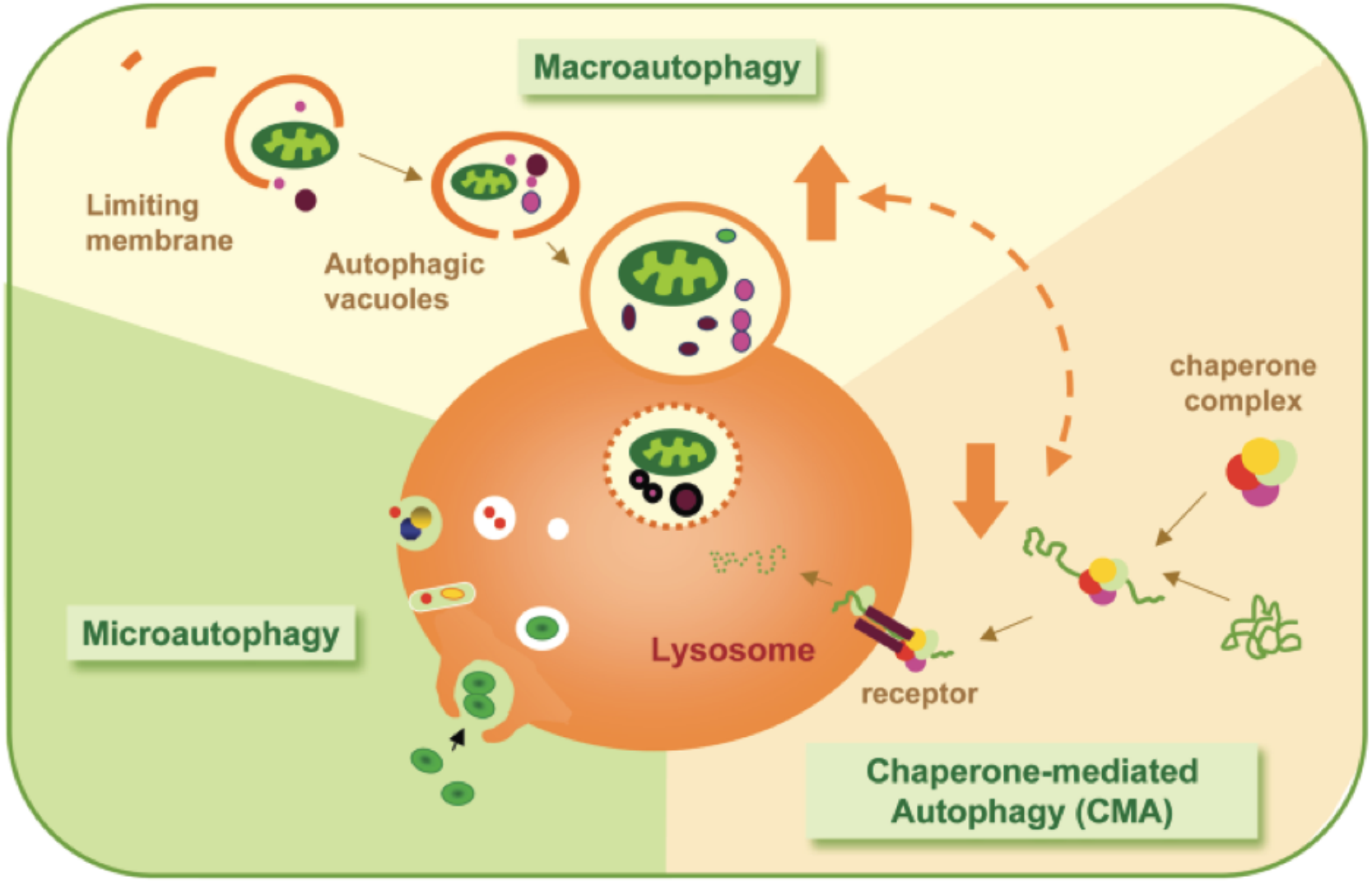
Autophagy

"Eat one's self"

Lysosomes take up, digest, and recycle damaged molecules to amino acids and fatty acids



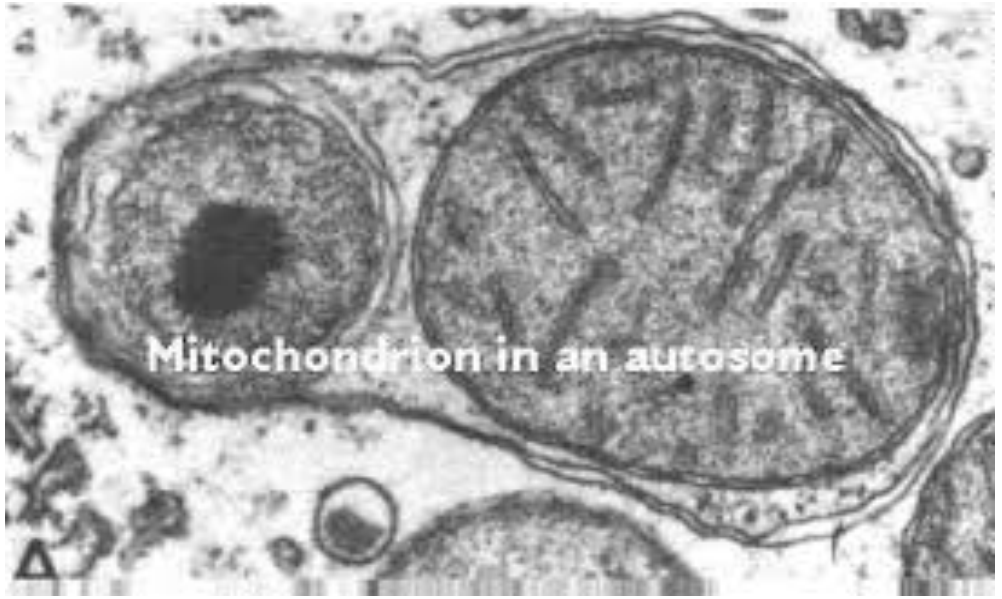
Autophagy clears several types of damage



Massey, Cell Cycle 2012; 5:1292-1296

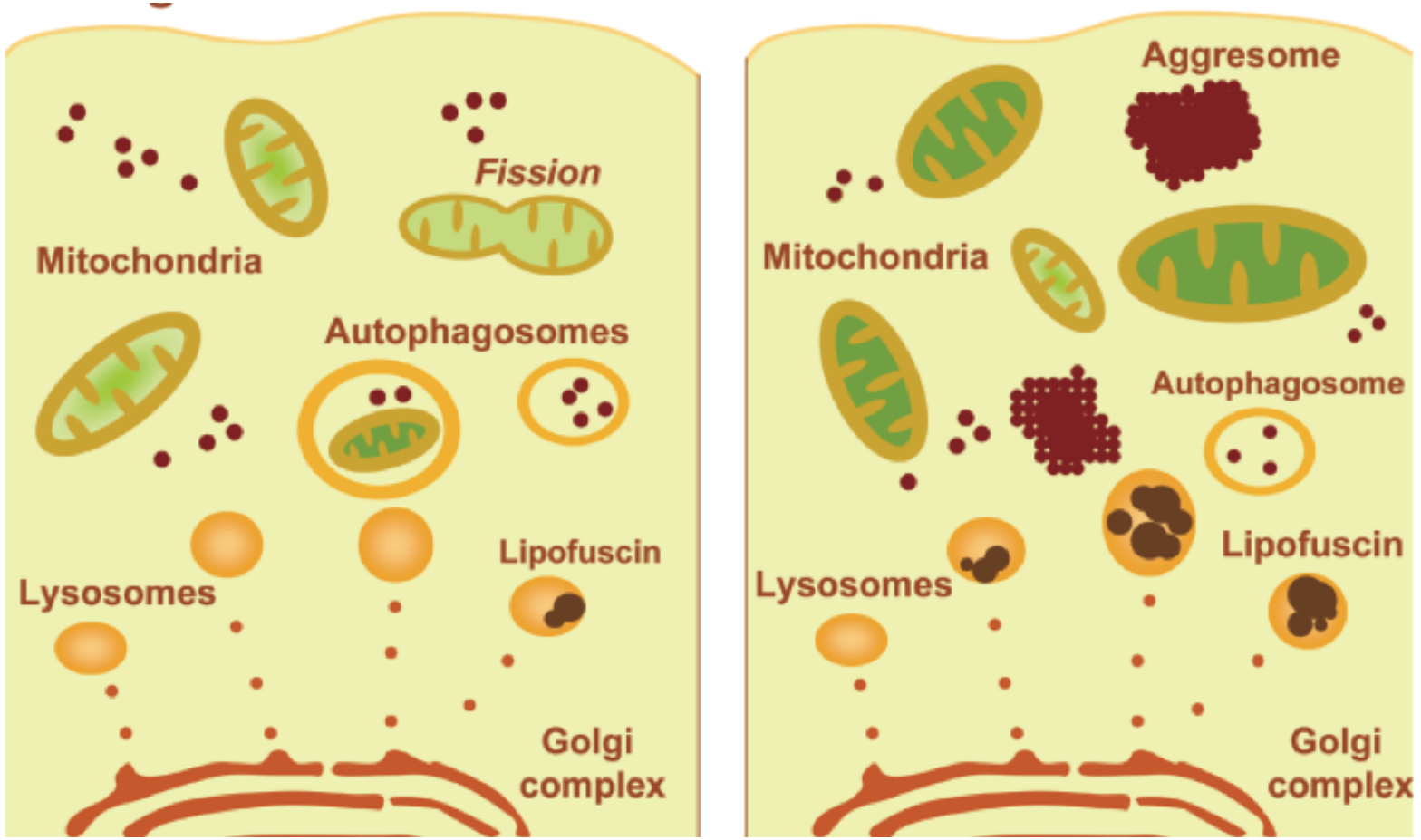
Mitophagy

- Lysosomes take up and recycle old and damaged mitochondria



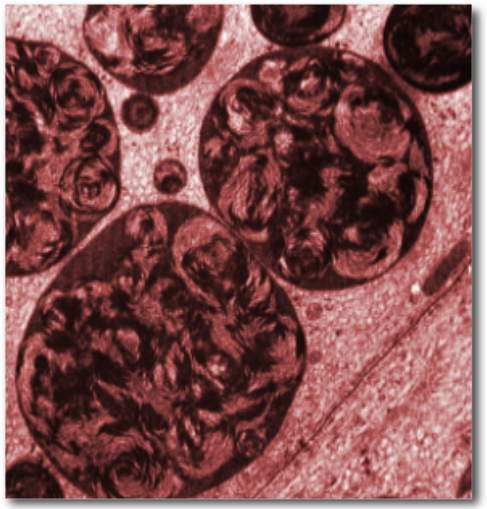
Autophagy decreases with aging

Damaged proteins, lipids accumulate



Autophagy fails with aging

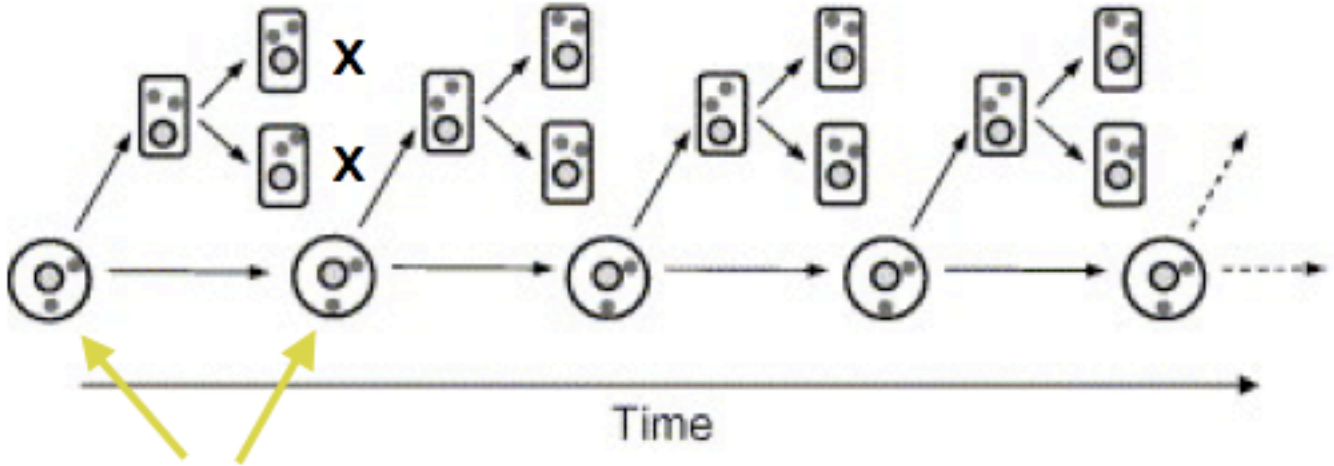
- Lysosomes fill with lipid-protein-metal garbage that cannot be digested
- This and damage to lysosomal enzymes and membranes further decreases autophagy…
- → Lysosomal constipation, visible as lipofuscin ‘goo’



Replicating cells

Shorter lived cells

In tissues made of short lived cells, old & damaged cells are replaced from ‘stem cells’



Replaced from progenitor cells (stem cells)

Examples:
Blood cells
Bone cells
Intestinal lining cells
Hair follicles

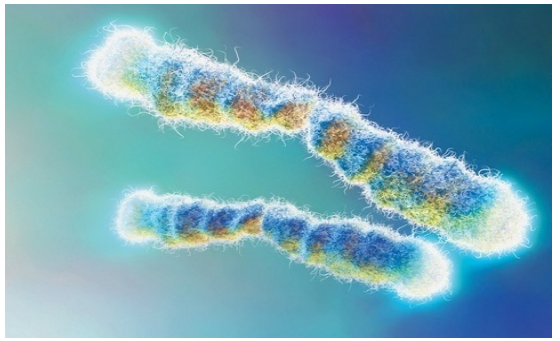
Alexi Terman, et al. Mol Aspects Med 2006;471

Capacity to replicate decreases with aging

- Stem cells become less efficient
- Replication reaches a limit – about 30 doublings
  - “Hayflick” phenomenon
- With aging, there are fewer and less efficient stem cells to reproduce and replace old and damaged cells
  - For examples, aging leads to decreased wound healing or replacement of muscle tissue after injury

Telomere *theory* of aging stem cells

- Progenitors (MSC and satellite cells) can divide only about 30 times
- Telomeres shorten with each cell division
- Reaching a critical length, cells stop replicating and become senescent
- A popular concept with by conflicting supportive evidence

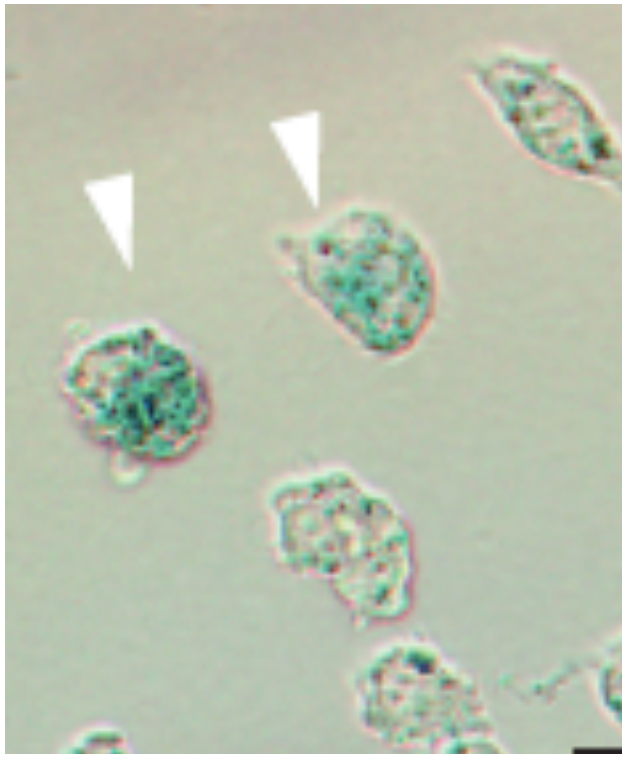


Caps on ends of chromosomes

Cellular senescence

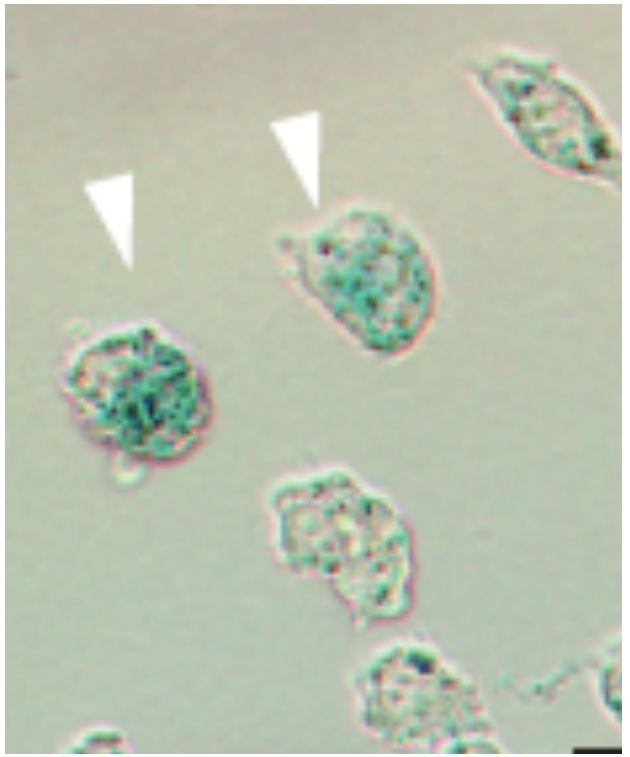
Senescent cells

- When cells lose the ability to divide
- Many persist and produce more inflammatory cytokines
  - Called “Senescence Associated Secretory Phenotype” (SASP)
  - Includes markers of inflammation, eg IL-6
  - SASP impairs function of other cells



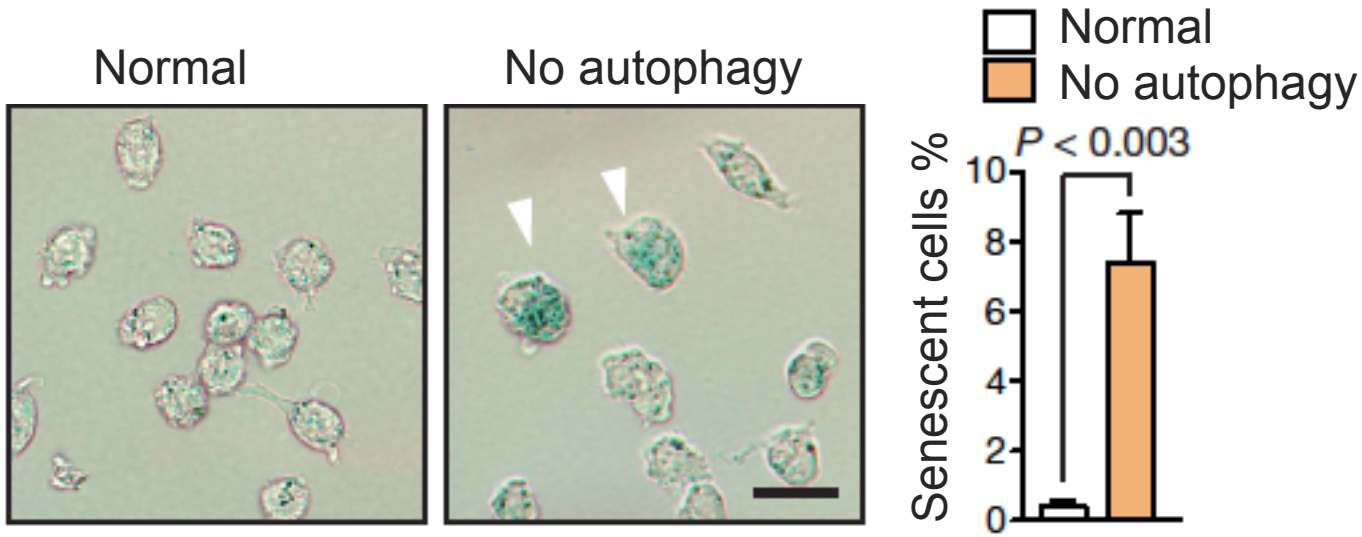
Senescent cells

- Senescent cells accumulate with aging in many tissues
  - Up to about 3% of cells
  - Most of the adverse effects are due to SASP
- Probably contributes to many aging-related diseases



These processes are linked

- Blocking autophagy caused senescence in muscle satellite cells



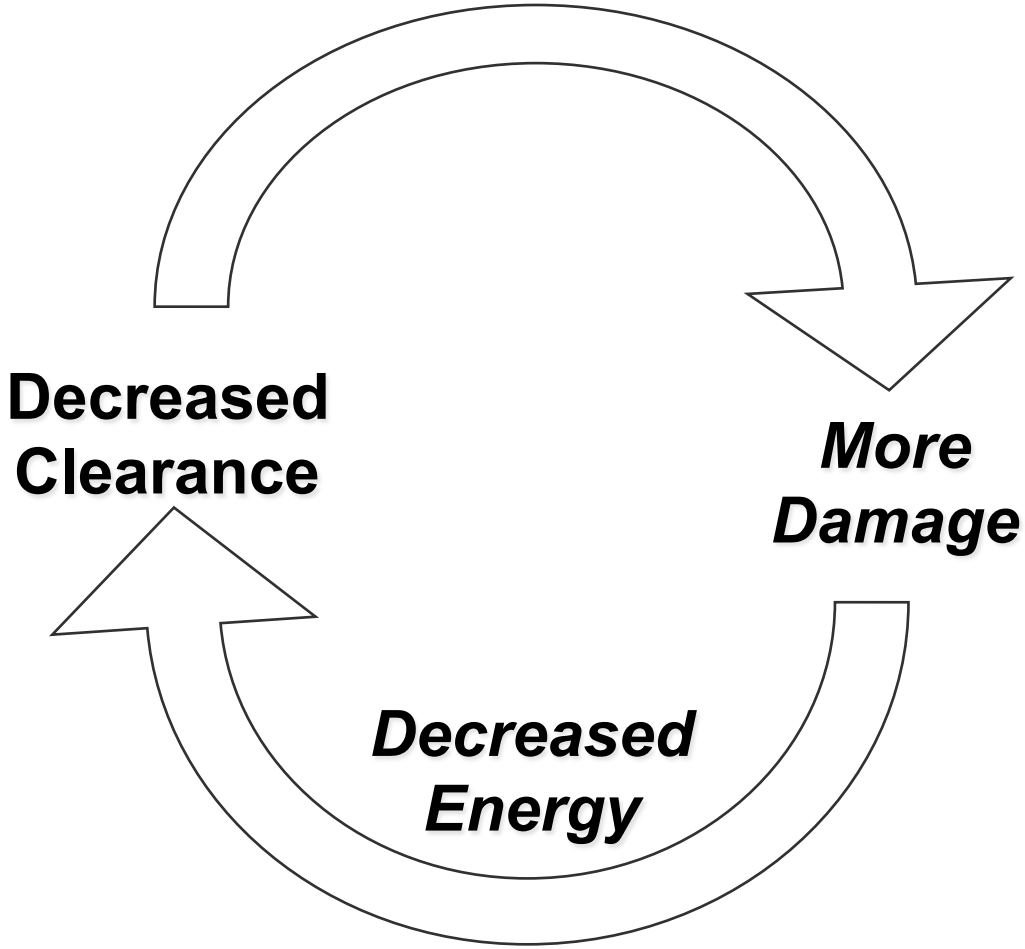
García-Prat, Nature 2016;529:37

Summary

- Energy: its production necessarily causes damage
- Damage results from other processes, too
- Damage is cleared by
  - Replacing the cell

  Or,
  - Clearing the damage inside the cell
- Aging is due in large part to a very small then increasing imbalance between damage and clearance of damage
- Cell senesence is one consequence of the imbalance

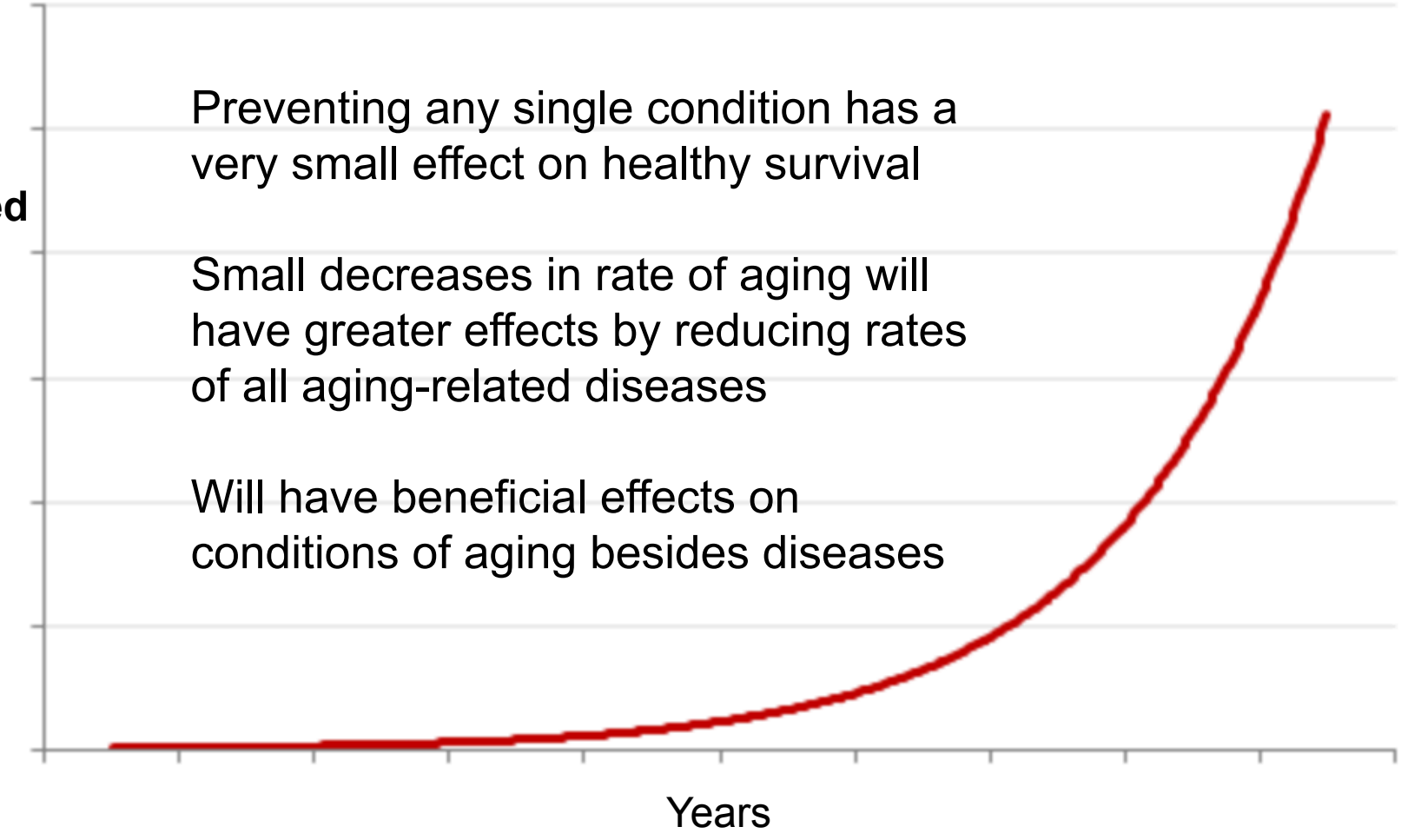
Death spiral of cellular aging



Positive feedback cycles lead to exponential rates of failure*

Implications of this model for preventing disease and prolonging healthy life

Risk of aging-related Conditions:
Death
Dementia
Disability
Stroke
M.I.
Hip fracture
etc.



Immortality is impossible

- Some damage accumulates that cannot be cleared
- Cellular processes necessarily become less efficient and prone to error
- The capacity to generate energy necessarily declines with time
- Exponential failure might be delayed but not avoided
- Can the 125 year limit be extended?

Questions

”Treatments” that work

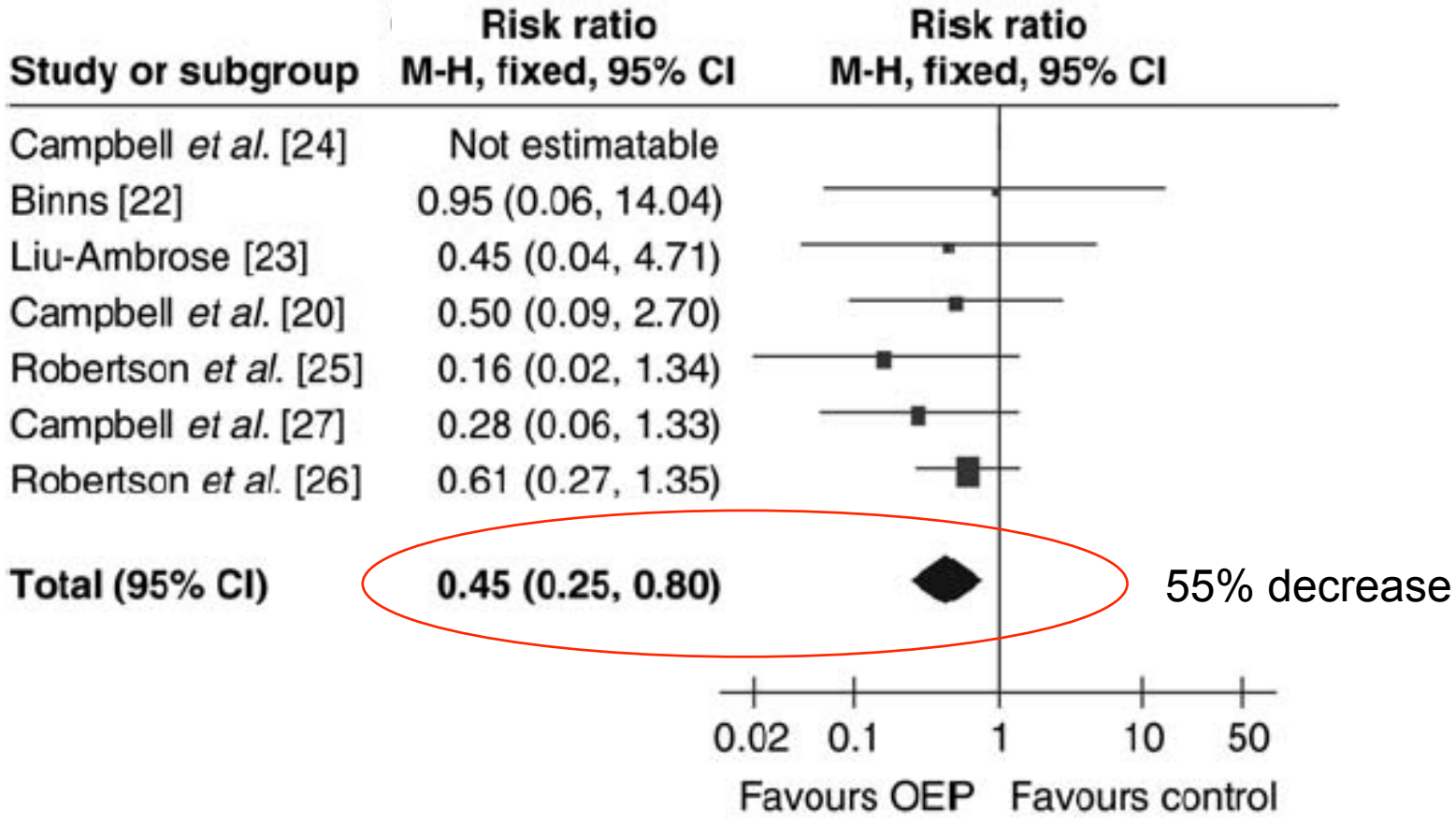
- Caloric restriction
- Exercise

Exercise

- Particularly aerobic exercise increases autophagy and mitochondrial biogenesis

Exercise reduces mortality in older adults meta-analysis of randomized trials

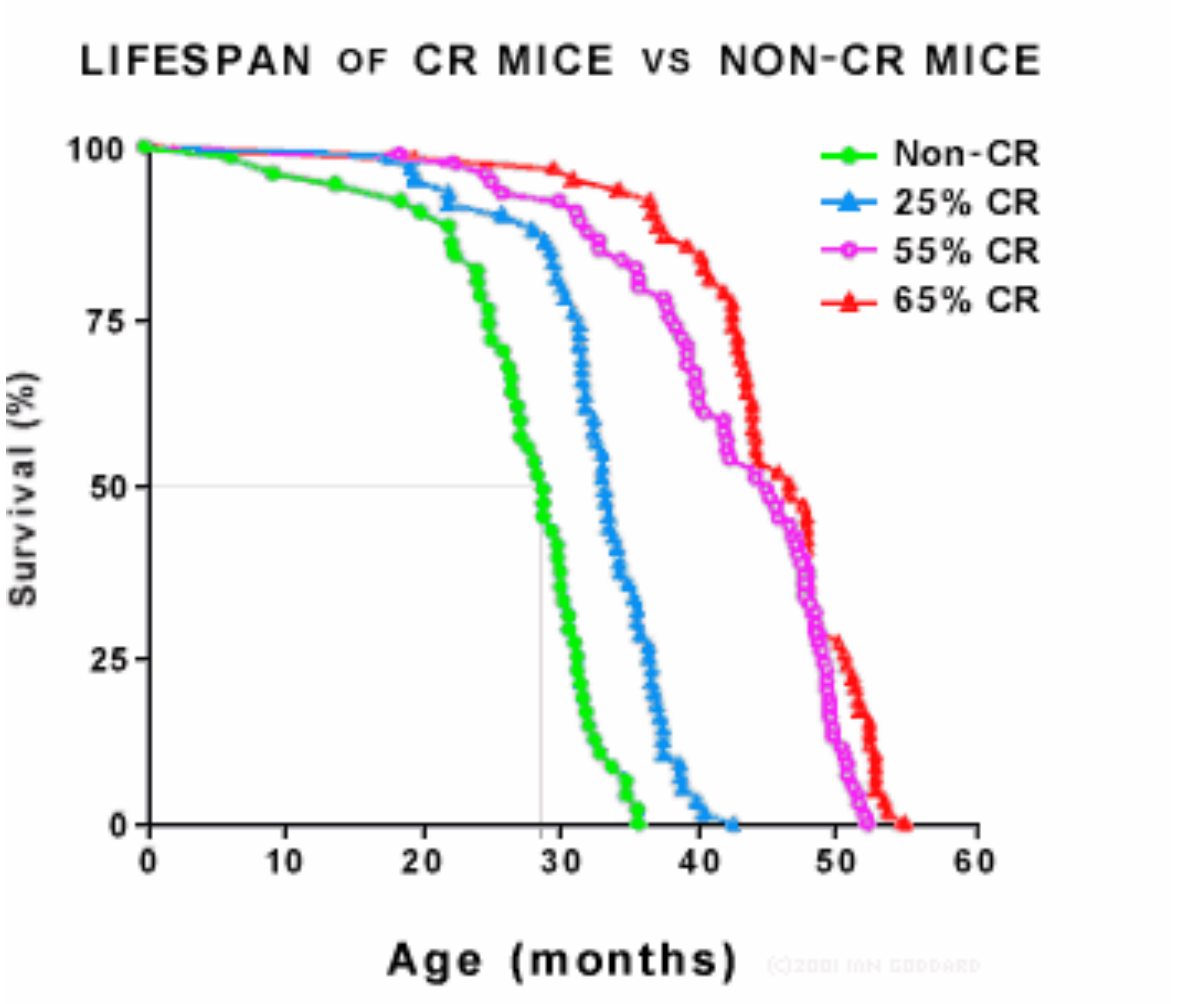
‘Otago’ program: resistance and balance exercise, and walking 3 times/



Calorie restriction

- Decreases oxidative damage
- Stimulates mitochondrial biogensis
- Increases autophagy
- Prolongs lifespan of worms, flies, & mice

Calorie restriction (CR) prolongs the lifespan of mice



Calorie restriction slows aging in monkeys

Human study, CALARIE, found physiologic benefits of 10-15% restriction

2 trials found increased vs. no change in *overall* survival from all causes

Anderson, Toxicol Pathol 2009;37:47

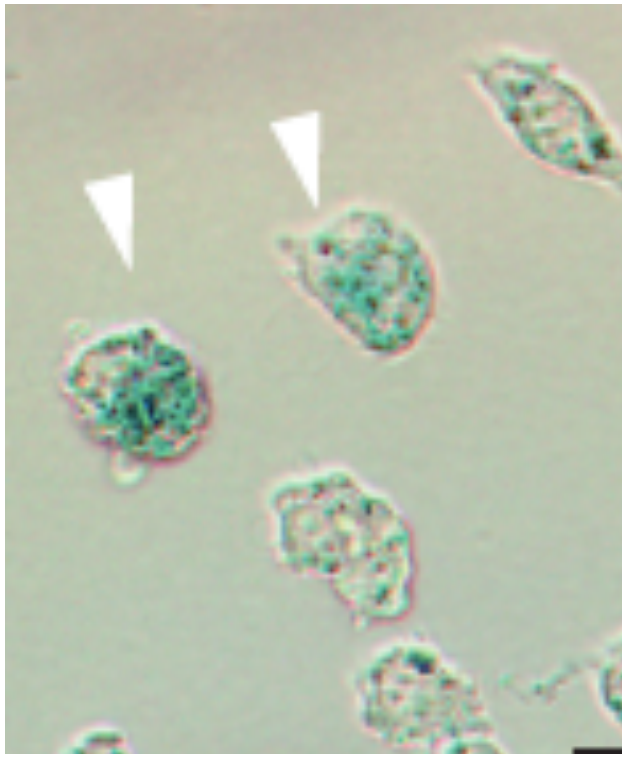
Some current dietary practices

- Occasional caloric restriction
- Short periods of intake
- Very low sugar diets
- Based on experiments in mice

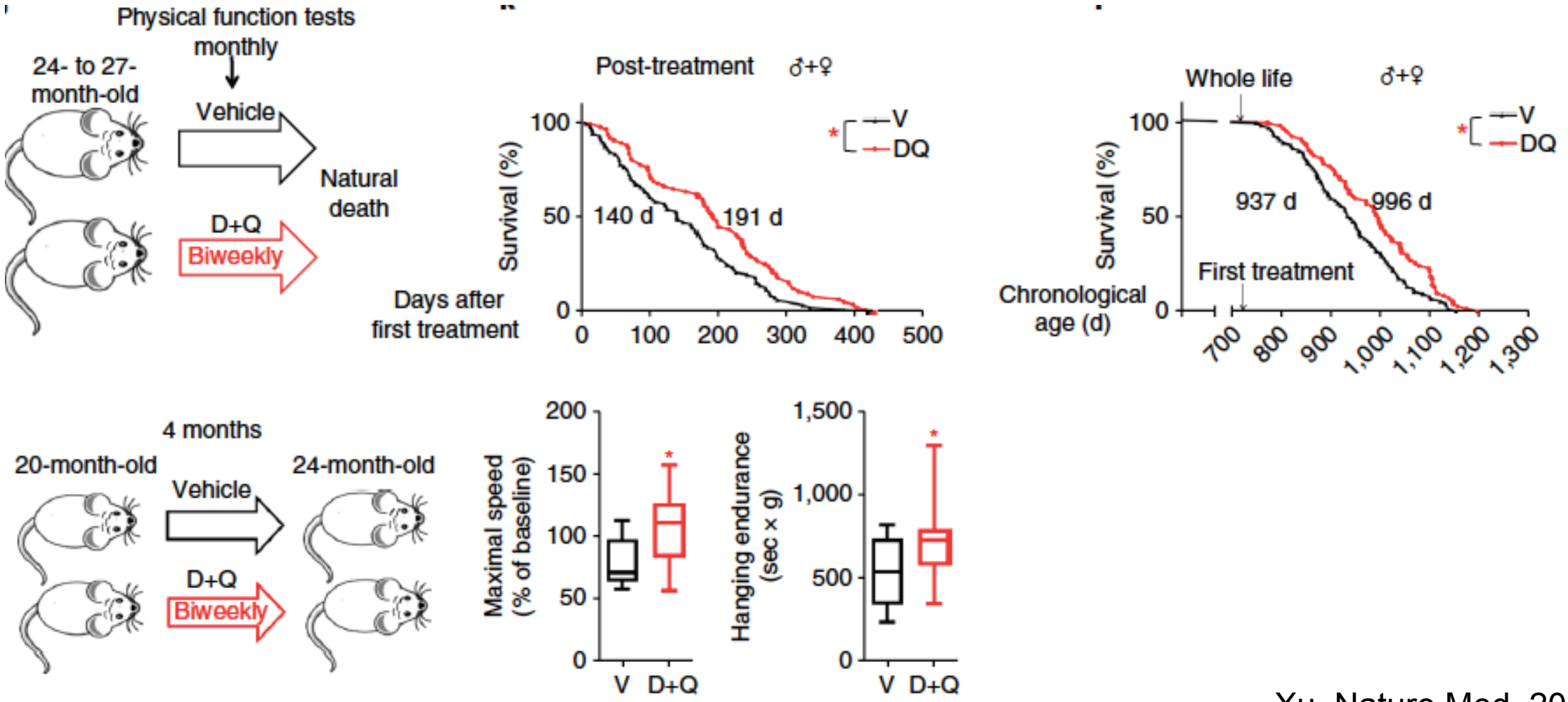
Senolytics

Senescent cells - review

- Cells lose the ability to divide
- They produce inflammatory cytokines
  - Called “Senescence Associated Secretory Phenotype” (SASP)
- Senescent cells accumulate with aging in many tissues
  - Probably contributes to many aging-related diseases



Senolytic treatment prolonged survival and improved function in older mice



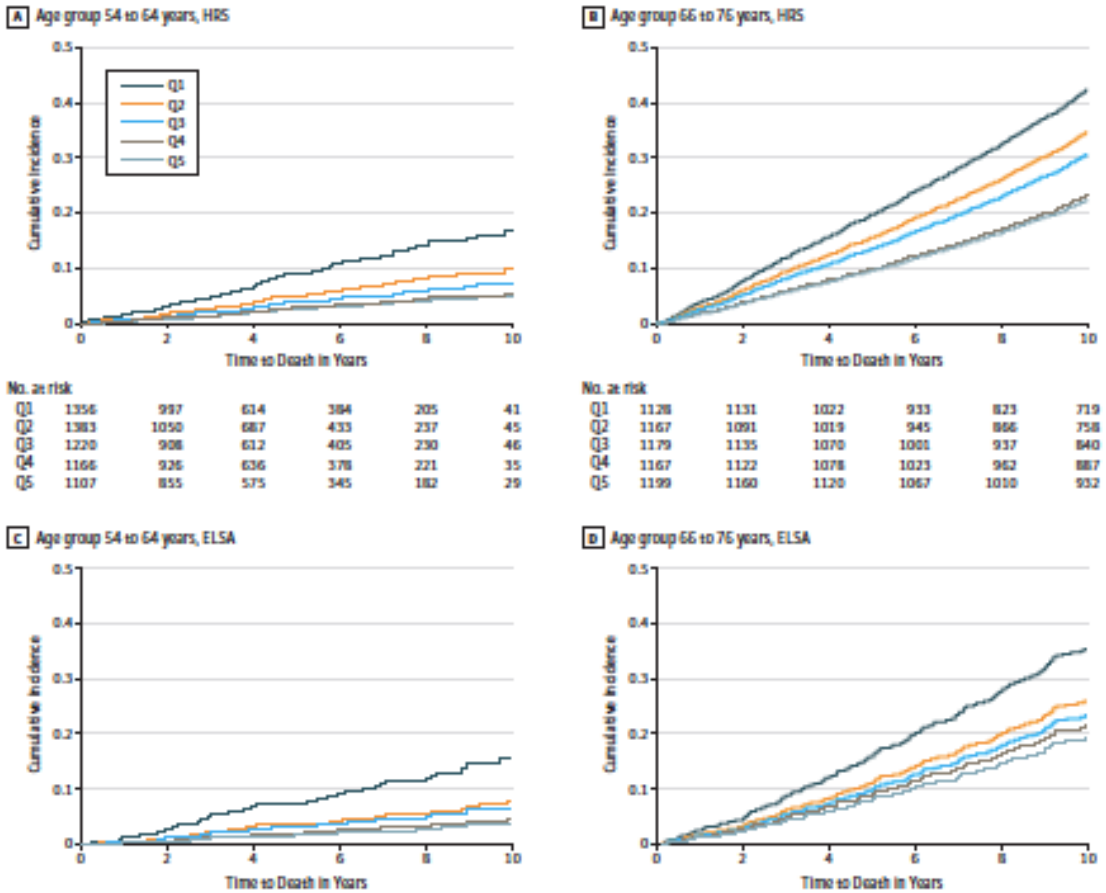
Xu, Nature Med, 2018

Senolytic treatment is unique

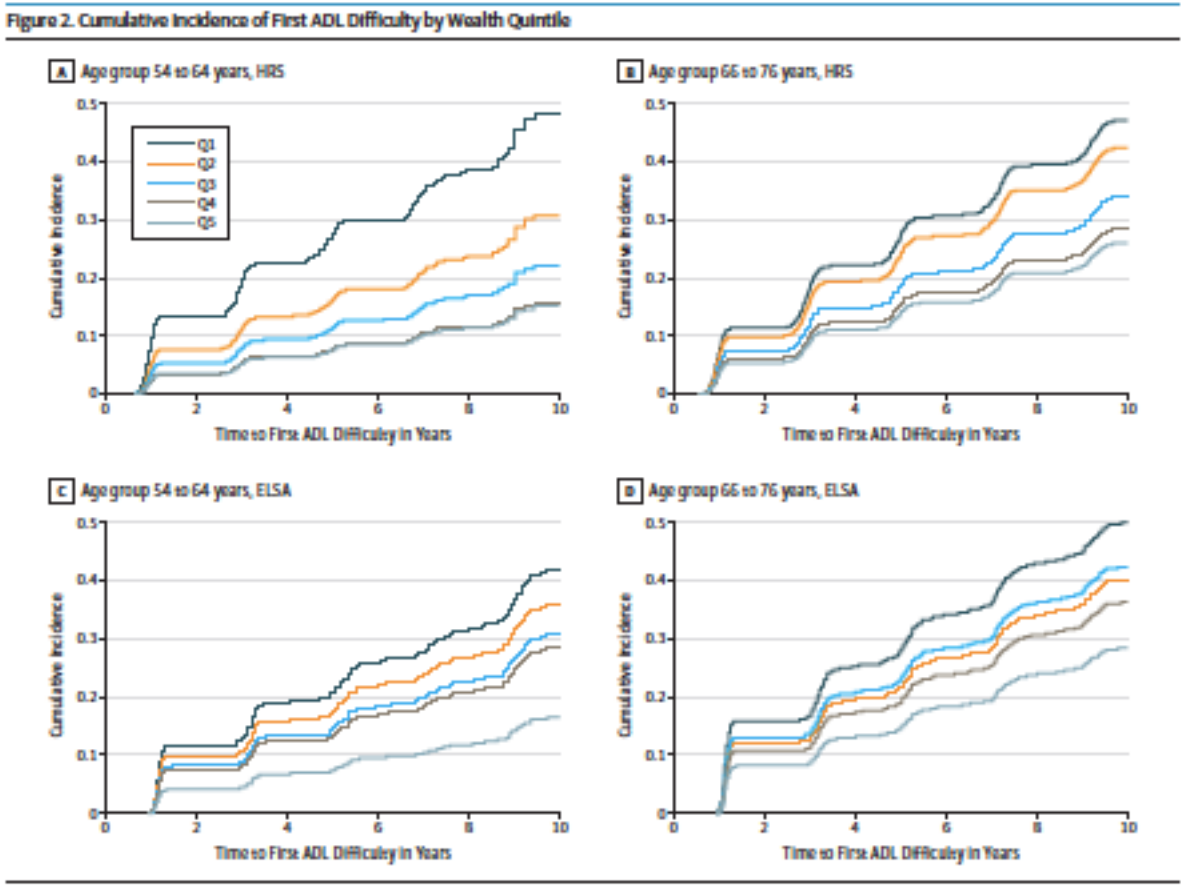
- Started late in life when senescent cells have accumulated
  - Does not need chronic use at periods of low risk
- Given intermittently for short periods
  - Will this be safer?
- Some effective agents are nutriceuticals
  - Fesitin and quercitin
- Numerous clinical trials are underway

An important cause of aging

A major determinant of mortality



A major determinant of disability



Do social circumstances influence survival and disability by biological mechanisms

- Wealth, income and education are very strong determinants of mortality, disability, and many age-related conditions
- Almost no research about the biological differences between rich and poor
- A good research opportunity for a young epidemiologist

Summary

- The effects of biological aging on disease, disability, and death is characterized by exponential failure
- The cellular biology of these aging conditions requires interactions between fundamental processes
  - Rate of damage exceeds clearance
  - Decreased generation of energy for all biological processes
- Exercise and (probably) ‘caloric restriction’ slow aging
- Senolytics offer a paradigm to ’treat aging'