Chapter 5- Genetics of Aging and Longevity

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Recommended reading:
How we age, Colleen Murphy (2023).
Age later : Nir Barzilai

Aging and genetics/12 bar blues

Aging and genetics they go hand in hand x2
Were doing this course to try to understand understand
How aging and genetics they go hand in hand
We'll learn from Yeast,
No That magical beast
That aging and genetics they go hand in hand

Some people live for a hundred years x2
They smoke cigars and they drink their beers
And yet they're healthy for hundred years
How can they smoke
And still not choke?
Cause aging and genetics - they go hand in hand!

Today we reach a highlight of the course in terms of the molecular understanding of aging. We will use the awesome power of yeast genetics to pinpoint molecular drivers of aging in yeast cells. We will then leap across the tree of life to the species of primary interest- us humans. We will use data from healthy centenarians, from rare diseases of rapid aging and from twin studies to find a grand convergence and see what might be the molecular drivers of aging in us. Add menopause GWAS.

Then, in upcoming lectures we will talk about how this information can be used to design (future) interventions to expand healthspan and perhaps eventually extend maximal humanlifespan.

Budding yeast is a good model for cellular aging

As a model organism yeast has great advantages. It is a single cell with rapid growth and powerful tools

to read the dna and write in the dna. it derives from the same ancient Lineage of cells as humans- a eukaryote with a nucleus and many other shared features with our cells (unlike the prokaryote *E. coli* that has no nucleus).

Yeast (budding yeast S cerevisiae) reproduces by making a bud. The bud splits off and becomes
a fresh new cell, whereas the mother cell keeps a scar where the bud split off, as well as most of the damage.

the lifespan of a cell is the number of times a mother cell can bud before stopping and dying - known as replicative aging . The survival curve is in units of generations. A typical lifespan is 20 generations. This means that in an exponentially growing population, old mothers are a tiny part of the population and most cells are 1-2 generations old.

The mother cell retains damage so that the bud can be fresh and undamaged. The buds' lifespan is independent of the mother's age, except for buds of very old mothers. This creates accumulation of damage over generations in the mother.

Keep in mind that mammalian stem cells push damage to the daughters. So yeast mothers are a type of
Model for the differentiated cells.

To find longevity genes, one deletes a gene from the genome or does some other genetic change and sees how the mean lifespan is affected. Longevity interventions increase median lifespan.
Counting buds- replicative aging- yields longevity genes that are remarkably relevant to longevity in mice, humans, worms and flies.

Other types of yeast aging studies do not count daughter cells, but instead starve the yeast and see how long it survives (death is determined by inability to make a colony on a fresh agar plate with food). But the genes that extend this ‘chronological aging’ lifespan are less relevant to longevity genes in mammals.

A genetic screen for mutants that affect both lifespan and steepness of The survival curve

To do a replicative aging survival curve is not easy- you need to watch the mother cell , remove the buds with a thin needle every couple of hours, and put the yeast in the fridge overnight when you get tired. Working with worms is actually easier…
Mcormick Kaeberlin , Kennedy et al (2015) et al did a heroic screen of 4600+ gene deletion strains. For the first two years Kennedy and Kaeberlin, newly minted assistant professor and a postdoc, did hours of assays every day. They then recruited a group of researchers to help. It took ten years but they did it! They published a dataset of median lifespans for thousands of mutants, with over 2 million dissected buds . The screen identified several hundred longevity

genes. They kindly sent us the full lifespan dataset so we could evaluate the survival curve steepness.

A statistical note- since most survival curves in the dataset have only a few tens of cells there is sampling noise. A good estimator for steepness is the mean lifespan divided by the std of the lifespans. It seems less noisy than using the IQR. error bars are evaluated by bootstrap-sampling the lifetimes with returns.

Naveh Raz found a surprising feature of yeast survival curves. Pooling together all wild type controls from this genomic study gives data on nearly 10,000 cells. Fitting the sr model shows that surprisingly $\beta = 0$ - in other words, yeast has no trucks! The houses plus noise make damage unchecked by trucks, namely $\frac{dx}{dt} = \eta t + noise$ so that on average $x = 1/2\,\eta\, t^2$ that reaches Xc at about the median lifespan of 25 generations. The width of the distribution is due to noise, whose amplitude is not huge- noise alone would take 140 generations to reach Xc on average, which is about 6 times longer than the median lifespan.
This resulting hazard curve is quite different from a pure Gompertz law. Although there is an initial exponential-like rise of hazard, the hazard slows down its climb at about 10 generations and turns into a power law- rising with t^2 as predicted by the SR model with no trucks.

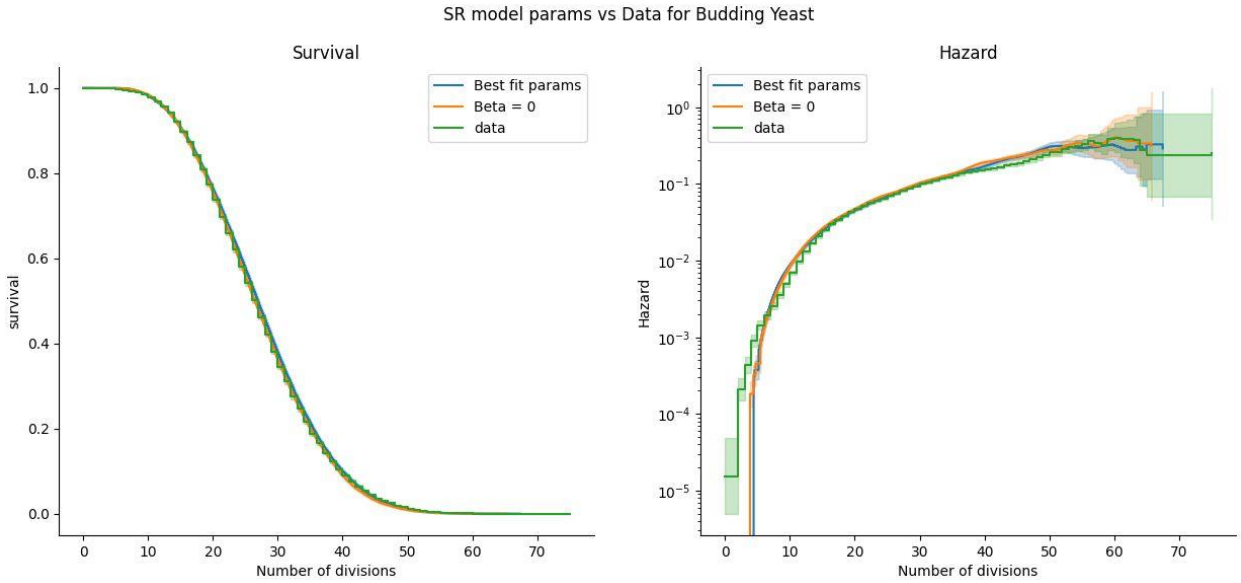


Fig 9.1 yeast replicative aging survival and hazard curves, along with the SR model best fit. Data form
Kaeberlin et al WT control experiments at 30C, based on 6000 cells. Assuming no trucks- $\beta = 0$ - provides a good fit to the data. Unpublished work of Naveh Raz.

Most importantly for us now, the SR model provides a map to understand what the gene deletions do.
The survival curve shape can tell us whether each mutant affects houses η, threshold Xc or noise. This provides an opportunity to dissect the biochemical nature of the damage x in yeast.

To do so we take each mutant's survival curve, evaluate its median lifespan and steepness, and plot the mutant on a longevity- steepness plot (normalized to wild type). Mutations that affect houses (η) should be in quadrants 2 and 4 (short lived and steep, long lived and shallow). Those that affect Xc or noise in quadrants 1 and 3 (long lived and steep, short lived and shallow).

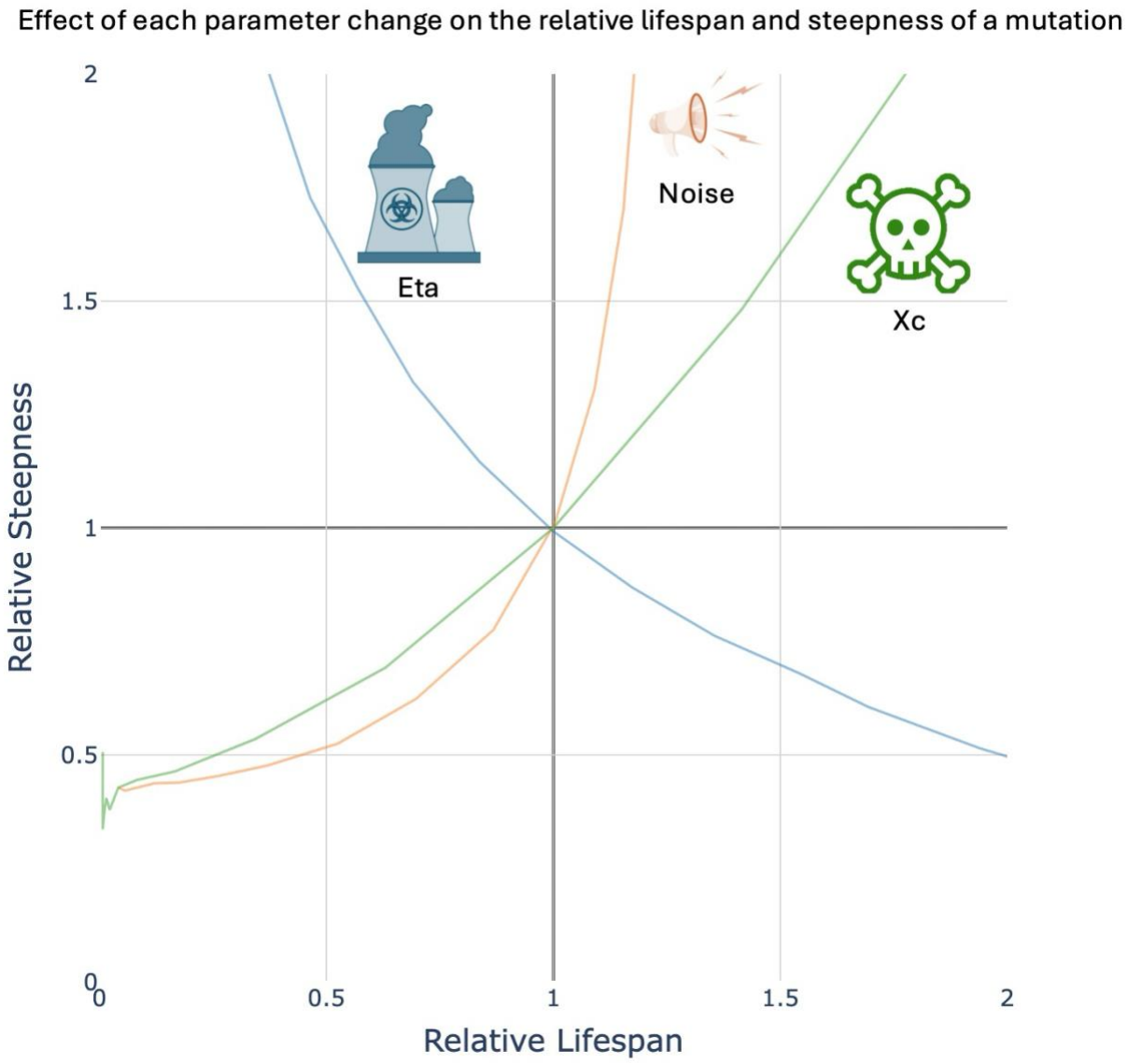


Fig 9.2 The SR model can help decipher whether a yeast intervention changes parameters for houses (η) threshold (Xc) or noise (ϵ). The curves show the effect of changing each parameter on lifespan and steepness of the survival curve for yeast.

One way to think about it is that deletions that affect houses affect the accumulation rate of age-related damage. The larger η cells die earlier, and also have less time for noise to act and thus less randomness - a steeper the curve-namely cells die at more similar times.

The deletions that affect threshold cause age-independent damage of the same kind as made by houses, let's call it x_1 . They thus add to the rising SR damage x(t) a constant $x_{1\,st}$, and therefore effectively reduce the threshold to $Xc - x_{1\,st}$. Similarly, deletions that reduce age-independent damage raise Xc.

Both types of deletions provide clues to the identity of the driving damage X. We are after this holy grail, no less.

Geneticist Dan Jarosz told me that genetic screens take you on a trip- the genes you find can be anything, leading you to pathways you never thought you'd work on. It's unbiased discovery. Some screens end up with incoherent genes you can't interpret easily. Others end up with a coherent set with pathway functions that tell a story.

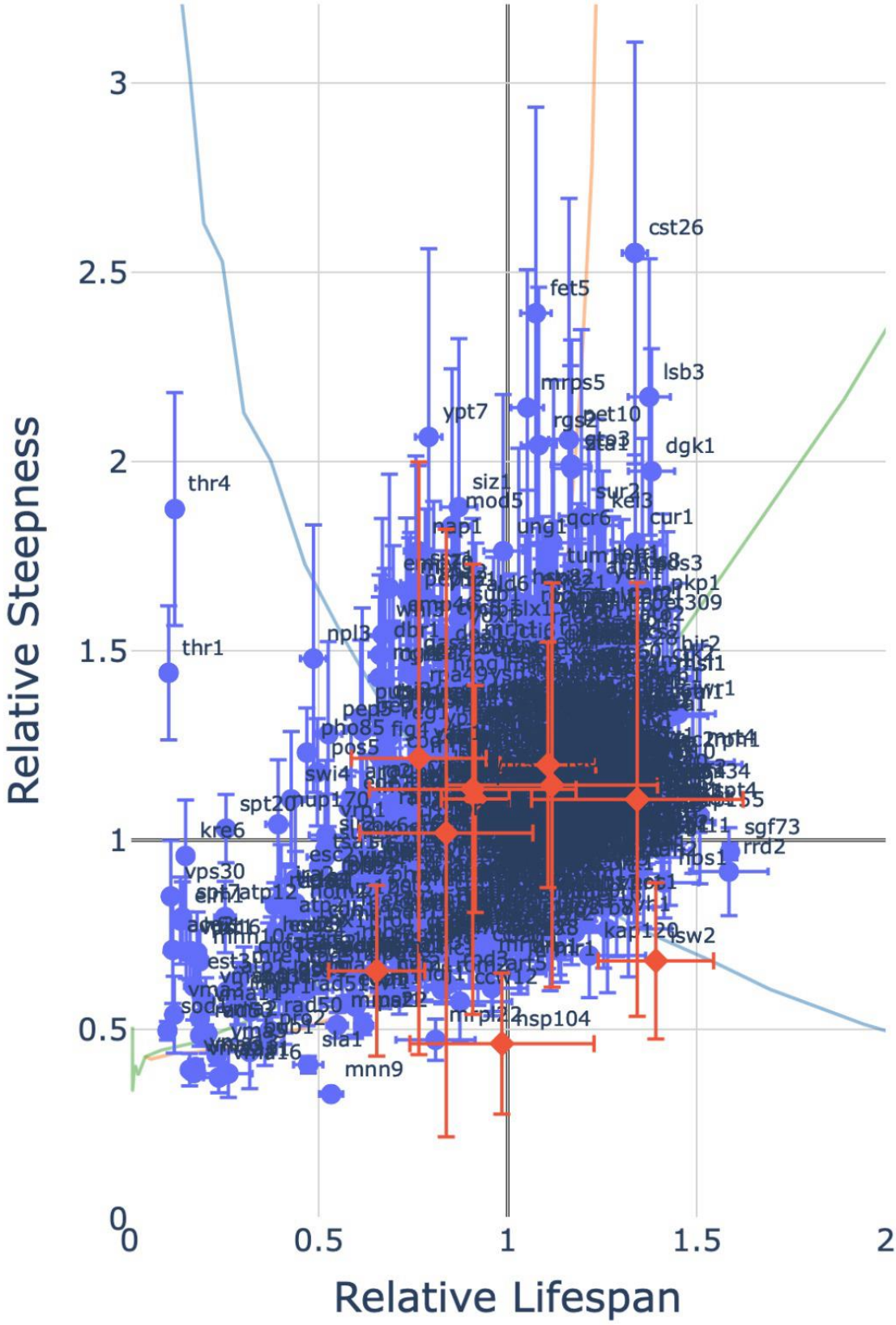

Relative Steepness
Relative Lifespan
0
0.5
1
1.5
2
2.5
3
cst26
fet5
lsb3
mrps5
ypt7
pet10
rgs2
dgk1
thr4
siz1
mod5
sur2
cur1
thr1
spt20
kre6
sgf73
rrd2
vps30
hsp104
mnn9
sla1

Fig 9.3 steepness and mean lifespan of 1500 yeast deletion (blue) and overexpression (red) strains in the Kaeberlein dataset (). Steepness and lifespan were normalized to wild type. Error bars are large since most strains had only a few tens of cells on their survival curves. Unpublished, Tomer Levy and Avi Mayo.

Two pathways of aging - mitochondrial and chromatin

This genetic screen provides a coherent set of pathways!

The majority of gene deletions don't affect lifespan or steepness significantly. Those that do can be interpreted in two modes of dying.

Mitochondrial mode:

The lysosome (vacuole) is a space in the cell that is acidic and helps degrade proteins, store amino acids and do other housekeeping functions. The vacuole in mother cells has reduced acidity with age - this is one of the first age related events and acidity drops linearly with age (Fig 9.x), Acidity drops due to the retention of a plasma membrane proton pump *pma1* in mother cell and not in the daughter. This pump removes protons from the cell, and the vacuole exports protons to the cytoplasm to keep the cytoplasm pH at a normal level-
The vacuole is always there to help the cell keep Homeostasis. There is also a lack of assembly of a vacuole proton pump. All of the many vacuoles pump components are Xc.
The daughter vacuole has high acidity, helped by not having *pma1* on its membranes initially, so the daughter is reset to age zero, (and so does the vacuole in spores after meiosis- an analogue of the fertilized egg in mammals).
Reduced vacuole acidity causes some amino acids normally stored in the vacuole to increase in the cytoplasm. The most toxic is Cysteine that causes iron shortage disrupting iron sulfur clusters and thus disrupting mitochondrial function- eg complex 1 and complex 2 of the ETC) (https://doi.org/10.1016/j.bbamcr.2019.02.011). The mitochondria's major ATP engine- the electron transfer chain- goes off kilter.

The mutants in the screen pinpoint which part of the mitochondrial electron transfer chain produces the age-related ros damage (complex 2, coq are η, and the next steps of the ETC- complex 3, cytochrome c and complex 4 - are Xc). This identifies the driving damage as superoxide released into the mitochondrial Matrix by complexes 1 and 2. For example, deletion of genes for enzymes essential for synthesizing coenzyme Q (CoQ) are η genes - they lack CoQ that takes electrons from complexes 1 and 2 and passes them to complex 3 . CoQ is a hydrophobic membrane antioxidant crucial for the electron transfer chain. This leads to impaired electron transfer chain, low atp and high ROS.

Indeed superoxide dismutase genes *sod1* and *sod2* that handle ros are Xc deletions. Due to the high ROS levels the mitochondria accumulate unfolded protein complexes and protein aggregates which are degraded by mitochondrial protease, also an Xc deletion.

A tangent about mitochondria in human exercise: anaerobic exercise makes the mitochondria hypoxic- low on oxygen- they are the sink of oxygen since they use it to burn fat and sugar. Low oxygen reduces production of ros- i mean the at low level ros that are not harmful- instead the low level ros is a biological signal sensed by the cell (by the HIF hypoxia inducible transcription factor) to upregulate antioxidants and enzymes that counter ros. It also enhances production of new mitochondria and recycling of damaged ones. Low level ROS also signals in the lungs and to sensors in the arteries that oxygen is low.

When you exercise , you can make more ATP and better resist oxidative stress and ROS as you age. That's one reason exercise is good for your mitochondria. The deadly ROS in the yeast mechanism is at much higher levels and causes damage to proteins, membranes and DNA, killing the cell.

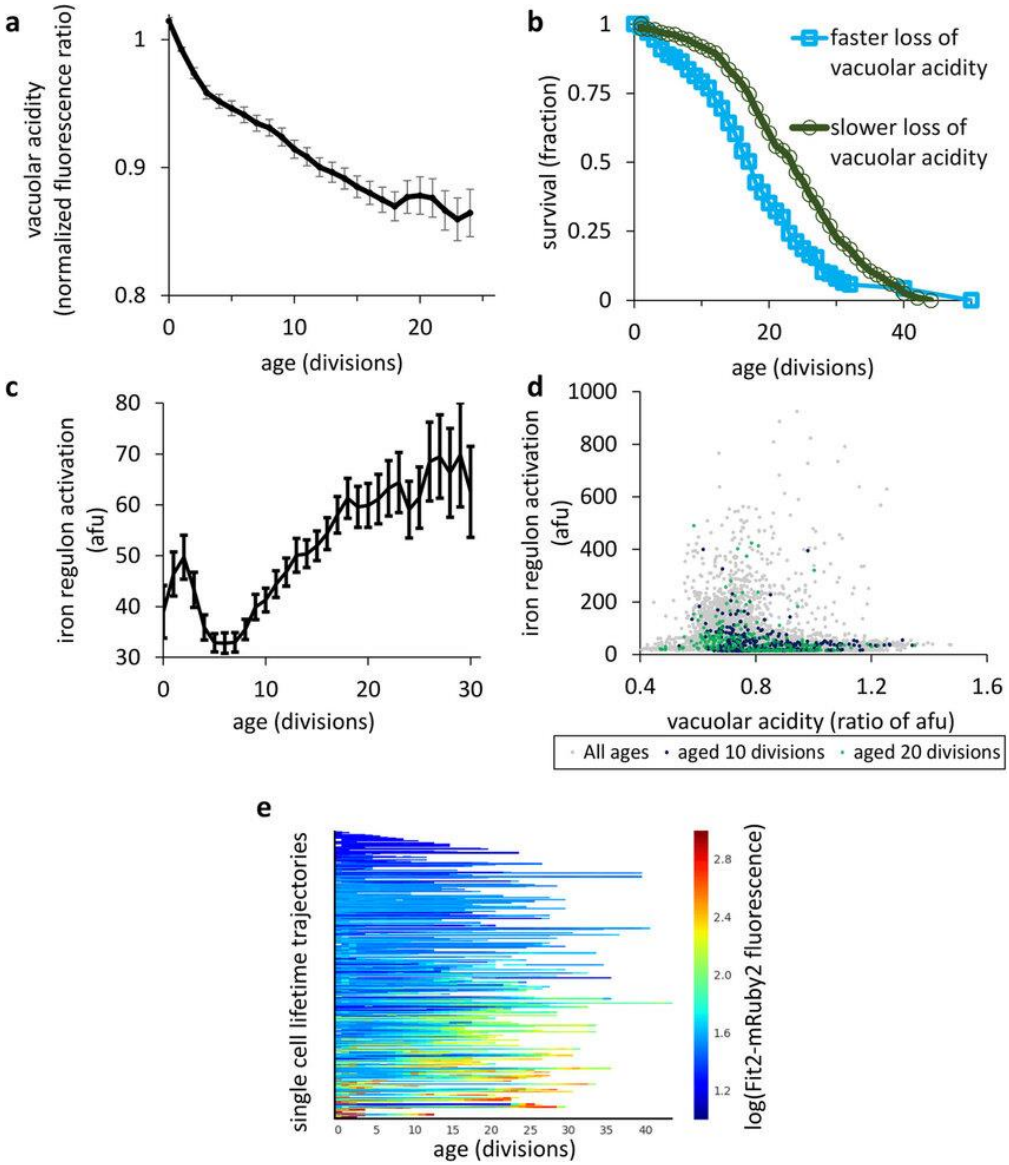


Fig 9.4 vacuole acidity drops continuously with age in yeast. Half of the cells have iron deficiency caused by this deacidification. source Wasko2020

https://doi.org/10.1007/s11357-020-00159-3

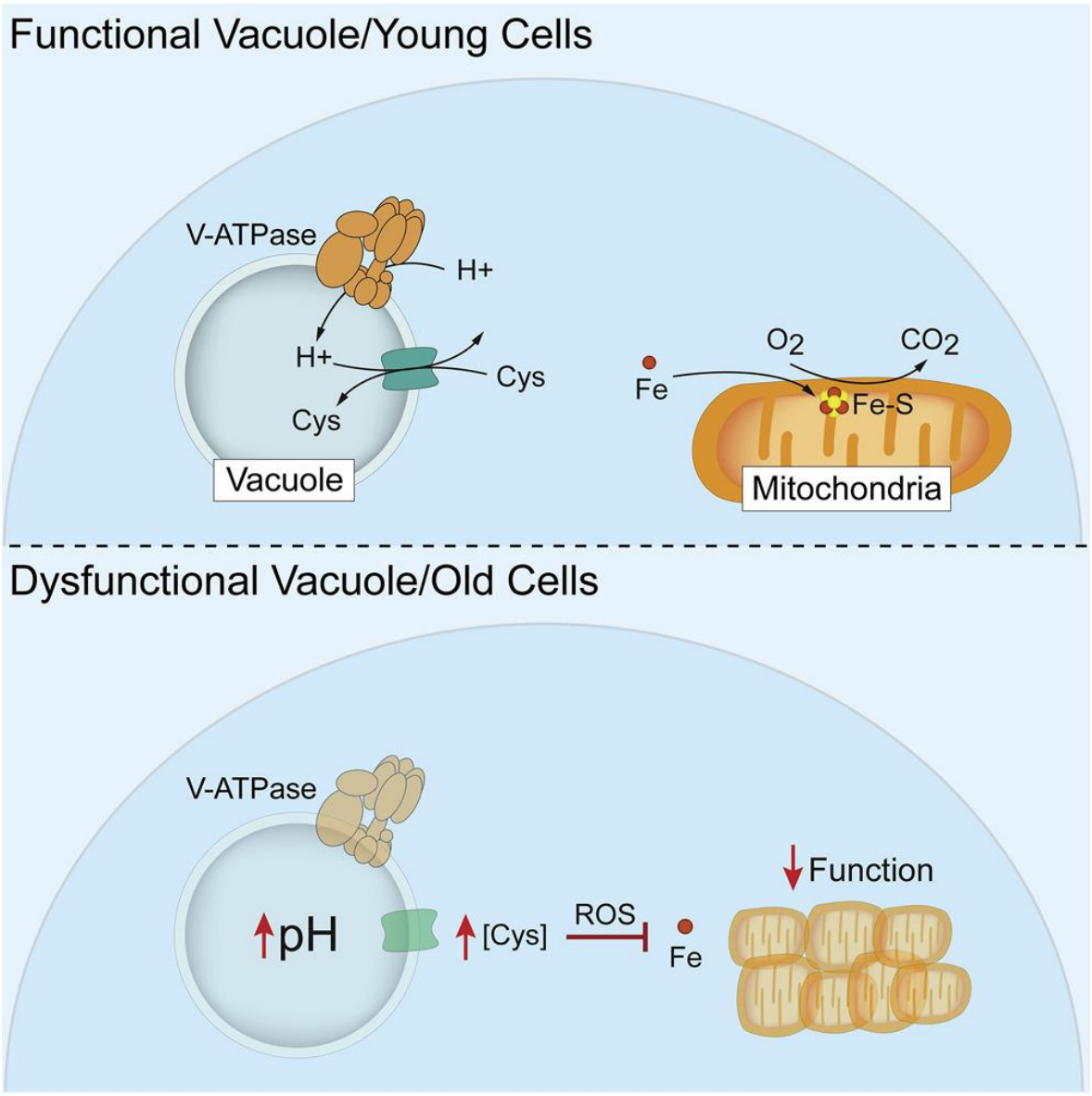


Fig 9.5 When the vacuole is fresh and acidic, it stores amino acids including cysteine. When it becomes deacidified (high pH) with age, cysteine is elevated in cytoplasm. Cysteine at high level is toxic, it inhibits iron and iron-sulfur clusters essential for the electron transfer chain. This causes mitochondrial function to decline, with small fragmented mitochondria. Source:Hughes 2020 (doi: 10.1016/j.cell.2019.12.035.)

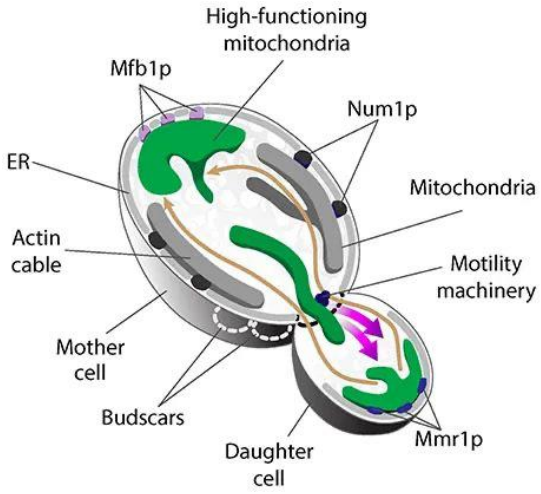


Fig 9.6 Good mitochondria are tethered to the mother and the daughter tips, other good mitochondria plow against the reverse flow (daughter to mother) current on actin filaments and only the good ones make it to the daughter, bad ones remain in the mother cell. Source https://www.frontiersin.org/journals/cell-and-developmental-biology/articles/10.3389/fcell.2017.00120/full

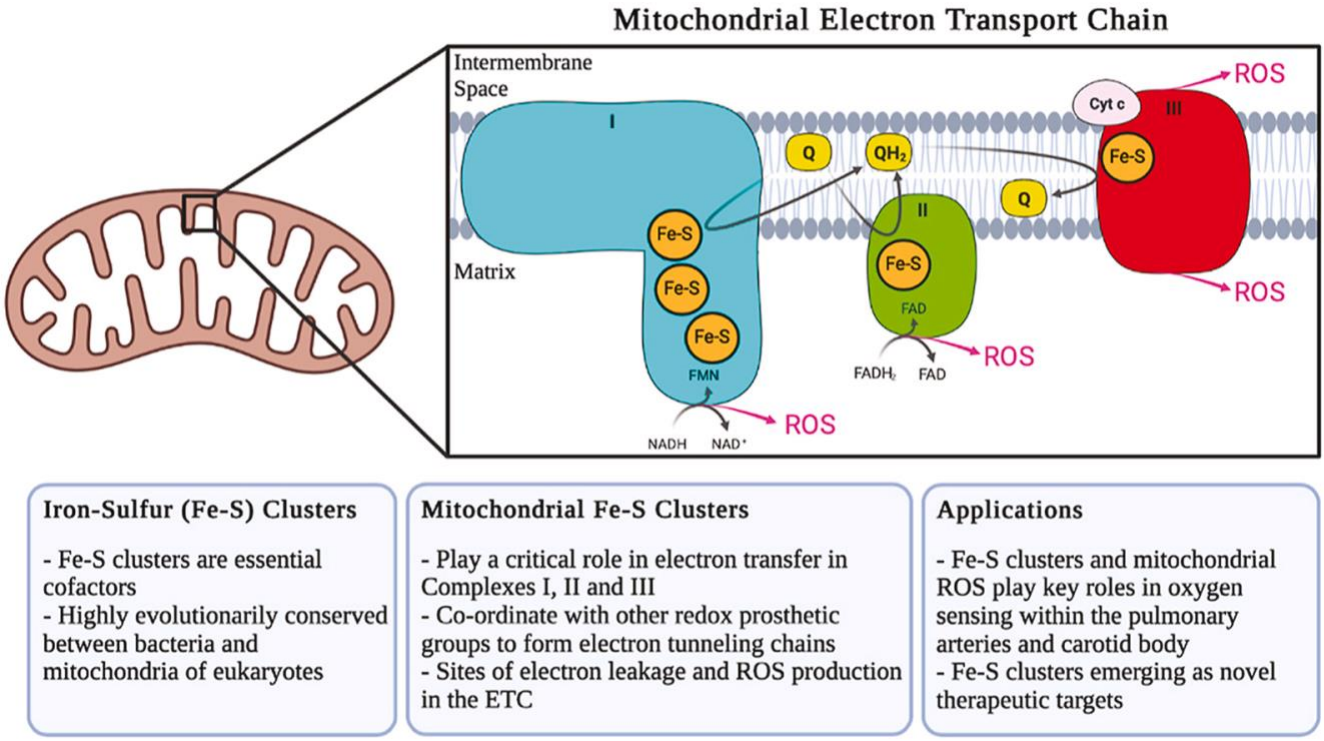


Fig 9.7 The first three complexes in the electron transfer chain depend on iron-sulfur clusters. Deleting complex 2 or Q increases eta, suggesting enhanced age-dependent superoxide leakage from complex 1 due to lowering availability of iron-sulfur clusters with age. Deleting complex 3, cytC or 4 causes age-independent superoxide production

from complexes 1 and 2 since Q has nowhere to donate the electrons, lowering Xc.
Source: https://www.sciencedirect.com/science/article/pii/S2213231721003244

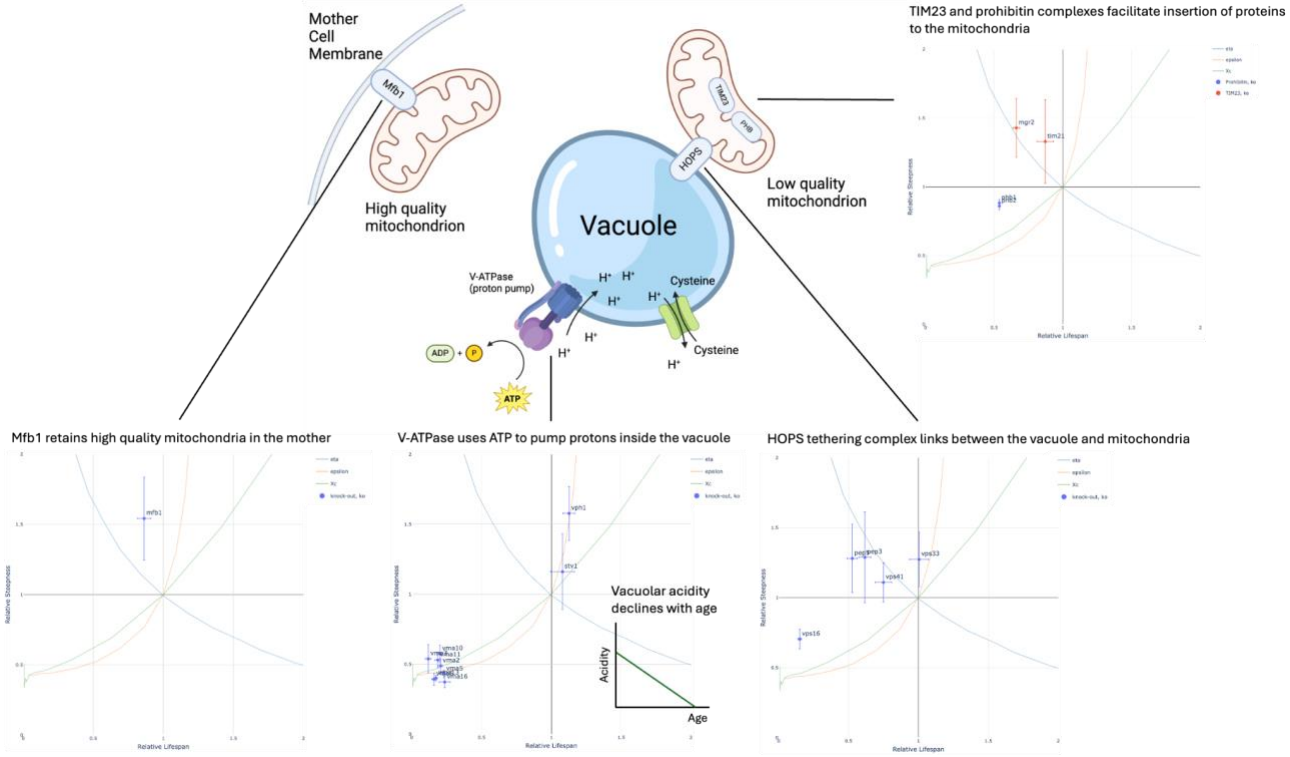


Fig 9.8 Vacuole deacidification and mitochondrial dysfunction rose with age in mother cells. Deletion of the vacuole proton pump causes constant age independent deacidification and is thus Xc. Deleting a tether of high quality mitochondria to the mother cell wall increases eta- more houses - indicating dysregulated mitochondria rise with age. Deleting genes that import proteins to the mitochondria also enhances η.

Fig 9.8a The

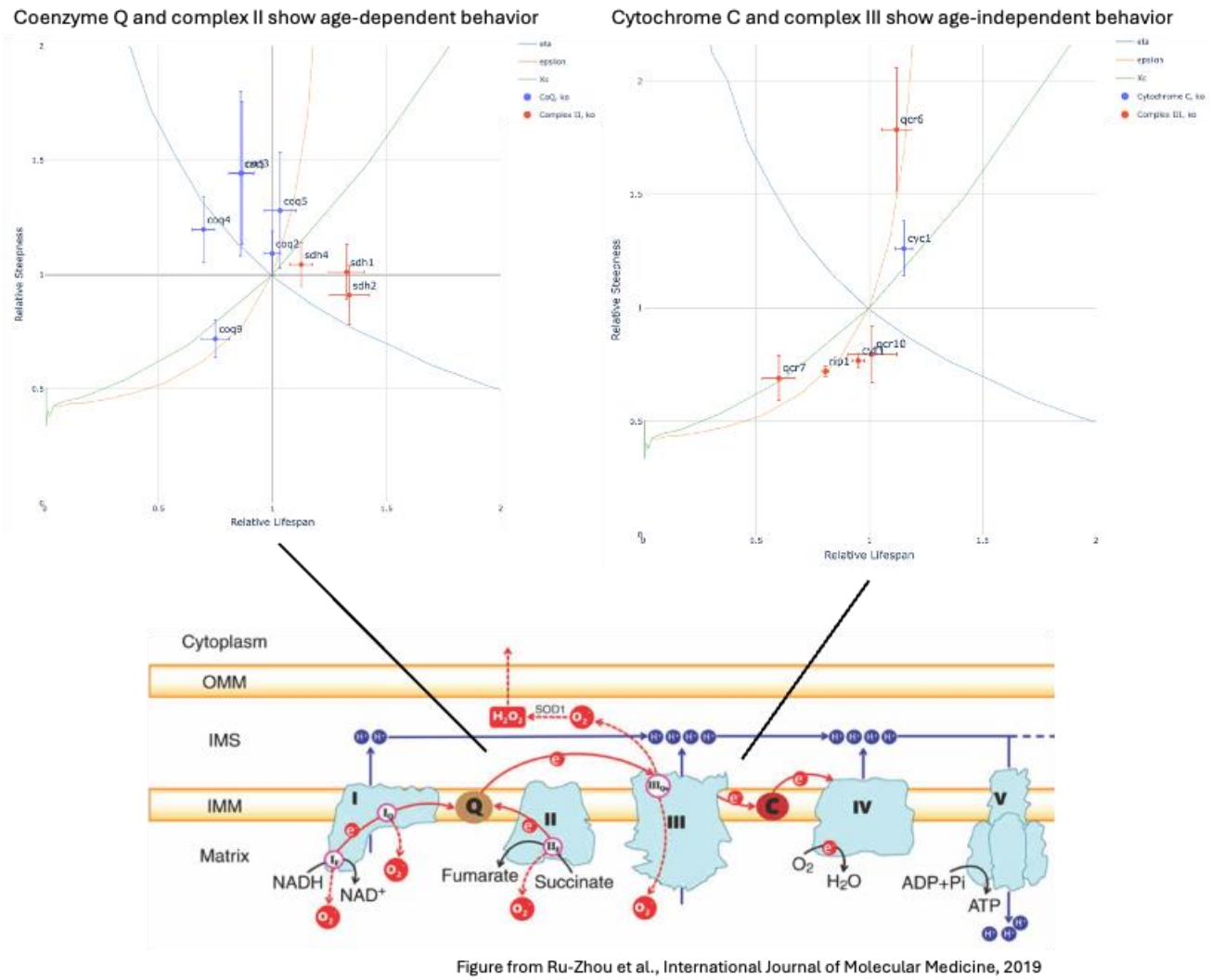


Figure from Ru-Zhou et al., International Journal of Molecular Medicine, 2019

Fig 9.9 The electron transfer chain in the mitochondrial membrane. Deletion of complex 2 decreases eta, suggesting that since it frees up Q to take electrons from complex 1, that superoxide (ROS) leaked into the mitochondrial matrix from complex 1 is a component of damage x. Deleting the many genes that synthesize CoQ raise eta, by enhancing the leakage from 1. Deleting complex 3 lowers Xc suggesting it creates an age independent leakage from the complexes before it, whereas deleting cytochrome C raises Xc.

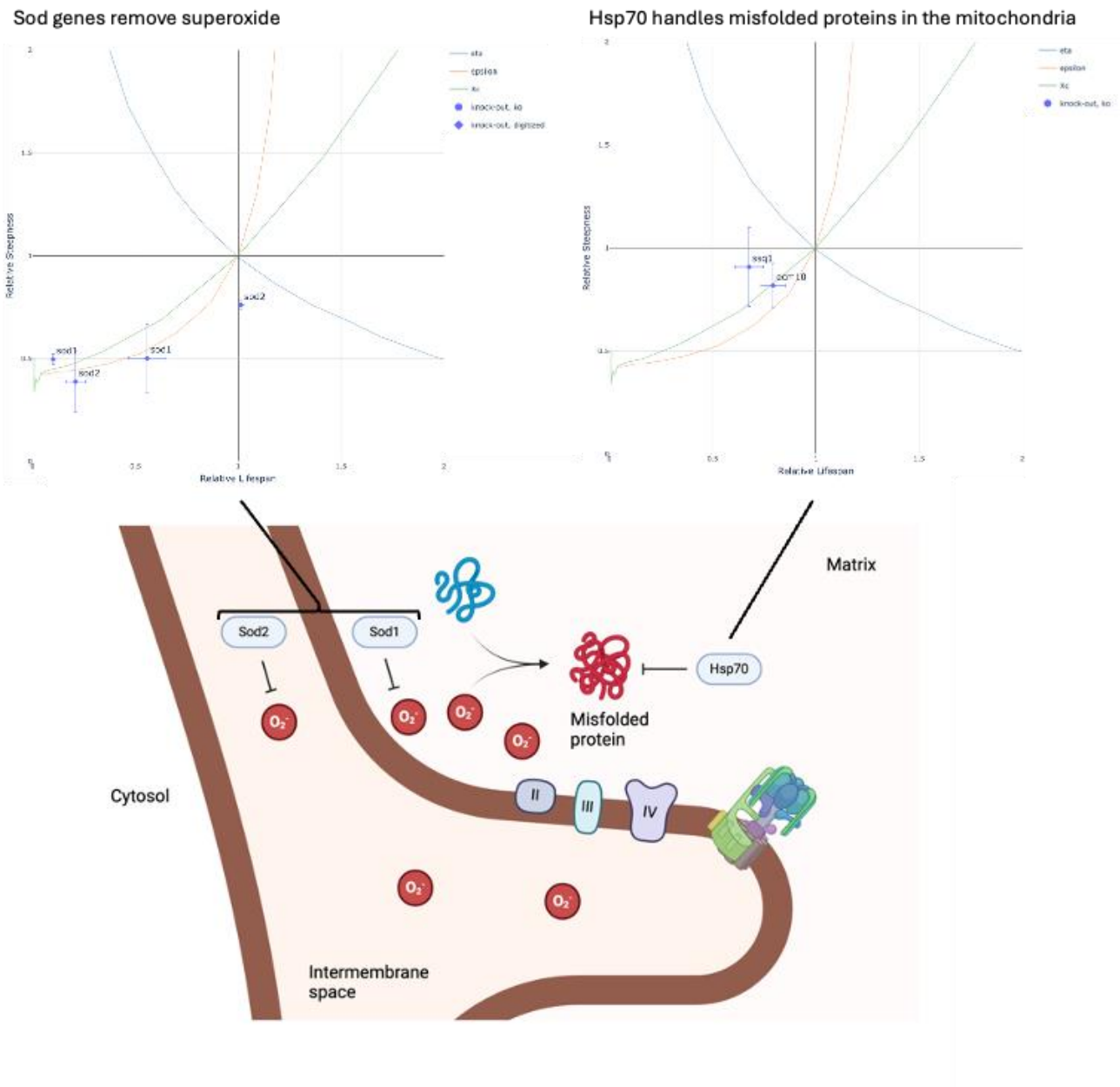


Fig 9.10 Superoxide (ROS) leaked to the mitochondrial matrix causes misfolded proteins that are cleared by protease hfp70, whose deletion lowers Xc by causing constant misfolding. The dismutases sod1 and sod2 reduce the superoxide, and their deletion causes constant ROS lowering Xc severely.

These mitochondria mode genes cease to affect lifespan when yeast is grown in conditions of caloric restriction (low glucose), exposing a second mode of aging-
a second layer in the onion of aging.

The chromatin pathway:

Note: in silencing the rDNA locution east causes large nucleoli and protein aggregates of ribosomes- we get ribosomal hits!

Here the η gene deletions point to modifications in two specific sites on histones. Histones are the protein complexes that DNA wraps around, and which determine whether chromatin is closed or open. The histones can be acetylated making them fall off the DNA opening the chromatin.

For example: acetylation of the lysine at position 16 in histone 4 makes the positive Lysine becomes neutral, and the histone more easily dissociates from the negatively charged DNA. The two histone acetylations picked up in the screen (both acetylation writers and erasers come up in the screen) are H4k16Ac, and H3k56ac, leading to opening of normally closed chromatin. The former acetylation rises with age in yeast.

Other η genes are the shelterin complex that protects the telomeres - suggesting that the acetylations are important in the telomere region.
The opening of (normally closed) telomere chromatin leads to aberrant transcription, in which mRNA erroneously binds to DNA - a formation called r-loops, as well as other structures like G4 quadruplexes that cause replication fork collisions. The collisions inflict telomeric double stranded DNA breaks (dbs)that are hard to repair, and cause telomere disruption. The screen picked up complexes that repair r loops and G4 quadruplexes including a helicase gene whose homologue in humans causes an accelerated aging disease when mutated - Werner syndrome discussed below. It also picked up dbs repair genes whose deletions are all Xc. The telomeric disruption and double stranded breaks set off Cell Cycle checkpoints to stop replicating.

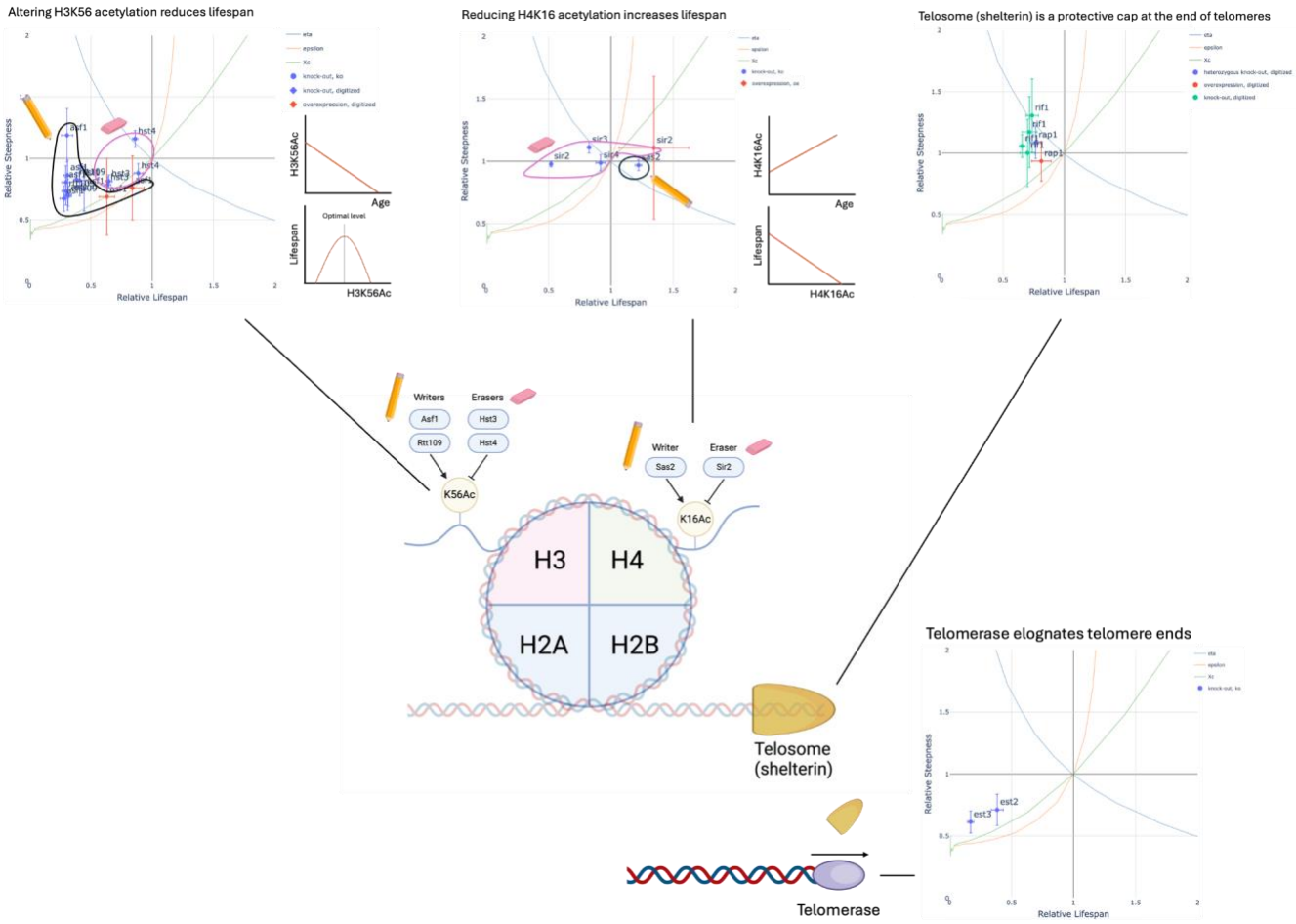


Fig 9.11 Histone acetylases and deacetylases (writers and erasers) of two histone sites contribute to eta - H3K16Ac and H4K56 Ac. this enhances the opening of chromatin. The telosome, called shelterin in mammals, increases eta upon deletion, suggesting that houses have to do with telomere instability. On this and coming graphs, ‘digitised’ means taken from the literature outside of the Mcormick et al dataset.

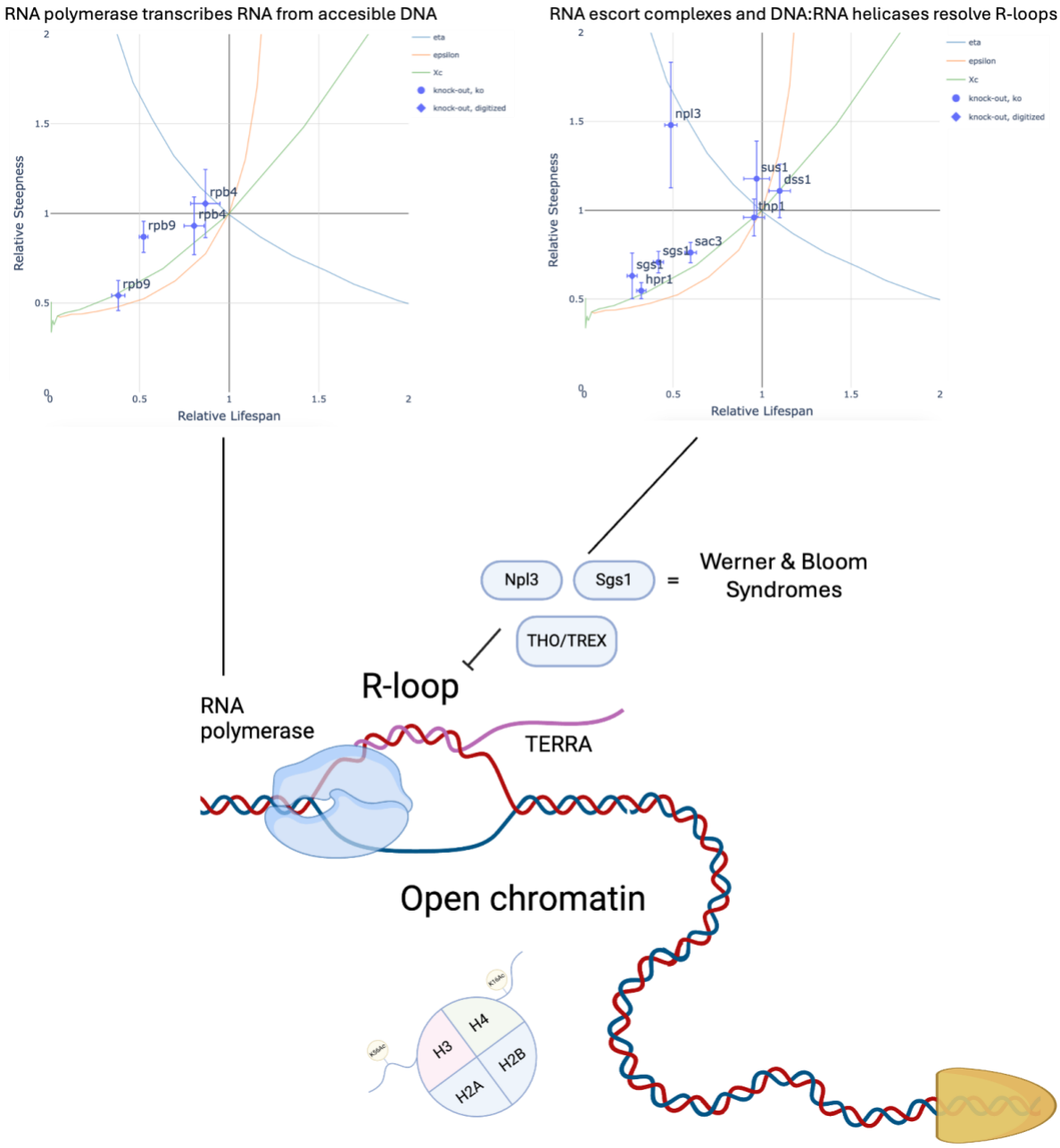


Fig 9.12 The opened chromatin is prone to uncalled for transcription. The mRNA can from an rloop by binding DNA

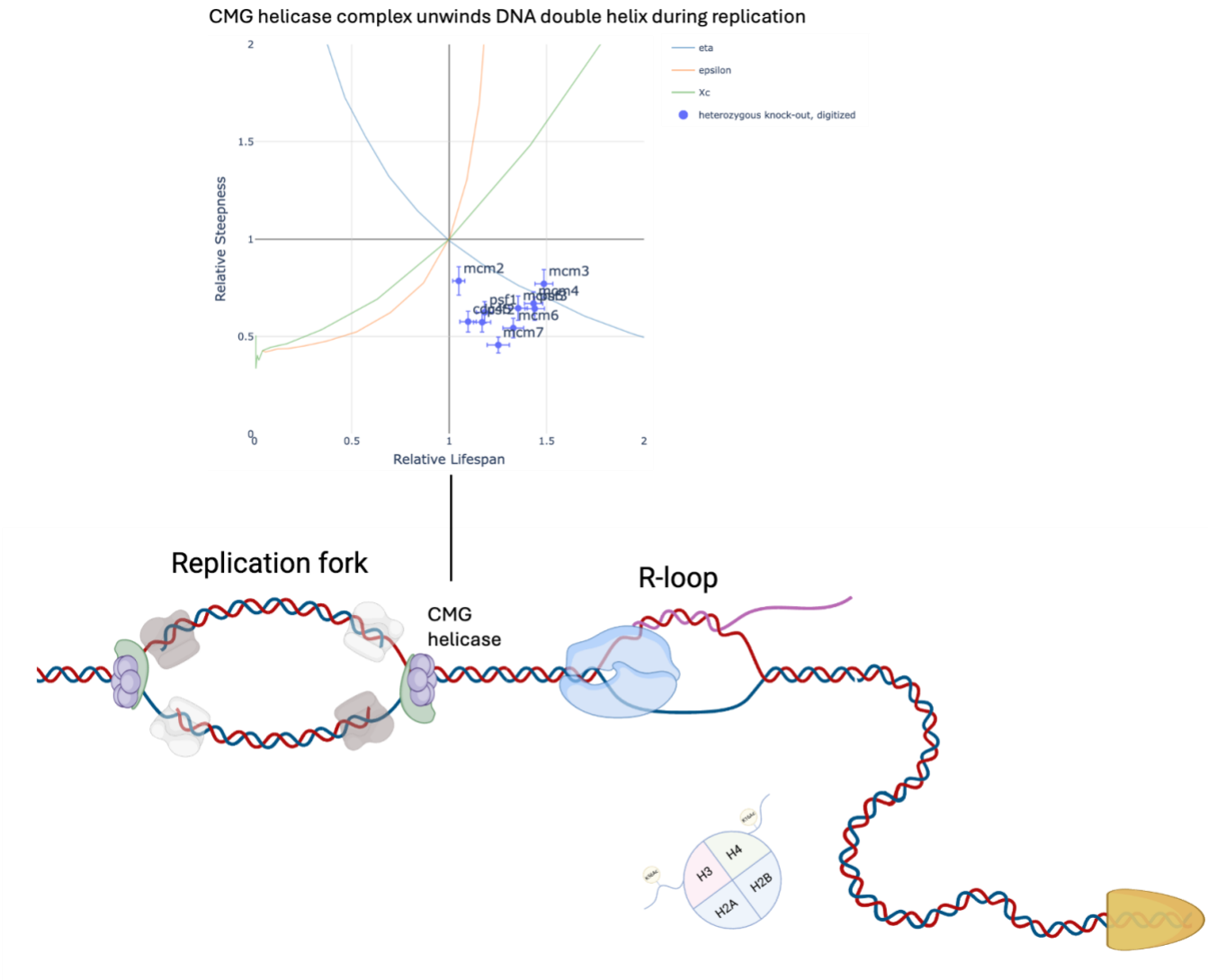


Fig 9.13 Replication fork helicases, the CMGF complex,help open up the two DNA strands for replication . Their deletion seems to reduce collisions with rloops and other DNA structures, reducing eta.

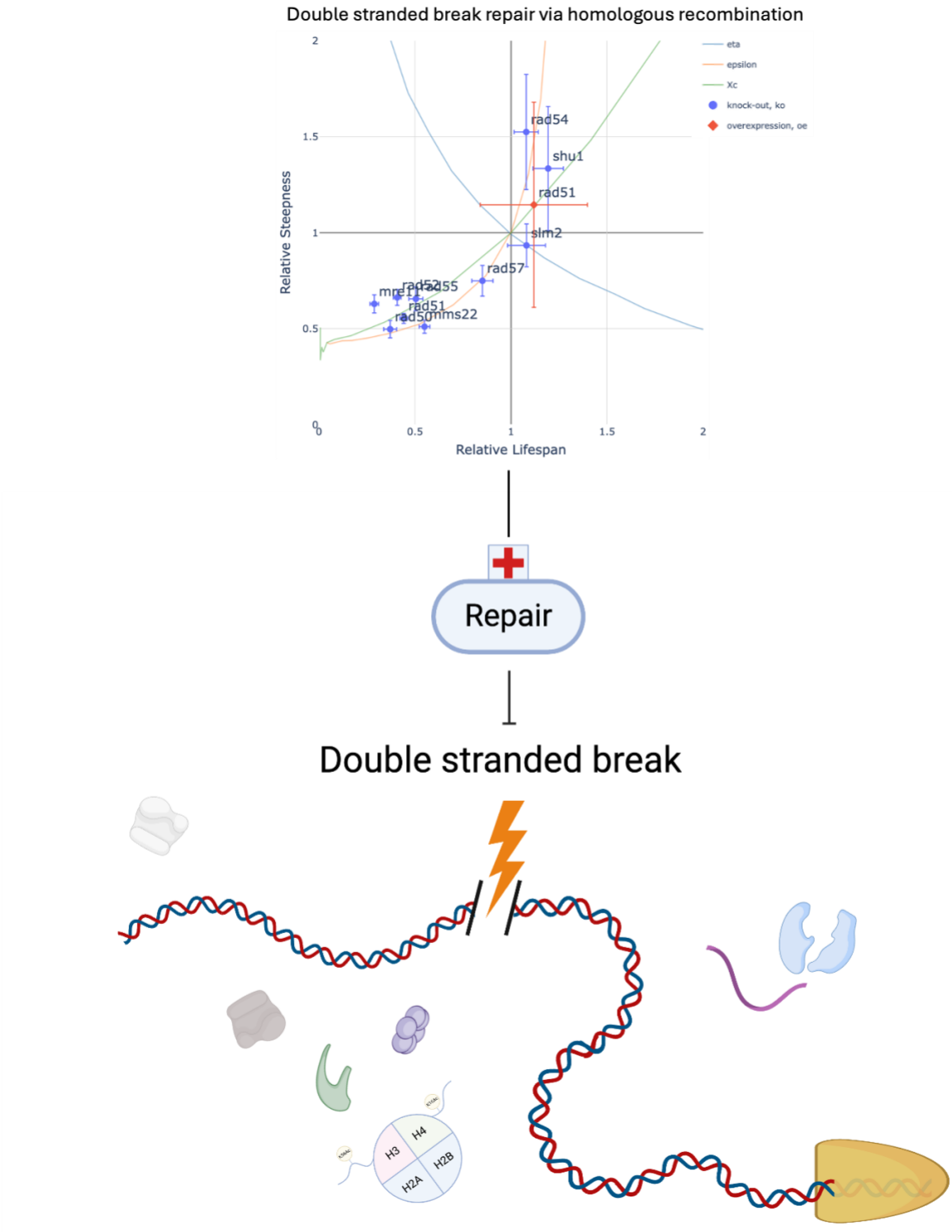


Fig 9.14 Deletion of double stranded break repair gene generally reduces Xc. Overexpression of key DNA repair enzyme rad51 increases Xc.

In humans, h4k16ac histone acetylation rises in human (blood cells) whereas h3k56ac drops (consistent with their changes in yeast aging)

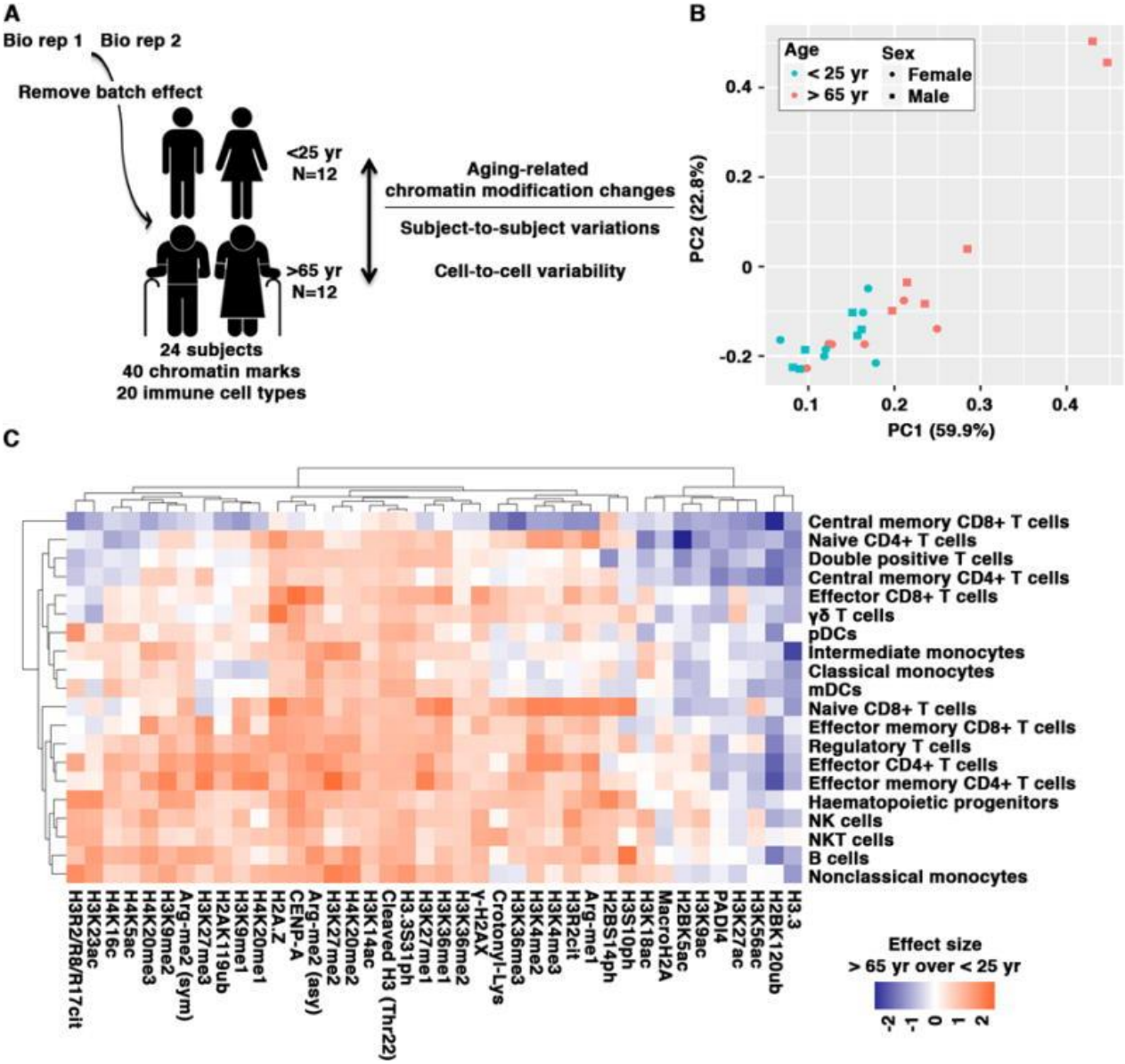


Fig 9.15 https://doi.org/10.1016%2Fj.cell.2018.03.079

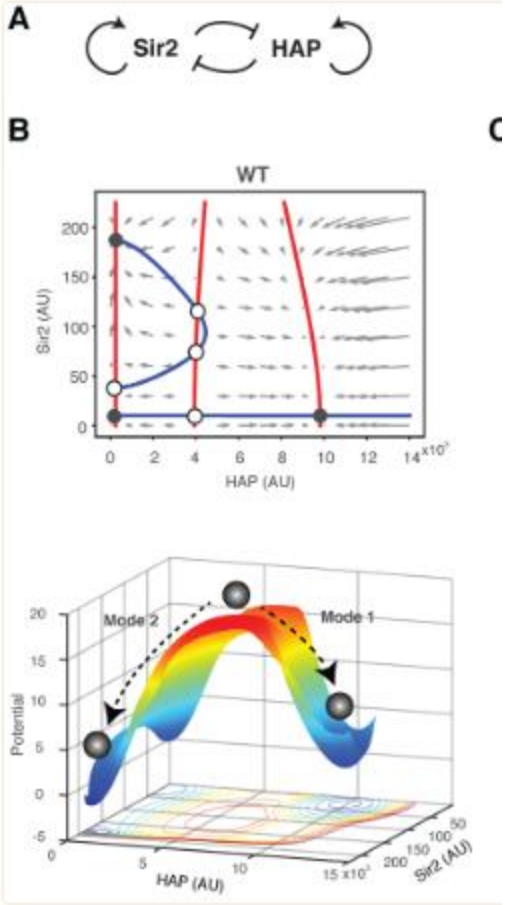
Yeast has two ways to die

These two pathways nicely correspond to the two modes of yeast death discovered by Nan Hao at ucsd in 2020. Old mothers produced either small round buds with mitochondrial problems and iron limitation , or elongated buds with large nucleoli and chromatin problems. The chromatin mode causes earlier deaths than the mitochondrial mode (fig 9.x).

Early on each mother cell makes a decision to upregulate one of two possible repair systems- mitochondrial biogenesis or histone deacetylation. It then dies later from the other damage. This is a toggle switch between *hap4* and *sir2*.
A toggle
Switch is a circuit of mutual
Inhibition and self activation that ensures that either one state is on and the other off or code versa (fig 9.16a).

Expressing both repair systems together led to a modest increase in lifespan. The yeast then shows normal mitochondria and normal chromatin, but dies of a third currently uncharacterized mechanism. Why only a modest lifespan extension? Perhaps the functions of *hap4* and *sir2* functions “collide” to a certain extent and it is suboptimal to simultaneously operate them.

What may be this collision? As one student in the class noted during the break- perhaps they are linked by the metabolite NAD, which is a limiting resource for both modes: in the mitochondria it limits NADH an electron donor for the ETC, and in the histone mode NAD is required for the deacetylase activity of *sir2*. NAD is thought to decline with age and NAD-raising supplements are researched as longevity interventions.


A
Sir2
HAP
B
C
WT
Sir2 (AU)
HAP (AU)
Mode 2
Mode 1
Potential
HAP (AU)
Sir2 (AU)

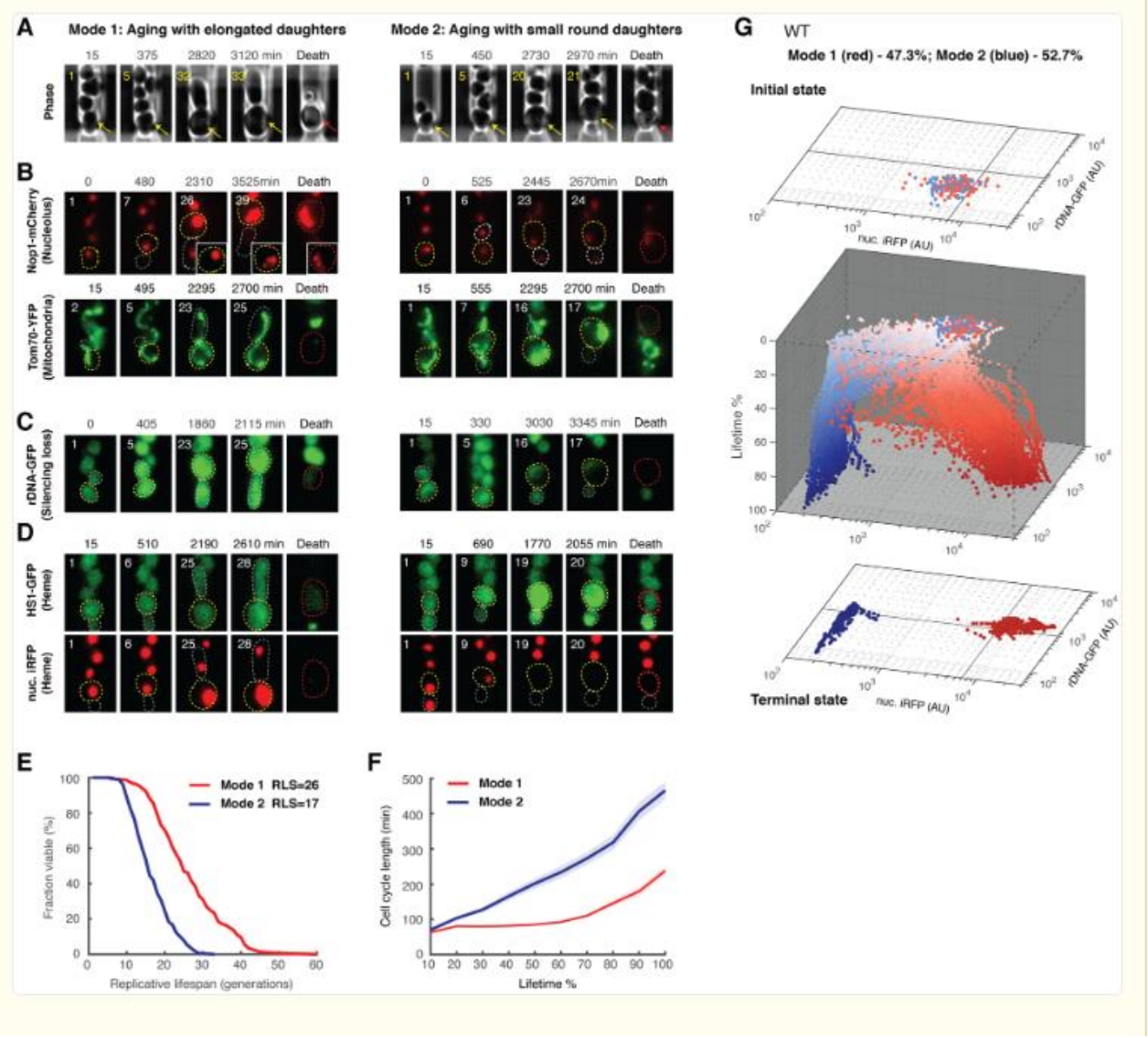


Fig 9.16 Yeast ages in two modes - elongated daughter cells with large nucleoli and chromatin silencing deficiency (mode 1) or small round daughter cells with mitochondrial dysfunction (mode 2). This is determined early on by a toggle switch between two repair systems - sir2 and Hap that repress each other and auto-activate. Mode 2 is shorter lived and has more rapidly increasing cell-cycle time over the generations. Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC7437498/

If these functions collide, the researchers reasoned it makes sense to separate the two repair functions in time. To do so, a brilliant experiment by Jeff hasty and Nan Hao engineered a synthetic gene oscillator in the cell that expresses *hap4* and then *sir2* in an alternating way. Instead of a toggle switch, they changed an arrow in the circuit and engineered a negative feedback loop that gives rise to a limit-cycle oscillator (Fig9.17c). The period of the oscillation pwas about ten hours, longer than a cell generation time. This oscillator produced a yeast strain that extends life by 82%- apparently the longest lived yeast ever attained by genetic manipulation! (https://pmc.ncbi.nlm.nih.gov/articles/PMC10249776/)

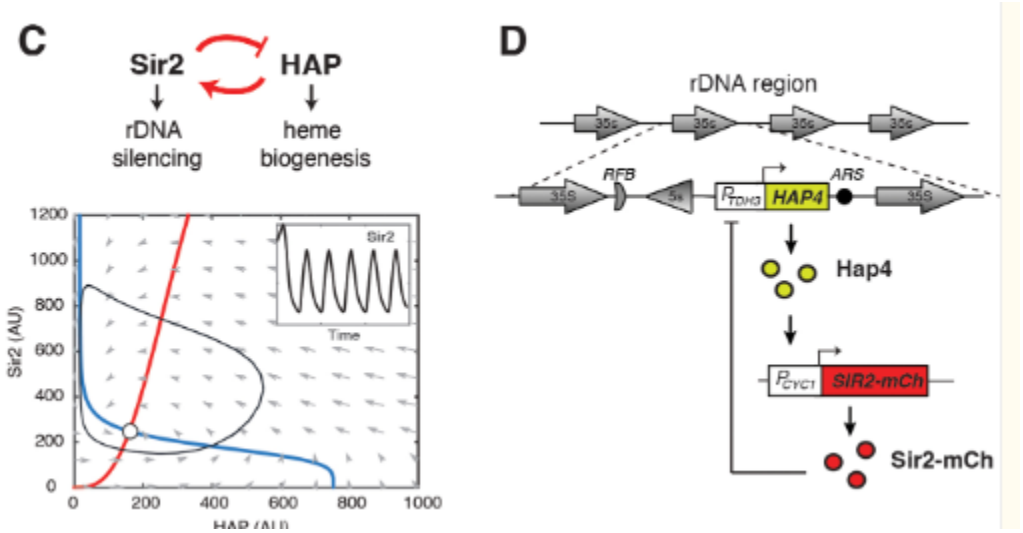


Fig. 3. Lifespan extension by the synthetic oscillator.

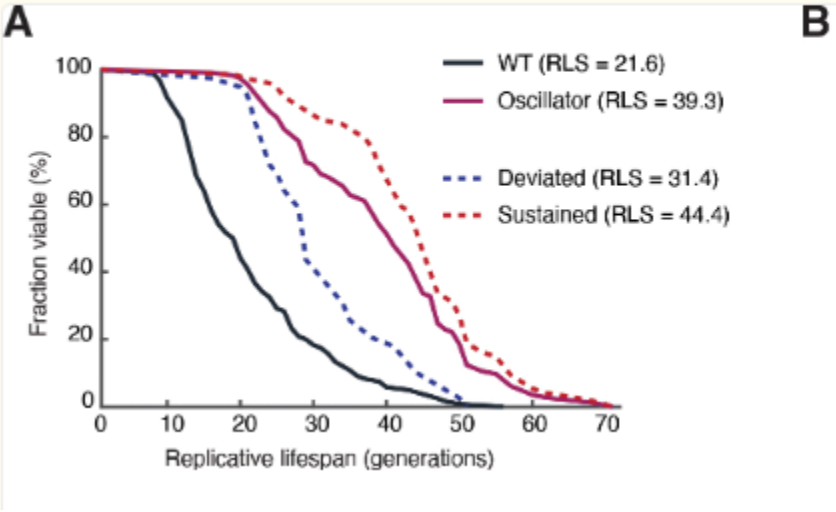


Fig 9.17 Hasty et al built a synthetic oscillator by changing the toggle switch between sir2 and hap4 into a negative feedback loop. The resulting strain was very long lived.
Source https://pmc.ncbi.nlm.nih.gov/articles/PMC10249776/

Incidentally, *c elegans* worms also have two modes of death- impaired pharyngeal pumping (the organ that grinds their bacterial prey) or breaching of the gut barrier, as discovered by David Gems.

Caloric restriction abrogates the mitochondrial pathway

Survival curves of the two modes show that the mitochondria one (mode 2) is more short lived than the dna one (mode 1). For some reason the two survival curves scale.
Caloric restriction (low glucose in the growth medium) prevents death by the mitochondrial pathway- increasing hap4, lowering translation and enhancing autophagy recycling and thus decreasing unfolded protein stress. Low glucose also prevents the loss of vacuole acidity (that only seems to happen at high glucose), and upregulates *sir2*.
This leaves only the longer lived chromatin mode 1. This finding explains how CR extends lifespan in yeast.

Tangent: in animals and humans Declining lysosome acidity causes raised **lipofuscin** in lysosomes which is a common marker of age . Lipofuscin is a yellow-brown pigment made up of lipid and protein residues that accumulate in lysosomes as cells age. Often called an "aging pigment" or "wear-and-tear" pigment, lipofuscin builds up in various tissues, including the liver, kidney, heart muscle, retina, adrenals, and nerve cells.

accumulation of lipofuscin is linked to oxidative stress and damage to cellular components like membranes, mitochondria, and lysosomes. Over time, this can impair cellular function and contribute to age-related diseases, including neurodegenerative disorders such as Alzheimer's and Parkinson's disease, as well as macular degeneration.

The yeast modes of aging transform the circle of hallmarks into a circuit

The hallmarks of aging in humans contain seven molecular hallmarks that act at the single cell level. Instead of a circle, our analysis places these hallmark in a certain causal sequence - a circuit. Whereas Hallmarks are general, large and vague, the proposed circuit distills a specific element from each hallmark.

Two additional hallmarks, stem cell exhaustion and senescence, describe the fate of the mother cell that ceases to produce new buds by cell cycle arrest before death. Cell cycle duration slows over the generation - only in the last generations in the chromatin mode, and more gradually in the mitochondrial mode (perhaps due to lowring atp and metabolic rate).

The multicellular hallmarks such as inflammahing and gut sysbiosys are of course missing since yeast is a single celled organism.

Mode 1

Epigenetic alteration (histone h4k16ac h3k56 ac in normally closed chromatin).——>telomere dysregulation (opening of closed telomeric chromatin)—->genomic instability (replication fork collision and double stranded breaks)

Mode 2

Nutirent deregulation (dietary restriction)

|

——-

Reduced autophagy and mitophagy (Vacuole deacidification)——>loss of Protestants (cysteine produced ROS and iron problems protein unfolding)——> mitochondroal deregulation (etc, protein import)

Mode 1, mode 2—> cellular senescence / stem cell exhaustion

We have worked hard, to celebrate let's take a nice deep sigh of relief.

From: Defective lysosomal acidification: a new prognostic marker and therapeutic target for neurodegenerative diseases

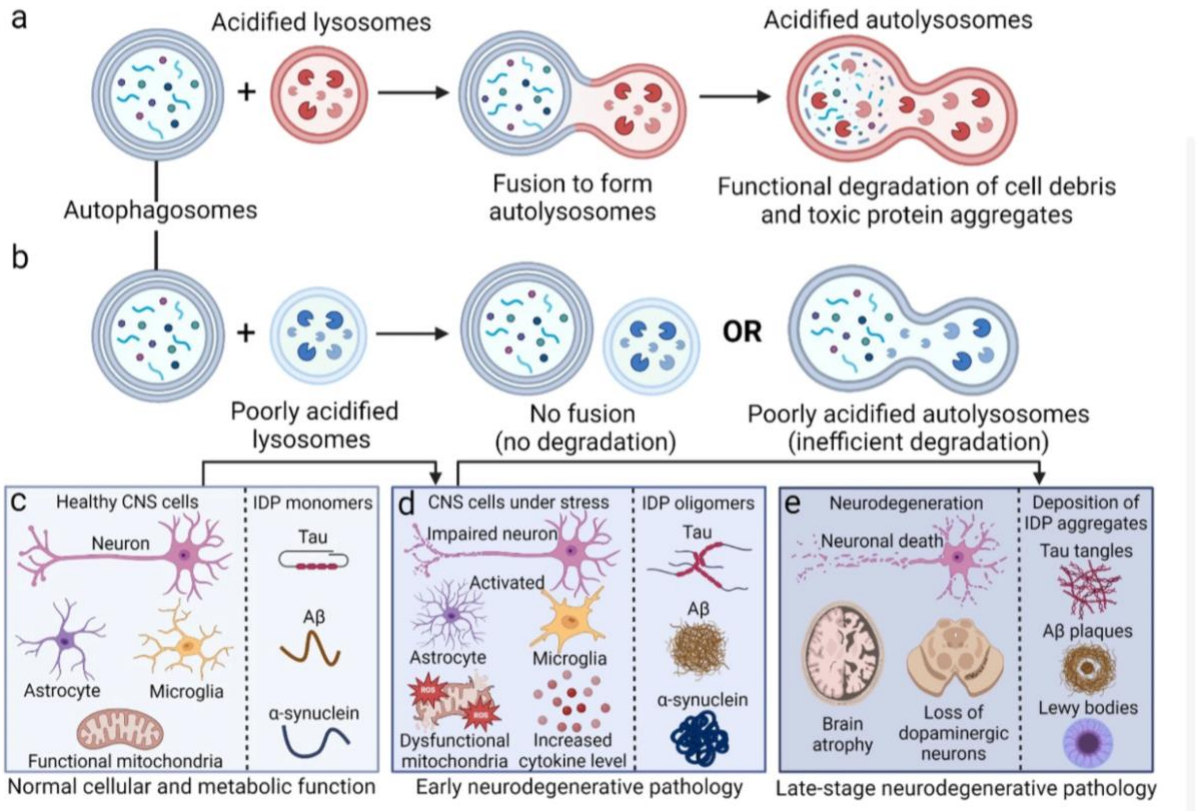


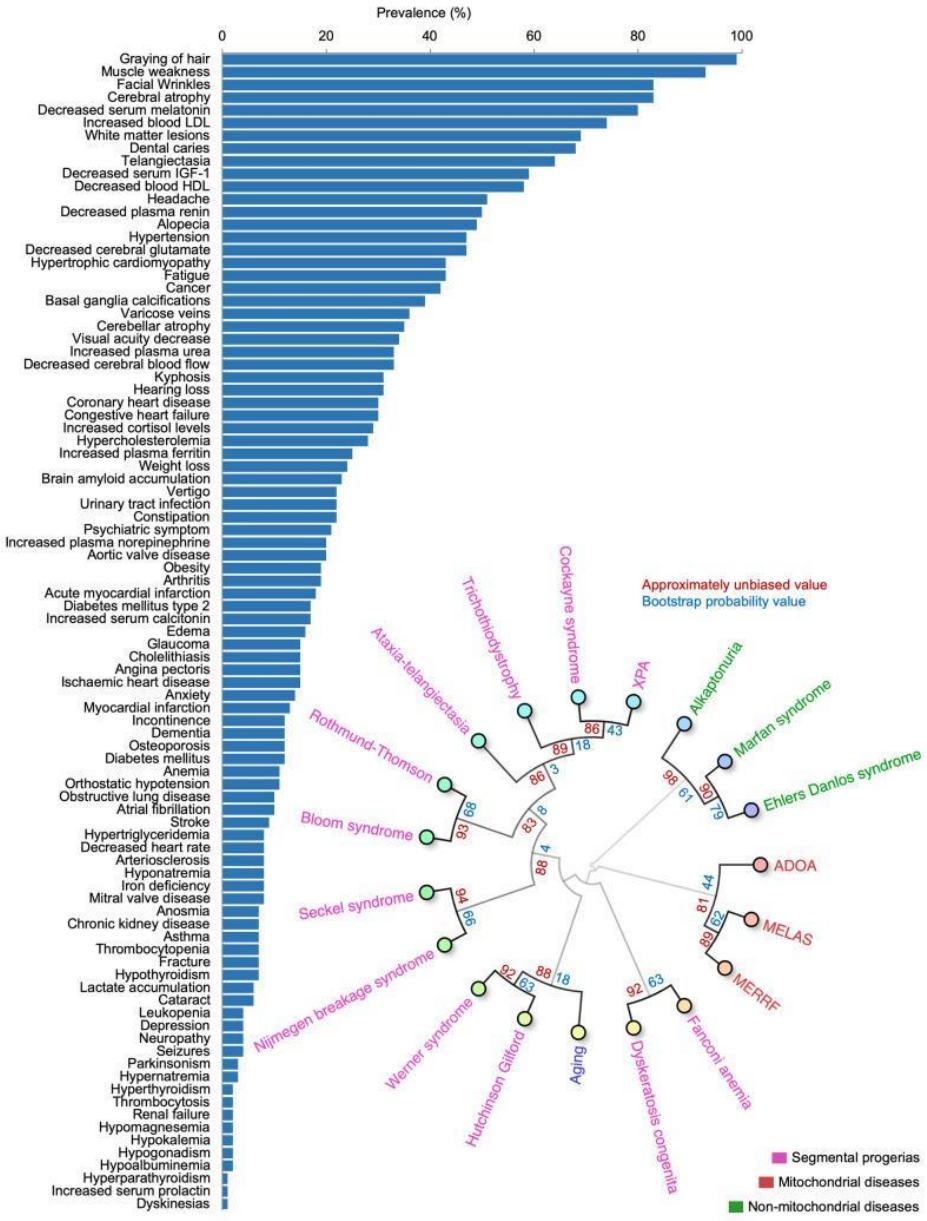
Fig 9.18 Lysosome (the human analogue of the vacuole) acidity decline in the aging brain is an early marker for mitochondrial dysfunction and neurodegeneration.

Part 2 genetics of human aging

We now jump across the tree of life from yeast to humans. Instead of experimental gene deletion, there are natural and tragic events where a baby is born with genetic changes that cause accelerated aging. We will learn from these genes. They map the two yeast modes of death into two human drivers, one for the body and one for the brain.
We will then consider the genetic changes accompanying longevity of the oldest old, the centenarians. These gene protect them from their own sometimes unhealthy lifestyles.

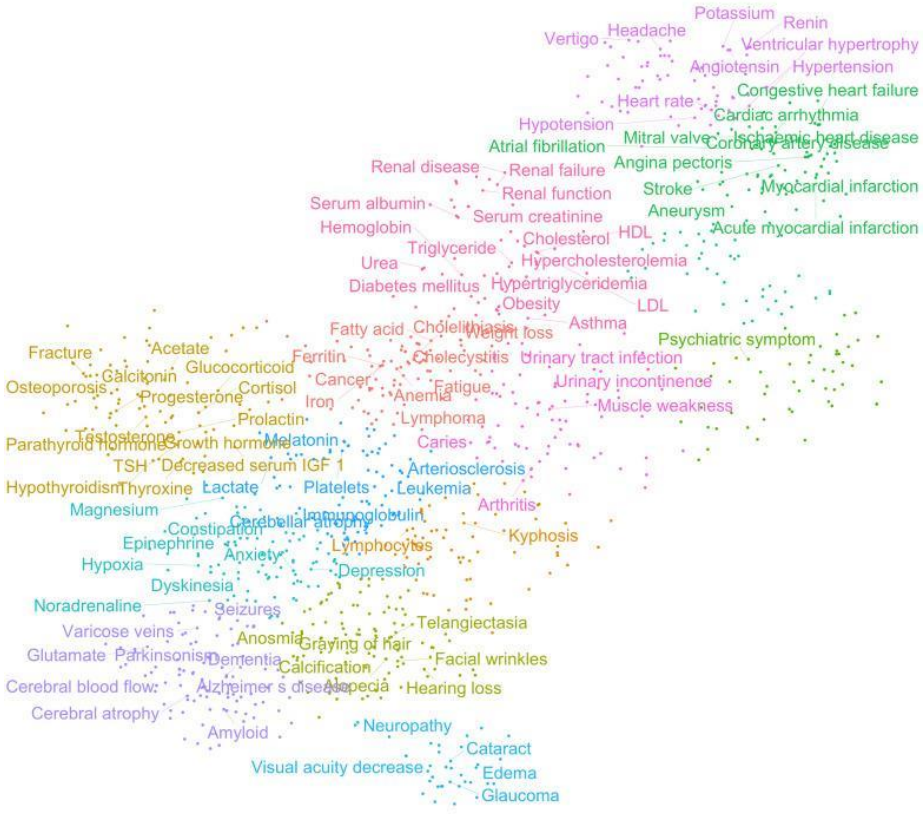
Progeroid diseases accelerate aging and involve DNA repair and chromatin structure

I am struck (and grateful) by how few mutations in the human genome give rise to a coordinated speedup in aging in all of its three Ds - death, disease and decline. These are the **progeroid syndromes**. This rarity may mean that (i) the core drivers of aging are very specific and / or (ii) altering them is usually lethal to the embryo.



H

Fig 9.19 prevalence of symptoms in normal human aging. From manually curated literature. Inset progeroid syndromes and their closeness to the normal aging phenotype show that HGPS and Werener are the closest. PMCID: PMC11627290 PMID: 31408848



To explore the range of such syndromes, Morten Scheibye-Knudsen did a nice analysis comparing symptoms of diseases. Each disease is a vector of the prevalence of symptoms, and the diseases can be clustered according to similarity of their symptoms vectors.
They first defined a vector of healthy aging- grey hair, skin wrinkles, loss of hearing, four horsemen, etc.(fig 9.19)
Using the symptoms of healthy aging, they could rank different genetic diseases as closer or farther from natural aging. Progeria (huchingson Guildford progeria syndrome) and progeroid disease (Werner etc) are the closest to natural aging symptoms as expected.

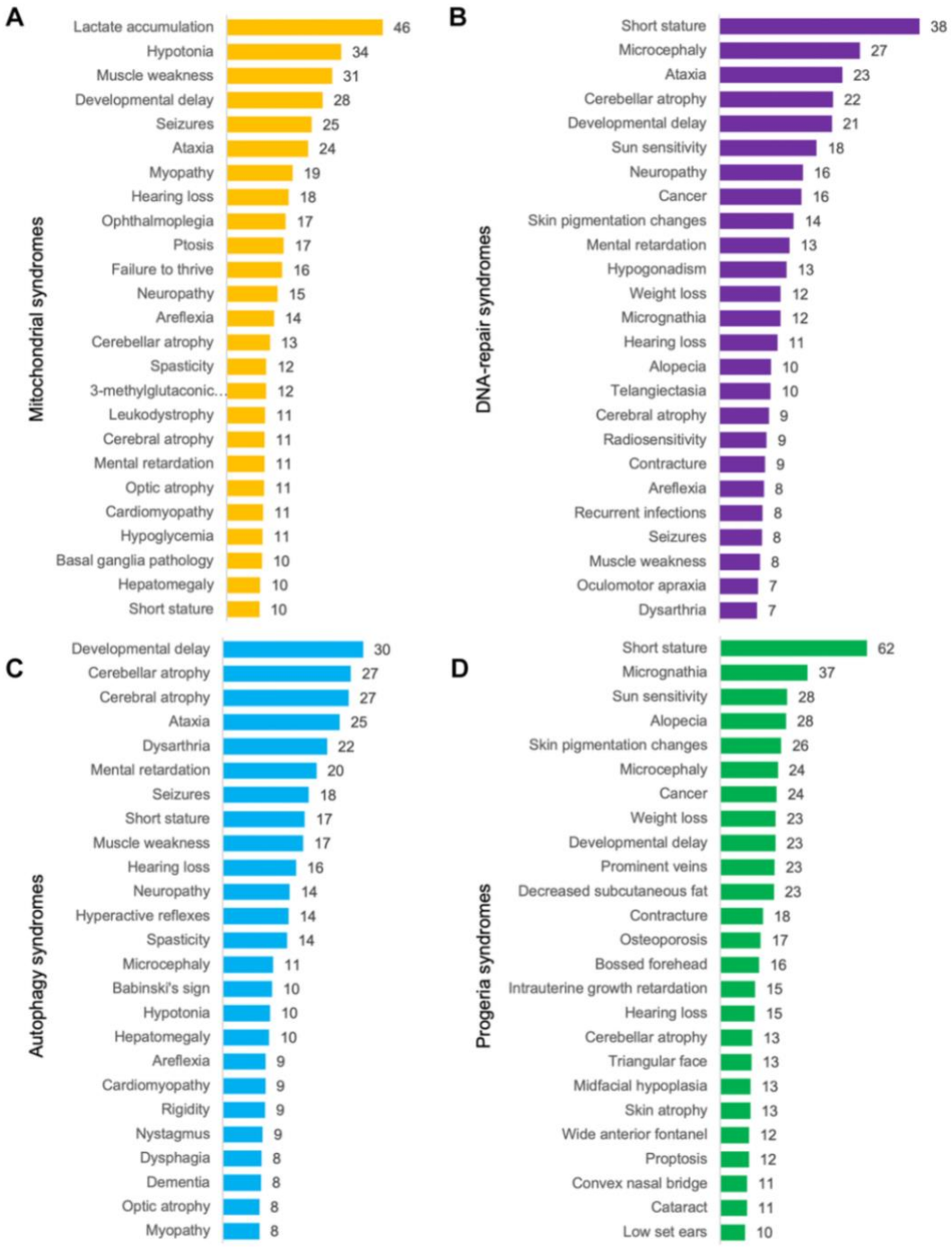


Fig 9.20 symptoms of progeroid and other diseases. Progeria is closest to DNA damage syndromes in terms of symptoms. Ataxia is uncoordinated motion and slow motion, alopecia is hair loss, microglia is small jaw. Dysarthria- motor speech disorder. Source: https://doi.org/10.18632/aging.205537

Progeria disease is related to nuclear structure and chromatin dysregulation. The relatively few other progeroid syndromes all have to do with DNA repair of specific types - recQ helicases and transcription coupled NER (cokayne syndrome).
That's all! The numerous other forms of DNA repair like the correction of a single DNA letter called base excision repair (BER) are not represented.

We can ask which rare disease are the next most close to natural aging. Morten finds that DNA repair diseases are the next closest to progeria.

Now it gets interesting- Mitochondrial and autophagy diseases are a bit farther, and have more brain symptoms. Lysosomal Storage diseases are even farther and have even more brain degeneration symptoms. This hints that the brain has a distinct clock related to lysosome and mitochondria, whereas the body has a clock related to DNA repair and genomic instability. Reminds us of yeast.

Progeria results from nuclear envelope disruption opening telomeric chromatin
The syndrome with the fastest aging is **progeria**, known as Hutchinson gilford or HGPS. It accelerates the aging rate by approximately 7 fold.

Progeria, called Hutchinson-Gilford Progeria Syndrome (HGPS), is a rare genetic disorder. Symptoms typically become noticeable within the first year of life, with affected children experiencing slowed growth, hair loss, aged-looking skin, and a distinctive facial appearance with a small face and jaw. As they age, they develop conditions commonly associated with old age, such as stiffness of joints, hip dislocations, and severe cardiovascular disease. Unfortunately, most children with progeria do not survive beyond their teenage years, often succumbing to heart attacks or strokes.

The cause of progeria is a mutation in the LMNA gene. It is a dominant negative mutation in one allele (somatic mutation). This defective protein ruins the structural integrity of the cell nucleus, leading to cellular instability and premature cellular aging. The mutation is typically not inherited but occurs spontaneously. Since LaminA is in charge of localizing the telomeres and other normally closed DNA regions to the nuclear periphery where they are silenced, its disruption causes telomere chromatin to open. Research shows a sequence of chromatin opening (in G phase) followed in S phase by telomere destabilization, telomeric dna damage, and cellular senescence. This is similar to the yeast chromatin mode of aging.

Werner Syndrome has a disrupted recQ DNA helicase

The next closest progeroid syndrome
To natural
Aging is Werner syndrome, also known as "adult progeria," it is a rare genetic disorder that results in premature aging. It is People with Werner syndrome generally appear normal during childhood but begin to show signs of aging in their early twenties. These signs include graying

hair, wrinkled skin, and a tendency to develop age-related diseases such as osteoporosis, cataracts, and cardiovascular problems.

The cause of Werner syndrome is a mutation in the WRN gene, which is responsible for producing a recQ DNA helicase that plays a critical role in DNA repair and maintenance - it protects the telomeres when DNA is replicated, and prevents structures in open chromatin in telomeres which can collide with the replication fork. The absence or malfunction of this protein leads to genomic instability, accelerated cellular aging, and an increased risk of cancer.

Another progeroid syndrome called Bloom Syndrome
has a mutation in a recQ helicase gene calle BLM. Individuals with Bloom syndrome often exhibit short stature, skin rashes that are sensitive to sunlight, and immune system deficiencies. The primary feature of Bloom syndrome is a high rate of sister chromatid exchanges, leading to chromosomal instability and a predisposition to various cancers at an early age.

Both Werner and Bloom genes are homologous to one of the genes in the yeast chromatin pathway - sgs1, a recQ helicase. Again a promising convergence!

These syndromes lack the fourth horseman, Alzheimer's
The syndromes closest to the aging symptom
vector (Progeria, Werner syndrome) are not associated with elevated neurodegeneration. **They generally spare the brain.**

We can thus form a two-driver hypothesis for humans:
Human aging is driven by two forms of damage- one for the body and one for the brain, or perhaps one for dividing cells and one for permanent cells.
We can hypothesize that the body has a stem cell driver based on
histone/chromatin/telomere/dsb pathway similar to yeast mode 1. The brain driver is the lysosome-iron-
mitochondrial pathway similar to yeast mode 2.

Indeed Alzheimer and other neurodegenerative diseases including ALS, Parkinson's and lewy body dementia have a shared temporal sequence in neurons long before symptoms emerge- lysosomal loss of acidity, followed by mitochondrial dysfunction, and then ros and protein aggregates. These aggregates include the infamous disease-associated aggregates called amyloid beta plaques and alpha synuclein Lewy bodies. Stay tuned for a future chapter on neurodegenration.

A specific brain aging driver, distinct from the body aging driver, might explain why the Alzheimer disease incidence curve is so different from all other age-related diseases. Alzheimer incidence rises by 15%per year and starts very low, whereas the other horsemen and almost all other age related diseases rise much more slowly at 3-8% per year (Katzir et al 2020). Alzheimer can not be explained by the SR model with its baseline parameters because it requires a disease threshold higher than the death threshold, as we mentioned in a previous

lecture. The brain aging driver thus needs its own SR model with different parameters. Stay tuned.

Other observations that favor a brain specific driver disrinct from the body: mice age in 2 years with many similarities to humans in their body decline and diseases, but rarely have neurodegenration (body clock is accelerated in mice by poor dbs repair for example).

Human functional declines in the body are correlated with each other, as are the declines of cognitive functions, but there is lower correlation between the body and brain clusters of functions. You can have a relatively healthy body and a sick brain and vice versa.

We conclude that progeria and related progeroid syndromes are caused by specific genetic problems in DNA damage repair or the nuclear lamina.

Cokayne syndrome-lots of neuron damage!
Defect in ecc6 Transcription coupled repair, neurons don't care about dsb, but transcribe so much they need to avoid transcription getting stuck in damage and need the ECC6!! Bjoern Schumacher - c elegans in l1 measures food, if food goes to larval stages l2,3,4adultnin 2 says. If not go to dauer, sealed off from
Environment by thick cuticle, not eating but moving to new environment. dauer rejuvenates to form
Adult despite living for months. Requires ecc6 to rejuvenate. Slow metabolism, even if UV irritated, causing dna damage in dauer, rejuvenates the neurons in the adult! Postmiroic neurons get rid of garbage and houses!. Dream complex
Represses dna repair in soma not germline in adults.

Alcin: meiosis generates new lysosomes , the old lysosome ruptures. Gets rid specifically of rDNA circles . Nucleoli of old yeast accumulate aggregates of ribosomal
Proteins due to chromatin de silencing. So it evolved to get rid of houses .
Also transfers only half the mitochondria.

Centenarians are enriched with protective genes

Centenarians (above age 100) are often healthy agers, and are studied to find longevity genes.

According to centenarian researcher Perls, "centenarians fell into three classes. About 38 percent were Survivors, diagnosed with at least one age-associated disease before the age of eighty; another 43 percent were Delayers, who developed such a disease after the age of eighty; and the last group consisted of Escapers, the 19 percent who reached their hundredth birthday without being diagnosed with any of the ten most common age-associated diseases. In fact, about half of centenarians celebrated turning one hundred without heart disease, stroke, or non–skin cancer, which is extraordinary."

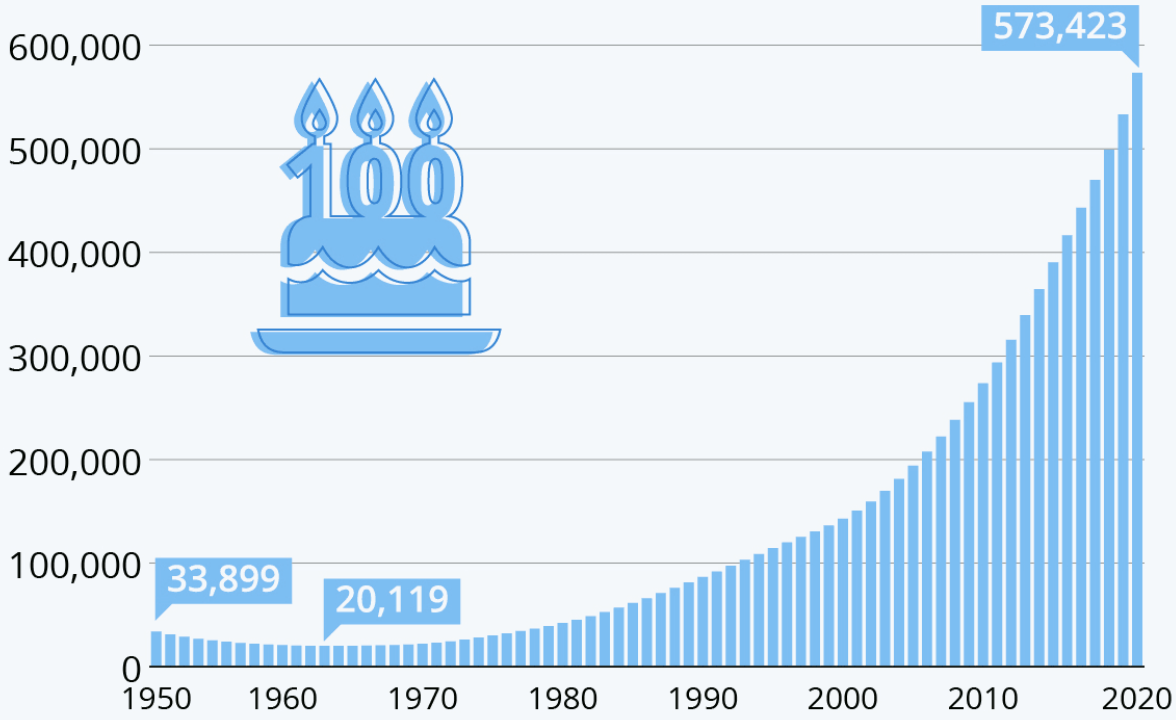
The upshot is that it biologically possible
For humans to reach 100 without major illness !

One might expect that to live long would require mutations that do the opposite of progeria- enhance DNA repair. But this is not so.

Centenarians are rare (but rising rapidly) and hence doing a big genome wide association study is difficult. Since you can study only thousands, you can see mainly common genetic variants and not rare mutations. But several studies were done on restricted populations - such as the Ashkenazi jew study by Nir Barzilay-as described in his enjoyable book "*age later*" . Centenarian cohorts are enriched with genetic variations found in study after study in different populations and countries.

Centenarians Are Becoming More Common

Number of people worldwide who are 100 years or older



Source: United Nations

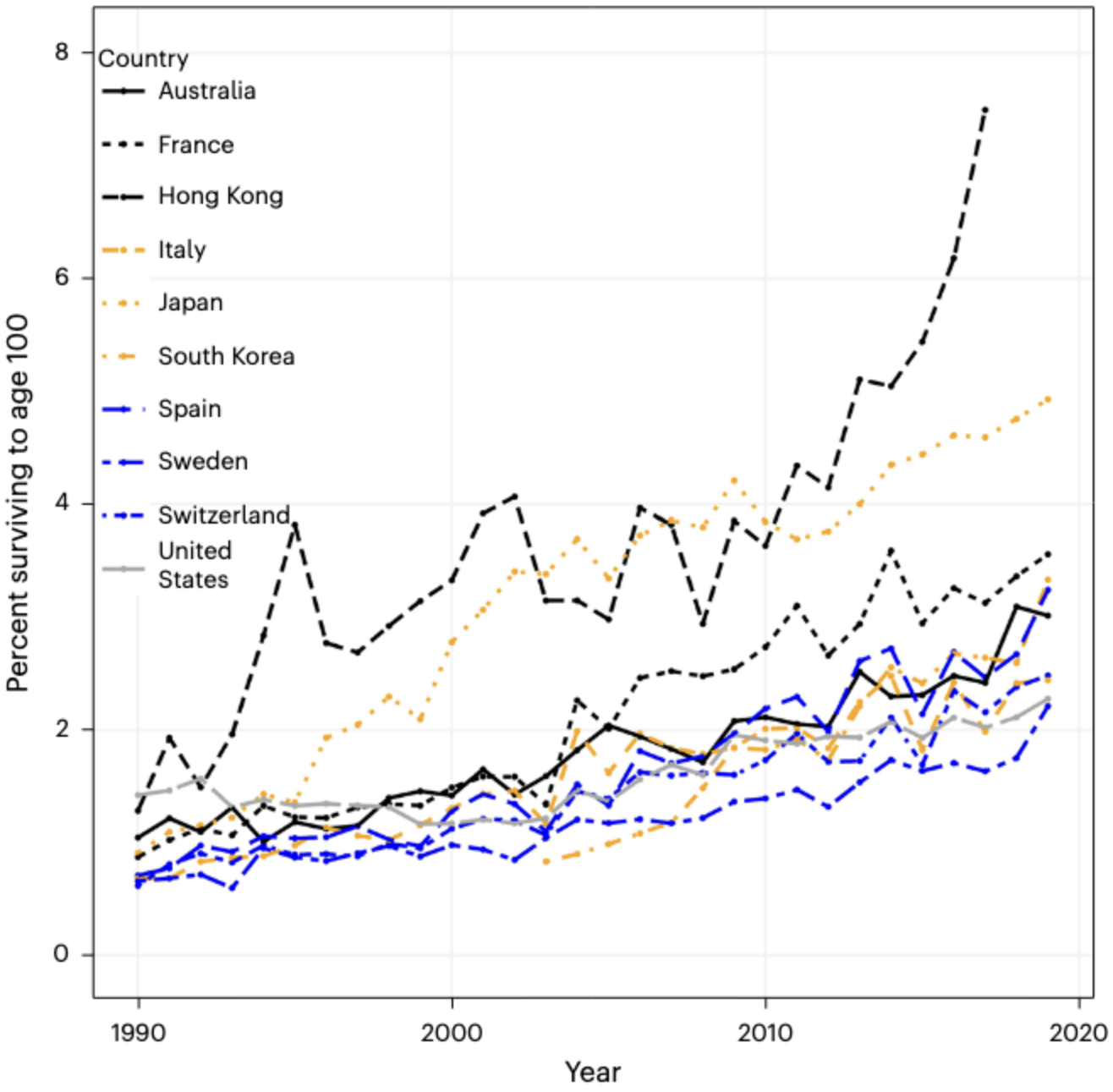


Fig. 2 | Observed percent survival to age 100 (males and females) in the eight countries with the longest-lived populations and in Hong Kong and the United States (1990–2019). Each line represents the proportion of each population in an annual life table who would survive to age 100 from 1990 to 2019.

Fig 9.21 Number of centenarians is growing. source: 10.1038/s43587-024-00702-3

The centenarian studies picked up common variants (that is, DNA sequence changes found in more than 1% of the general population) that are enriched or depleted in centenarians relative to control populations. It turns out that centenarian-ism is quite heritable.
As Nir says, To live to a hundred you need to choose the right parents.

The centenarian-enriched gene variants are protective - they allow survival despite high amounts of damage (increasing the death threshold Xc or disease thresholds Xd).
Indeed some centenarians drink, smoke and eat processed foods but seem to be protected from their own lifestyle.

Other centenarian-enriched gene variants seem to reduce activity of the mtor/igf1 pathway and hence raise cellular resilience by mimicking nutrient limitation signals.

Protective, Disease-preventing Xc genes:
1. APOE2 (Apolipoprotein E): a protective variant against Alzheimer and heart disease. Its prevalence is about 5-7% in the general population, and is enriched in centenarians. APOE is a protein that binds lipids to form lipoproteins, which carry cholesterol and other fats through the bloodstream. ApoE2 is commonly found in centenarians together (linkage disequilibrium) with a variant of mitochondrial membrane protein TOMM40.
There are three common variants (alleles)- ApoE 2,3 and 4. ApoE3 is the most common. The ApoE4 allele has a high risk for all cause mortality, cvd and Alzheimer. It occurs in about 25% of the population and is depleted in centenarian
populations.

2.. KL (Klotho): This gene has many functions involved in aging and has been linked to longevity and protection against age-related diseases. It can prevent Alzheimer even if the main risk gene apoE4 is present.

3. CHRNA3/5 (Cholinergic Receptor Nicotinic Alpha Subunits 3/5) involved in the cholinergic system and associated with cognitive function and longevity. The centenarian variants may be related to reduced addiction to smoking, according to uk biobank epidemiological data.

3. Anti inflammatory genes: SH2B3 involved in immune response linked to reduced risk of age-related diseases. Centenarians show anti-inflammatory variants.
B2M - involved in immune function and associated with longevity and healthspan. Centenarians have lower activity of this hla class 1 component, lowering inflammation.
Also variants that reduce the inflammatory cytokine IL6 and the immune recognition molecule HLA-DQ which is a risk factor for autoimmune diseases.

Igf pathway genes
In addition to these Xc genes, there are genes conserved all the way to worms and flies that seem to work at the level of cellular resilience- in humans they are expected to affect houses (η). One caveat is that raising eta by more than a few percent would produce lifespans way beyond 120Which is of course not observed- thus the igf1 pathway in humans might also be Xc.

2. IGF1 (Insulin-like Growth Factor 1) or its receptor, centenarian-enriched variants reduce function - igf1 is a hormone essential for growth and development, especially during childhood, that regulates cell growth, differentiation, and survival. Signals for nutrient availability.

2. FOXO3A (Forkhead box O3): centenarians often have variants that increase function. Foxo3 is a transcription factor inhibited by IGF1, it regulates pathways that collectively contribute to enhanced stress resistance, fat storage, apoptosis instead of senescence, improved DNA repair, and overall cellular homeostasis observed in centenarians.

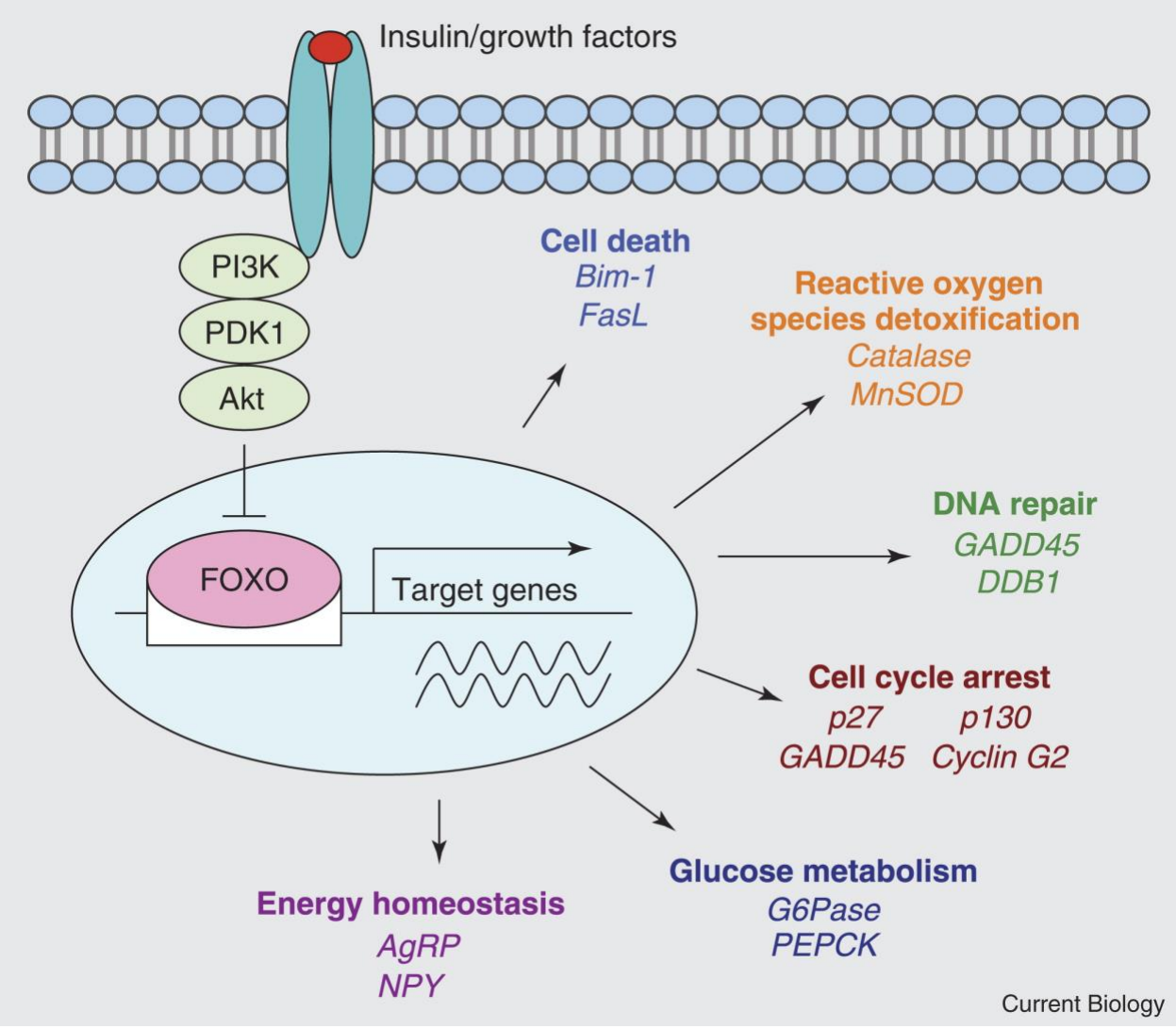


Fig 9.22 The IGF1-FOXO pathway. IGF1 binding to its receptor inhibits FOXO, which when active binds DNA to upregulate a wide range of protective gene pathways that help during starvation.

3. SIRT1 (Sirtuin 1) and SIRT 3 - genes in the sirtuin family associated with aging in many organisms like sir2 in yeast, regulates cellular processes such as transcription, and apoptosis through deacetylation of target proteins. sirt3 refikates mitochondrial function and oxidative stress.

5. mTOR (Mechanistic Target of Rapamycin): Encodes a protein involved in a signaling pathway that regulates cell growth, proliferation, and survival. It is a key player in cellular metabolism and is implicated in diseases like cancer and metabolic disorders.

2. CDKN2B (Cyclin-Dependent Kinase Inhibitor 2B): This gene is associated with cell cycle regulation and influences mouse lifespan. Centenarians have lower activity of their gene, a cell cycle inhibitor important in cell senescence. The centenarian variant may thus reduce senescence.

These genes have aging effects in model organisms:
1. FOXO3 (Forkhead box O3):
- Fruit Flies: Overexpression of FOXO extends lifespan by enhancing stress resistance and promoting DNA repair.
- Worms: Mutations in FOXO increase lifespan by improving stress resistance and reducing oxidative damage.
- Mice: FOXO overexpression linked to increased lifespan and improved metabolic health.

2. SIRT1 (Sirtuin 1):
- Fruit Flies (D melanogaster): Overexpression of SIRT1 extends lifespan by regulating cellular processes like apoptosis and stress response.
- Worms (C elegans): SIRT1 overexpression increases lifespan by enhancing stress resistance and metabolic health.
- Mice: SIRT1 overexpression has been shown to improve metabolic health and extend lifespan.

3. IGF1 (Insulin-like Growth Factor 1)
- Worms Reduced IGF1 signaling extends lifespan by decreasing cellular growth and proliferation.
- Mice : IGF1 pathway mutations linked to extended lifespan and reduced cancer risk.

4. mTOR (Mechanistic Target of Rapamycin)
- Worms: Reduced mTOR signaling extends lifespan by decreasing cellular growth
- Fruit Flies : mTOR pathway mutations extend lifespan by improving metabolic health.
- Mice : mTOR inhibitors linked to extended lifespan and improved healthspan.

Human lifespan is much more heritable than current textbook estimates

What determines human lifespan - genes, environment or intrinsic noise? If genetic heritability is high, we can learn about aging mechanisms form
Gene variants that affect lifespan, and perhaps gain some predictive power on personalized lifespan.

However many studies concluded that genetic heritability - the fraction of variance attributed to genes- is low. The best way to study this is by comparing the lifespan of identical twins (monozygotic) to non identical twins (heterozygous) that share only half their DNA on average. One measures the correlation of lifespans of me and dz twins rmz and rdz. The mz correlation includes genes and environment, and the dz correlation includes half the genes and environment. Heritability is thus defined by the Falconer formula h=2(rMz-rDZ), where the factor 2 corrects for the 50% of charged genes.

Such studies estimate genetic heritability of lifespan at 20-25%. Similar low heritability comes from many
Family pedigree studies that compare lifespans of siblings or parents and siblings. Recent studies using massive online family trees suggest an even lower heritability, below 10%!

Ben Shenhar has shown that these studies fail to adjust for a key bias, extrinsic mortality. This is death by infection, accidents and other extrinsic factors. The twin and family studies use cohorts born around 1900'or before, when extrinsic mortality was much higher than today. Back then about 1% died of extrinsic causes per year. So about 1 in five died of such causes before age 30!
Today extrinaic mortality is a factor of ten or more lower , closer to 0.1%/year.
Extrinsic mortality masks the true heritability of intrinsic lifespan, deaths caused by age related decline and disease. Ben used the sr model (and also other models) to adjust for extrinsic mortality given the twin data.
The upshot is that heritability of twin lifespan rises to 50%. This is twice the textbook estimates, and in line with the heritability of most other human traits.

This is the heritability of normal lifespan. Heritability of being a centenarian is even higher. This has been hard to pin down since centenarians have been so rare. The sr model shows that the chance of living to 100 if you have a centenarian sibling is about tenfold Higher than the average population.

The excess probability of living to age x if you have a sibling that died at x rises exponentially with x. The slope of this exponent is similar to The Gompertz slope of mortality. This prediction is well matched by data.

Thus genetics account for about ½ of the variation in human lifespan. Analysis of twin data suggests that. Environment seems to account for 1/6 or so. The remaining 1/3 is often considered a mystery in heritability studies. The sr model accounts for this by virtue of the intrinsic noise parameter epsilon.

Which sr model parameters vary between humans?

The genetic heritability suggests that each individual has different sr model
Parameters encoded in their genes. Which parameters vary most between humans ? Is it damage production rate eta? Truck removal rate beta? Threshold Xc? Noise epsilon?

Ben Shenhar showed that we can rule out large variations in two of these four parameters. We can rule
Out variations in eta and beta- rates of houses and trucks. The reason is that variations of more than a few percent in either of these parameters would lead to a sizable population that lives beyond 140 years.

In contrast, variations in threshold Xc or noise epsilon can capture the observed twin heritability without changing the extreme old age tail of the lifespan distribution. They are predicted to vary by about 20% in the population to generate the observed twin heritability, and still keep the chance
Of living to 120 below one in a few billion, and virtually never to reach
140 given the size of the world Population.

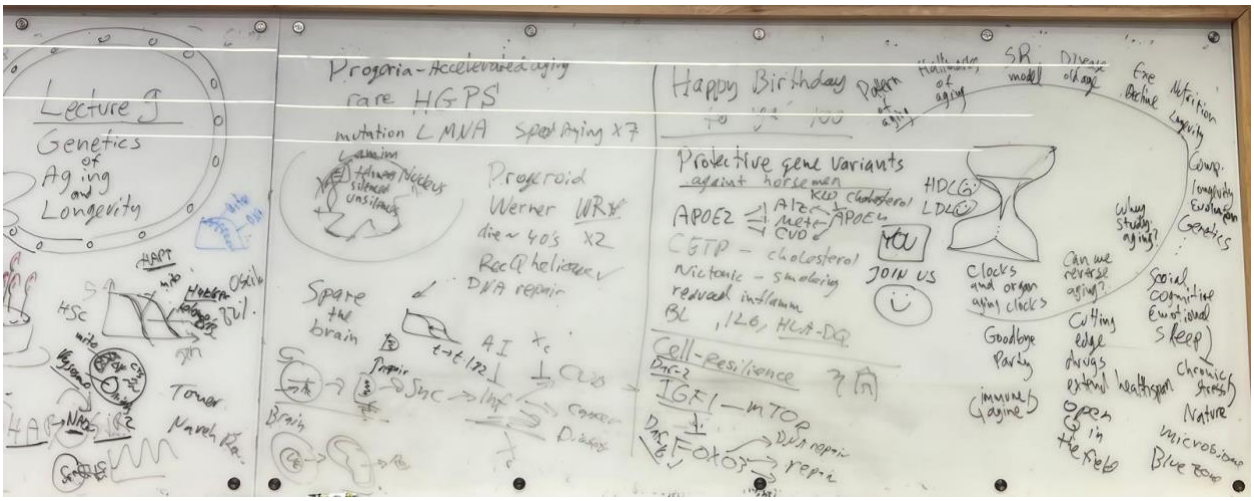
This finding is consistent with the centenarian genes. Many of these are protective- you die less at a. Given level
Of damage- and can be interpreted as raising the death threshold Xc and disease threshold Xd.

Genes for late and early menopause: surprisingly recent GWAS on early and late menopause came up with hits in the double stands repair pathway, recQ helicases and other genes in that vein. The advantage of menopause study is the huge number of people compared to centenarians- half of the population has menopause. This exciting development links the field of menopause with the more general field of human aging.

Summary:
We saw that the SR model in yeast can help detect genes that affect damage production and threshold. It thus enables a screen to find drivers of aging. Yeast has two modes of aging and death - one driven essentially by histone acetylation in the telomere region (H4K16Ac, H3K56Ac) causing DNA breaks, and the other driven by vacuole deacidification and mitochondrial dysfunction causing loss of ATP and high ROS.
Jumping from yeast to humans, we saw that diseases of accelerated aging are due to deficits in DNA double stranded break repair or open chromatin- similar to the histone mode in yeast. These diseases spare the brain - and we hypothesize the brain ages by the mitochondrial mode- since neurodegenerative diseases have lysosome deacidification, mitochondrial problems and protein aggregates like mode 2 in yeast.

We ended on an optimistic note- centenarians often enjoy health till very old ages, and have protective genes that lower risk of disease and protect them from their own often naughty lifestyles.

For a long life well lived, let's take a nice deep sigh of relief.



Appendix

Aged stem cells remain fresh by shuttling their DNA and mitochondrial to their differentiated cell progeny. The differentiated cells then divide several times (transit amplifying cells) and get damaged until they halt division and become senescent cells -in effect resembling the old yeast mother cells.

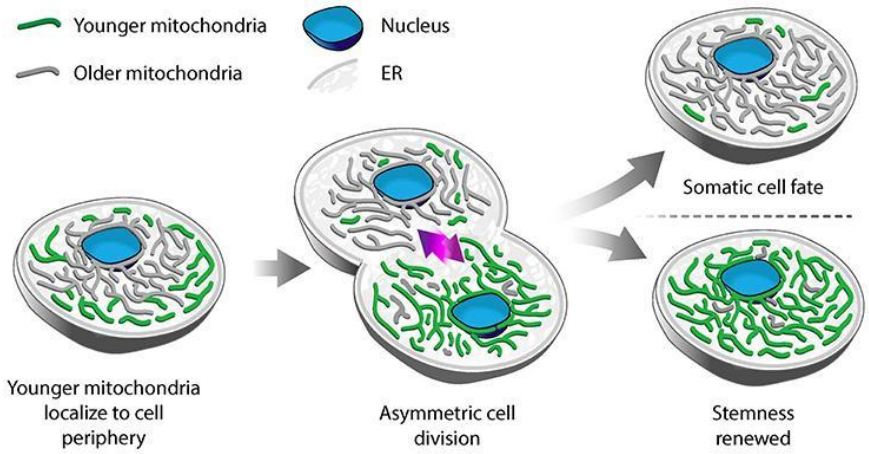


Fig 9.23 Stem cells divide asymmetrically, with one cell remaining a stem cell and the other becoming a differentiated cell. The stem cell retains young high-quality mitochondria.

Link for that: https://pubmed.ncbi.nlm.nih.gov/25190112/

The other more recent one is a preprint on bioRxiv from Patty Kane's lab:

https://pubmed.ncbi.nlm.nih.gov/39091794/

They suggest that V-ATPase disassembly in old age mother cells drives acidity decline, and that the V-ATPase is assembled okay in daughter cells.

Loss of ISCs impairs the activity and stability of ISC-containing proteins. Because of the connection between Aft1 and ISCs, we wondered whether ISC-containing enzymes were impacted by V-ATPase inhibition. Indeed, levels of aconitase (Aco1), a mitochondrial-localized ISC protein in the tricarboxylic acid (TCA) cycle (Gangloff et al., 1990), declined upon V-ATPase inhibition with kinetics that paralleled activation of the iron regulon (Figure 2E). Similarly, Sdh2 and Rip1, ISC proteins in mitochondrial respiratory chain complexes II and III, respectively (Cui et al., 2012; Van Vranken et al., 2015), both declined upon V-ATPase inhibition, but not in the presence of excess iron (Figure 2H).

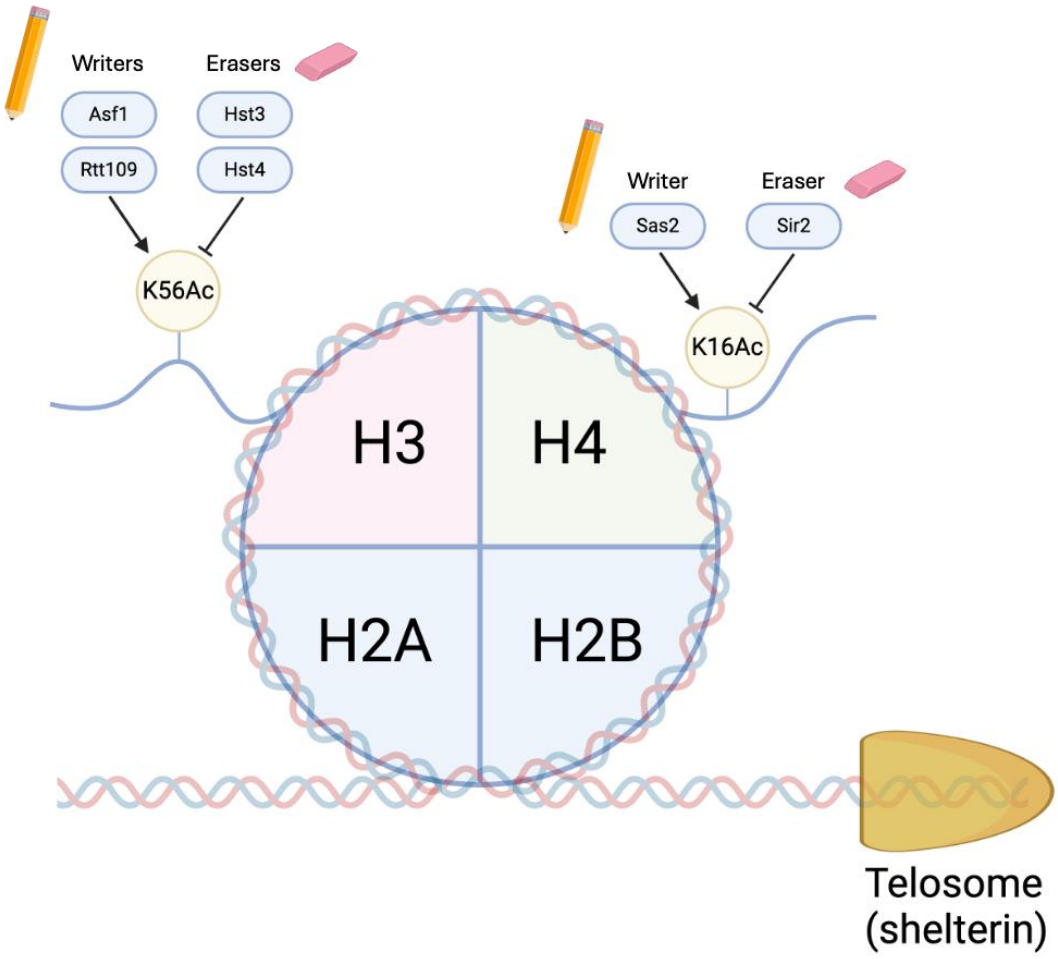
Paralleling the changes in these individual iron-containing respiratory chain proteins, Blue-Native PAGE (BN-PAGE) analysis indicated that assembled respiratory complexes II and III decreased with acute V-ATPase inhibition in an iron-dependent manner, although the level of non-iron-containing complex V was unaffected (Figure 2H). Consistent with these observations, cellular oxygen consumption was reduced after acute V-ATPase impairment to levels present in strains lacking mitochondrial DNA (and thus respiration) and restored with iron supplementation (Figure 2I). Moreover, ISCs outside of mitochondria were also impacted by vacuole impairment, as steady-state levels of GFP-tagged ISC-containing proteins localized to the endoplasmic reticulum (ER), cytosol, and nucleus all decreased upon V-ATPase inhibition (Figure 2J). Analysis of the turnover kinetics of two ISC-containing proteins, Lys4 and Twy1, using the recombination-induced tag exchange (RITE) system (Verzijlbergen et al., 2010), revealed increased turnover upon V-ATPase inhibition (Figure S2I). Thus, V-ATPase loss impairs mitochondrial function by limiting cellular iron, which hampers ISC-protein stability, depletes iron-containing respiratory chain complexes, and impairs mitochondrial respiration cells. We speculate that threonine may impact iron homeostasis by allosterically regulating cysteine metabolism, as threonine and cysteine are metabolically linked through homoserine in *S. cerevisiae* (Cherest et al., 1969; Ramos et al., 1991; Figure S5B). Consistent with this idea, D-threonine did not affect iron metabolism, despite being taken up by cells as efficiently as naturally occurring L-threonine (Figures S5C and S5D). Finally, our results indicate that elevated non-vacuolar cysteine, rather than a cysteine derivative, likely drives iron limitation, as other cysteine-related metabolites, including homocysteine, glutathione, and methionine, did not impact the iron regulon (Figures S5E, S5F, and 5A). Iron limitation was also not induced with S-

methyl-l-cysteine, indicating the sulfhydryl group contributes to cysteine's impact on iron homeostasis (Figure S5G).

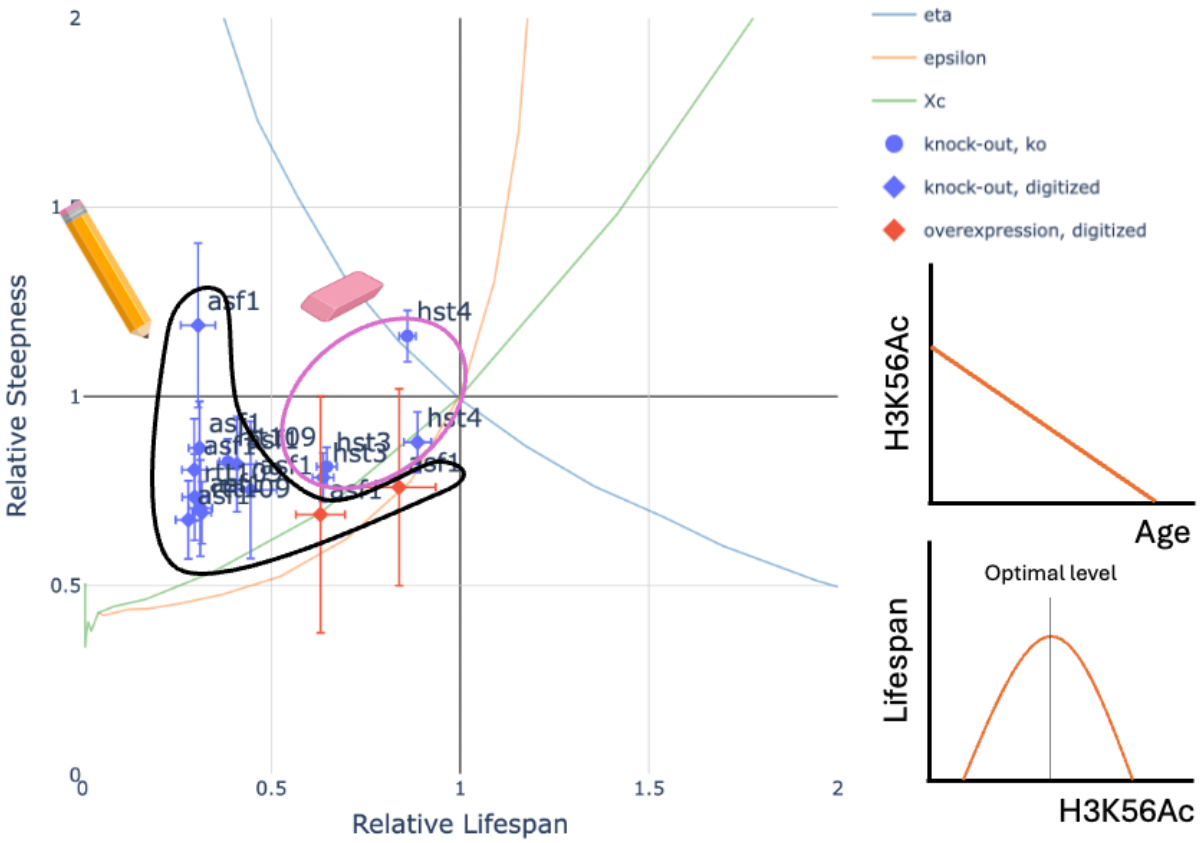
The main role of cholesteryl ester transfer protein(CETP) is the transfer of cholesteryl esters and triglycerides between high-density lipoprotein (HDL) particles and triglyceride-rich lipoprotein and low-density lipoprotein (LDL) particles. There is a long history of investigations regarding the inhibition of CETP as a target for reducing major adverse cardiovascular events. Initially, the potential effect on cardiovascular events of CETP inhibitors was hypothesized to be mediated by their ability to increase HDL cholesterol, but, based on evidence from anacetrapib and the newest CETP inhibitor, obicetrapib, it is now understood to be primarily due to reducing LDL cholesterol and apolipoprotein B. Nevertheless, evidence is also mounting that other roles of HDL, including its promotion of cholesterol efflux, as well as its apolipoprotein composition and anti-inflammatory, anti-oxidative, and anti-diabetic properties, may play important roles in several diseases beyond cardiovascular disease, including, but not limited to, Alzheimer's disease, diabetes, and sepsis. F

Pathways of aging in *Saccharomyces cerevisiae* replicative lifespan

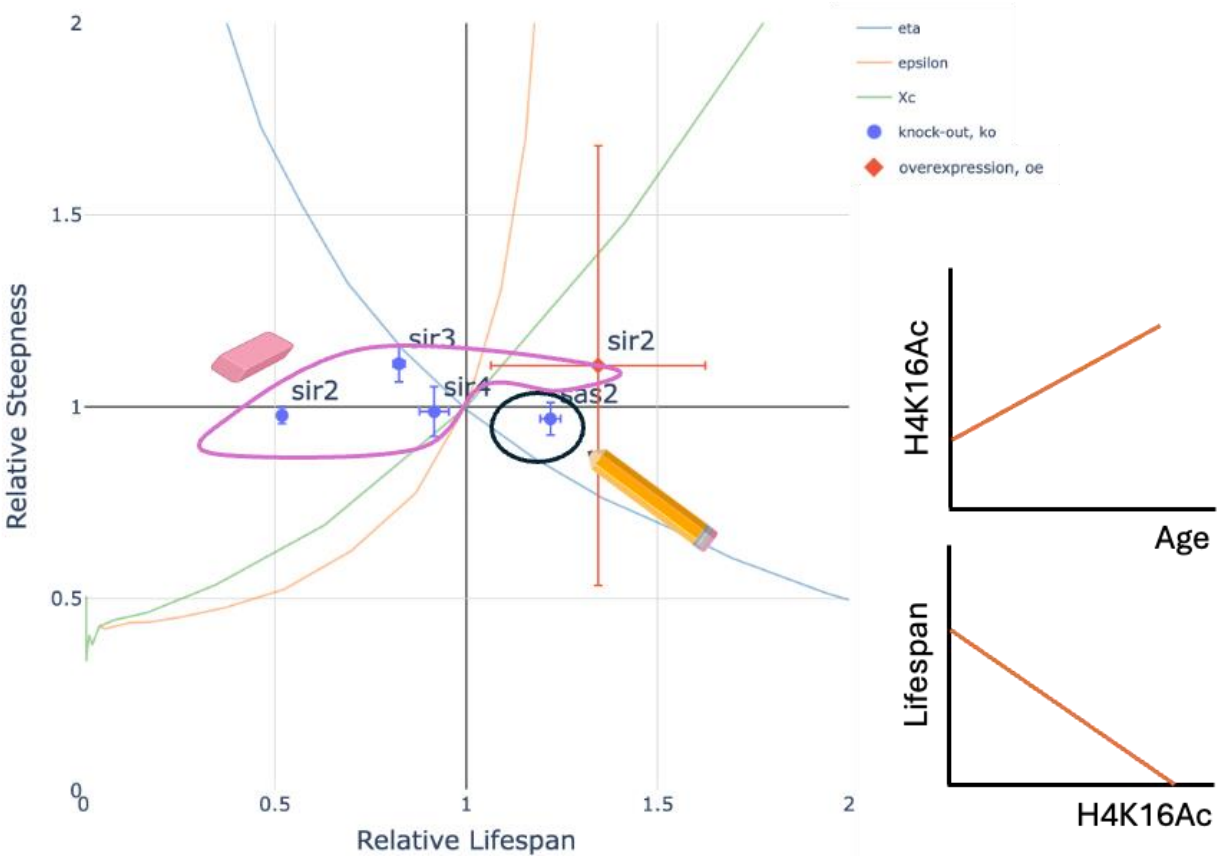
H3K56 and H4K16 acetylations on histones open telomeric chromatin. This enables transcription of telomeric DNA and R-loop formation


Writers
Asf1
Rtt109
Erasers
Hst3
Hst4
K56Ac
Writer
Sas2
Eraser
Sir2
K16Ac
H3
H4
H2A
H2B
Telosome
(shelterin)

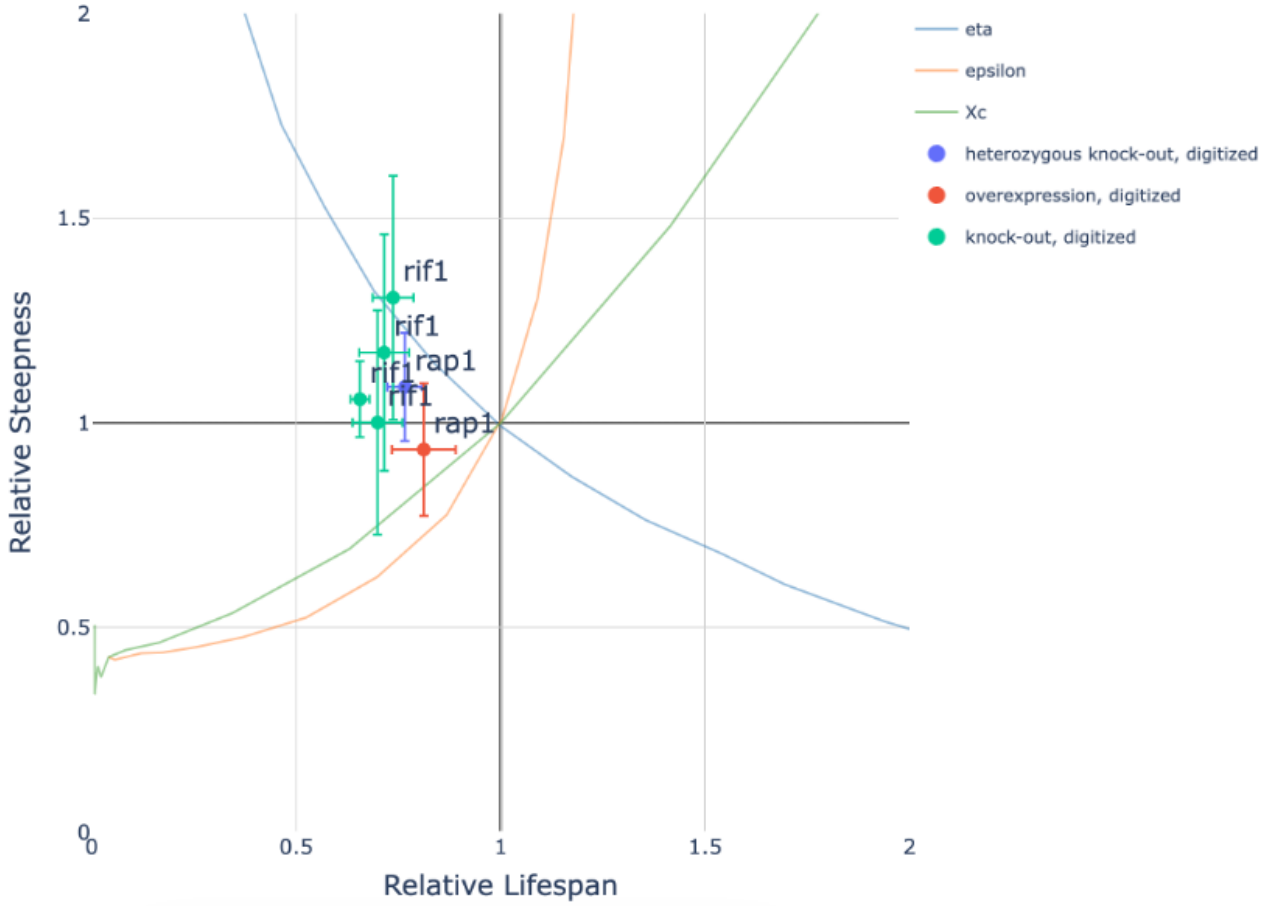
Altering H3K56 acetylation reduces lifespan

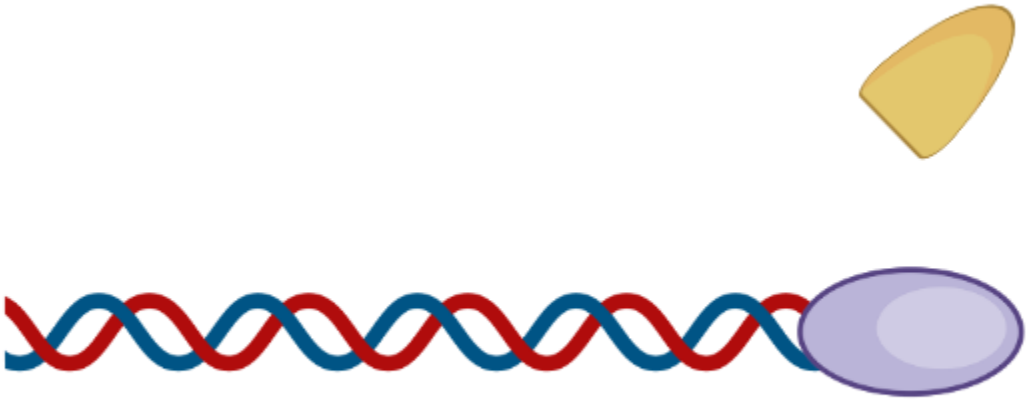


Reducing H4K16 acetylation increases lifespan

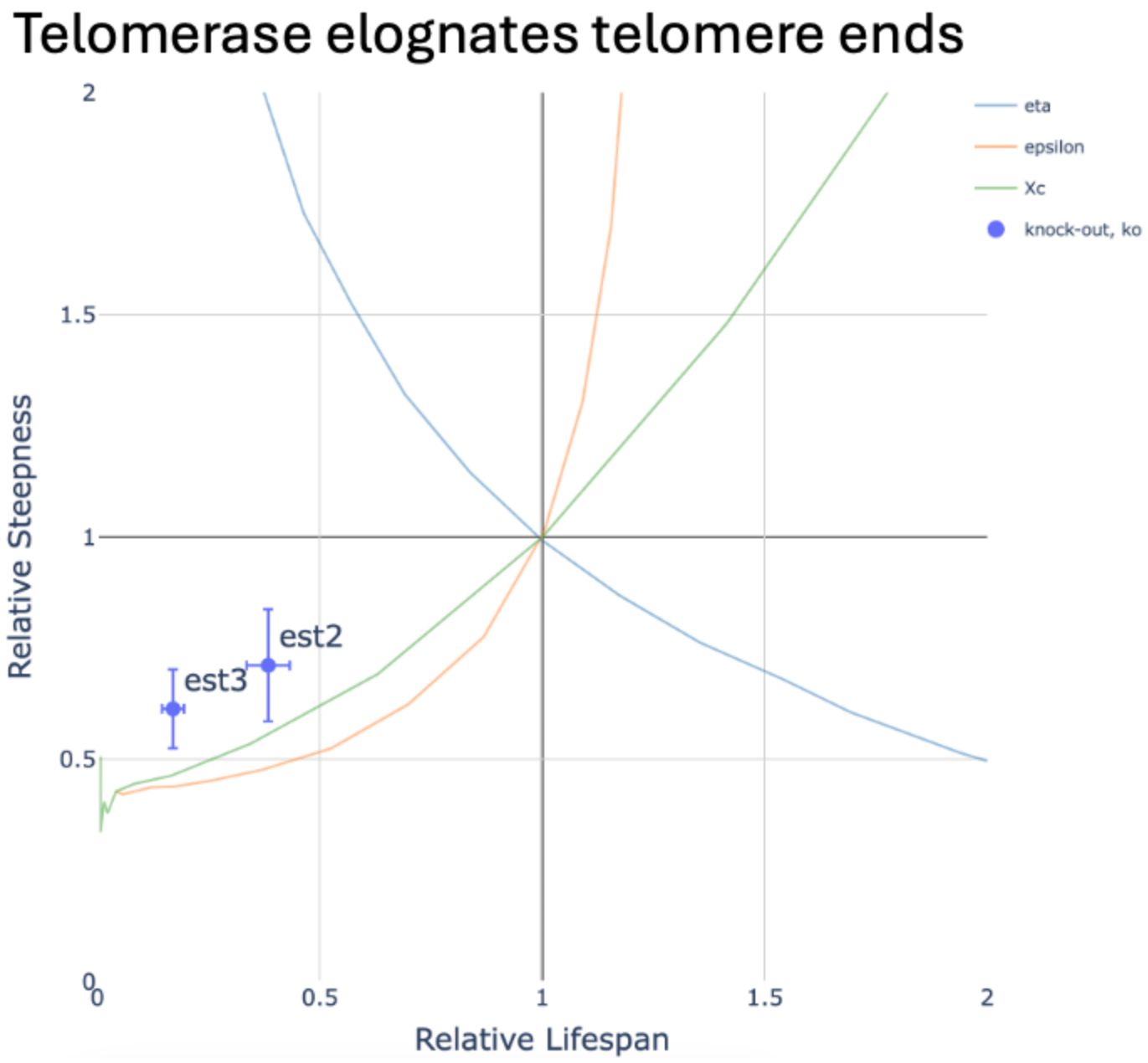


Telosome (shelterin) is a protective cap at the end of telomeres

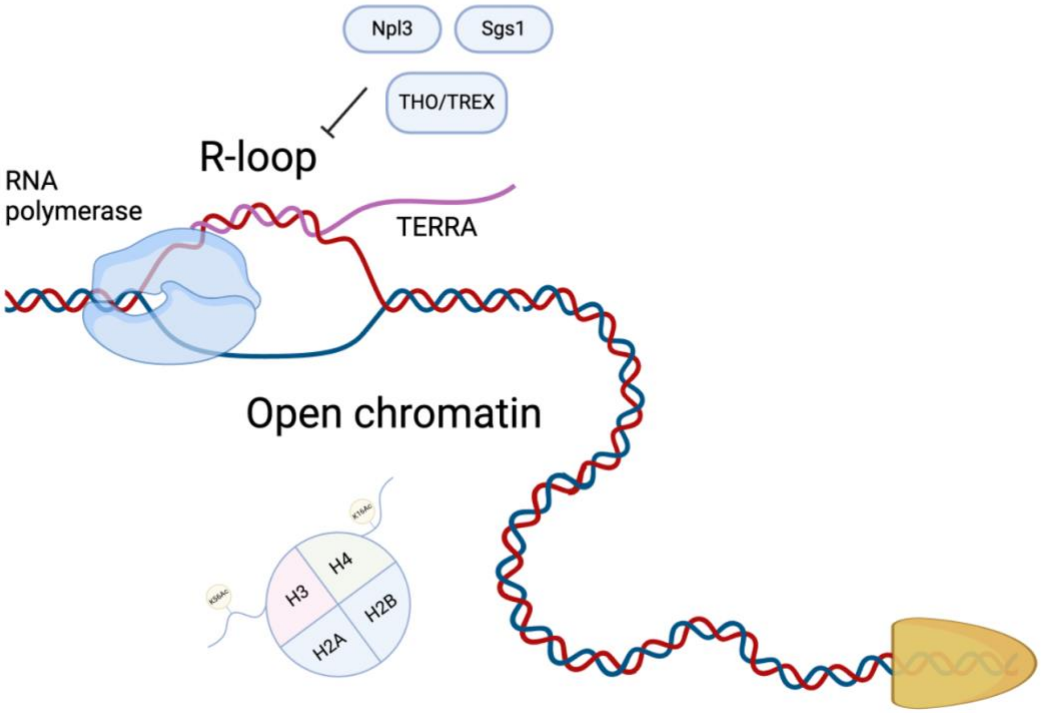




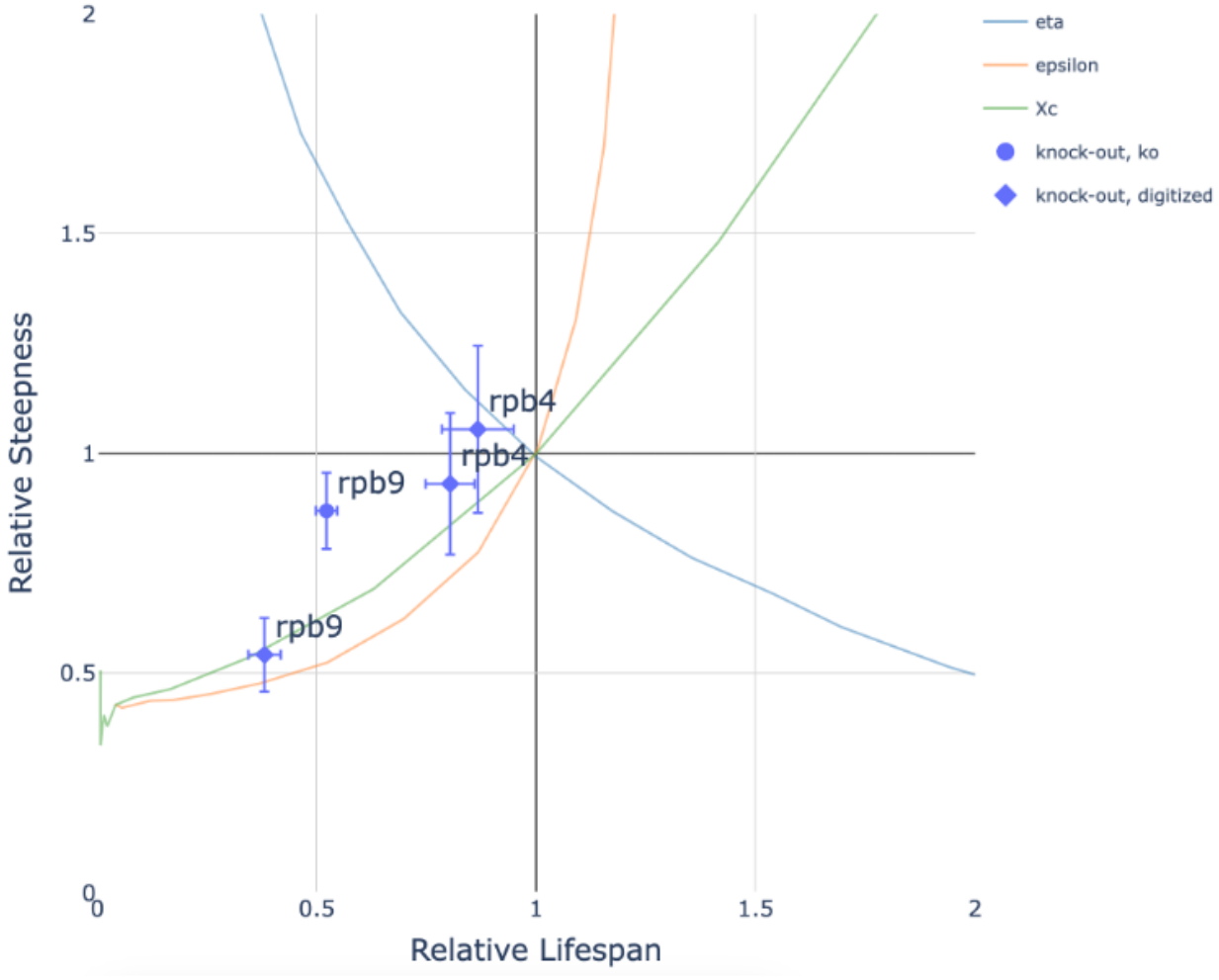
Telomerase

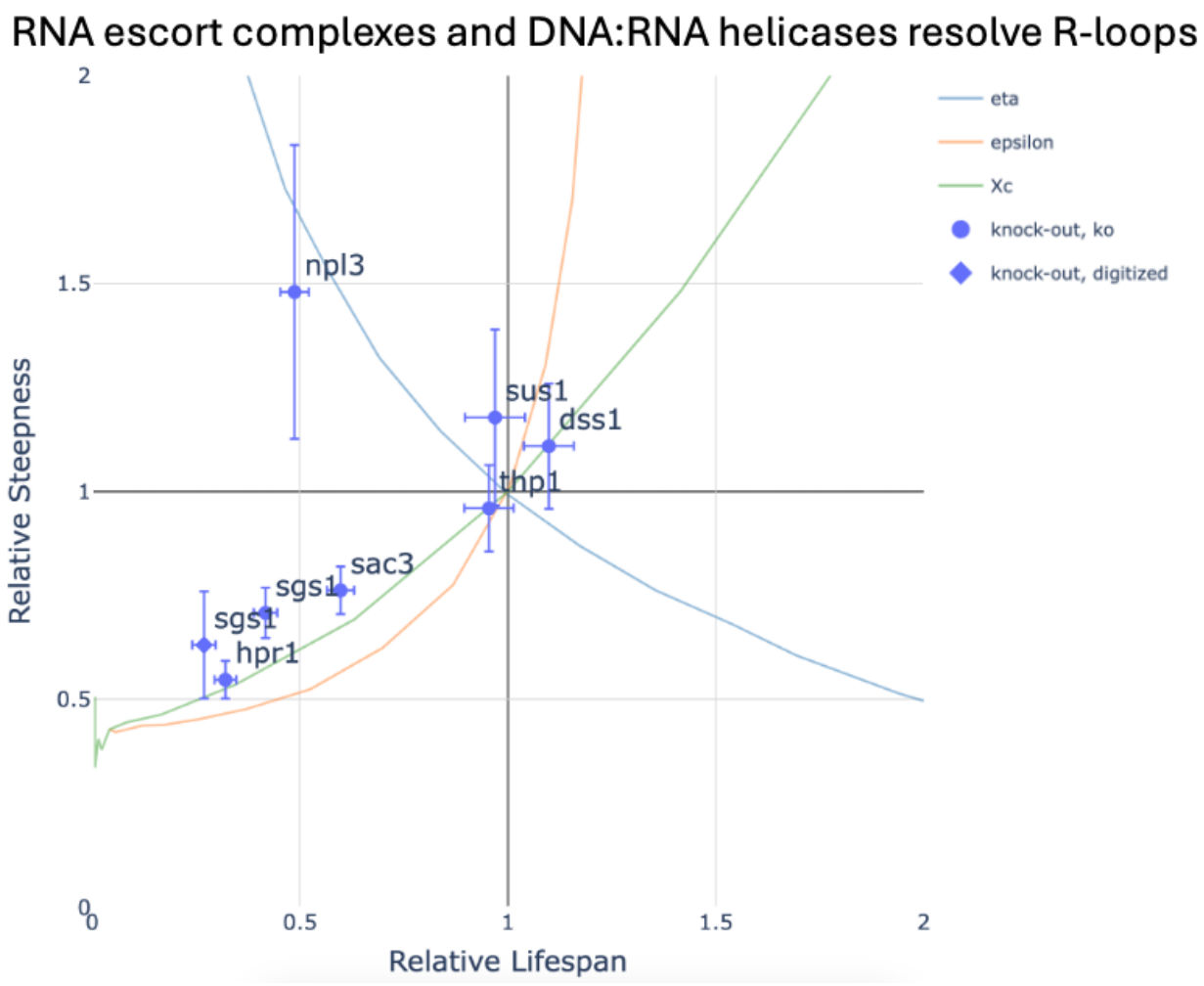


Active replication machineries collide with telomeric R-loops

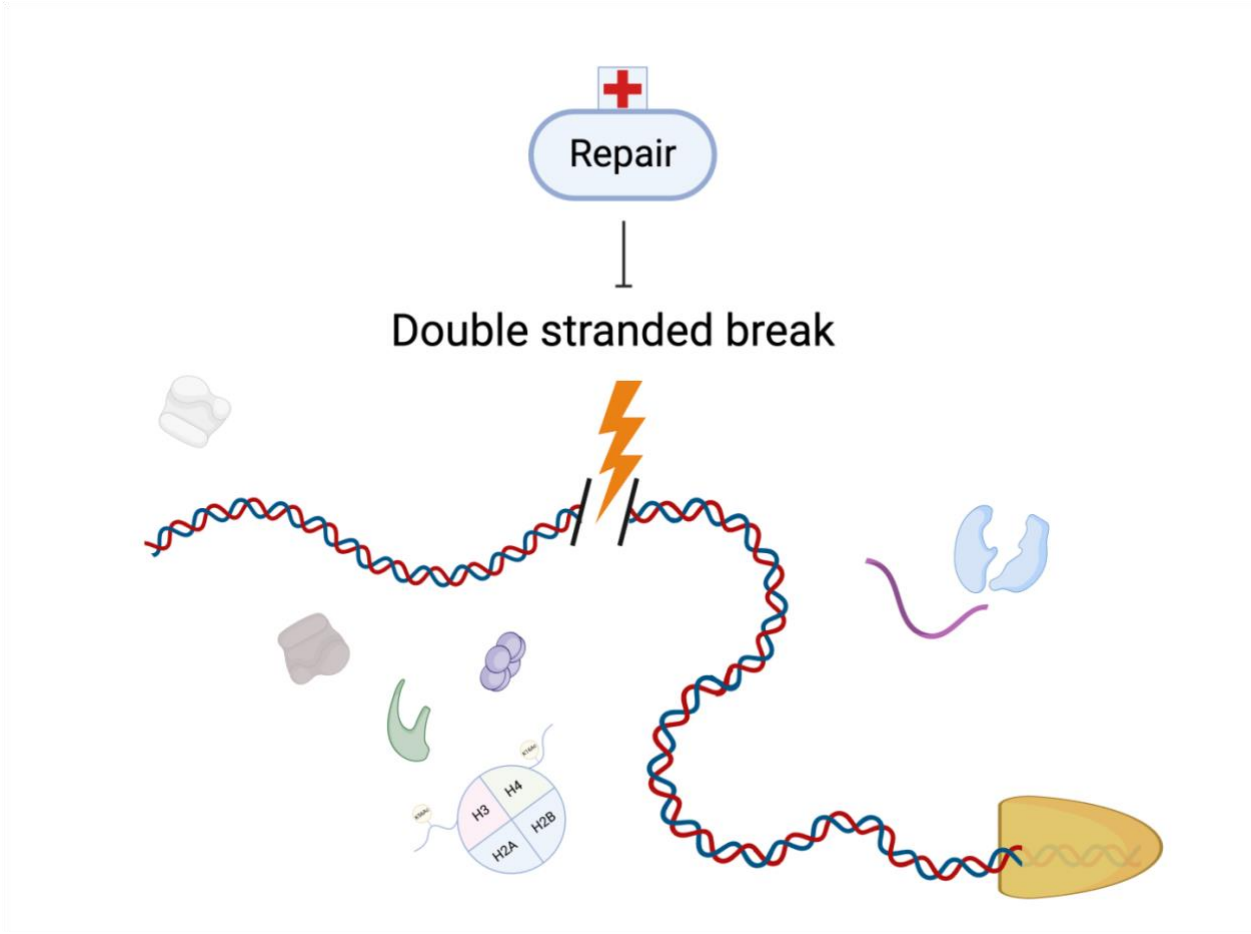

Npl3
Sgs1
THO/TREX
R-loop
RNA
polymerase
TERRA
Open chromatin
H4
H3
H2B
H2A

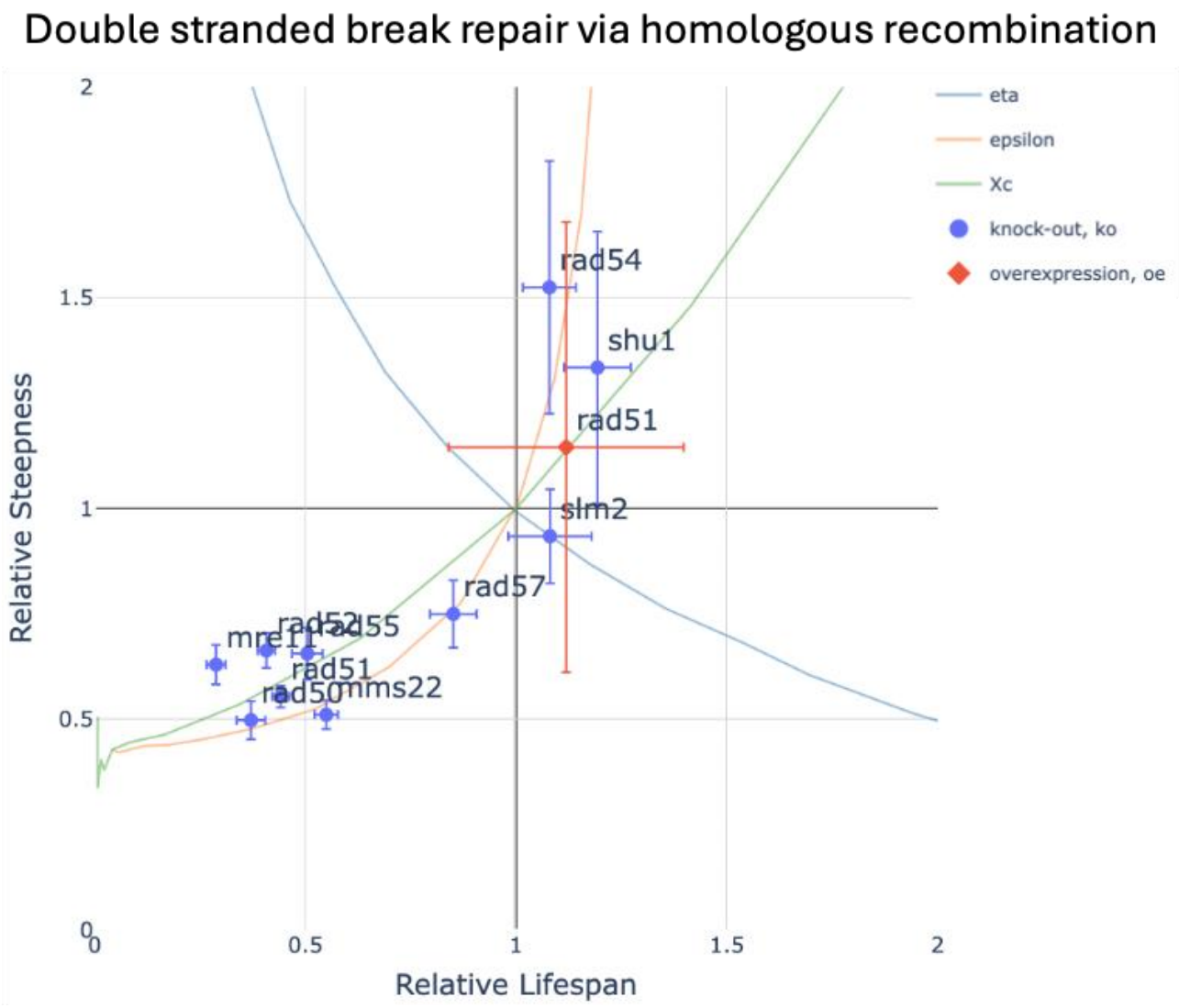
RNA polymerase transcribes RNA from accesible DNA



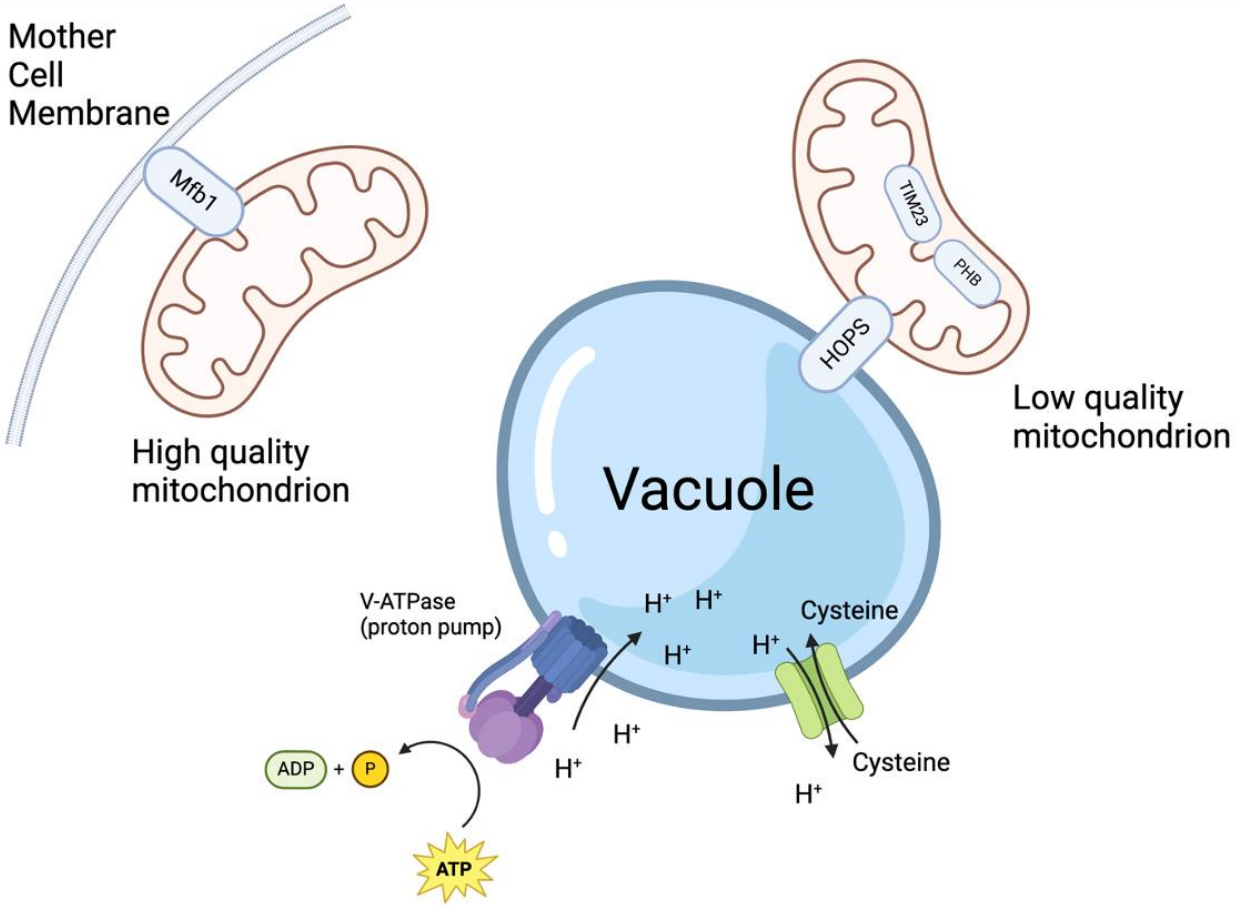


Collision of replication and transcription induces double-stranded breaks

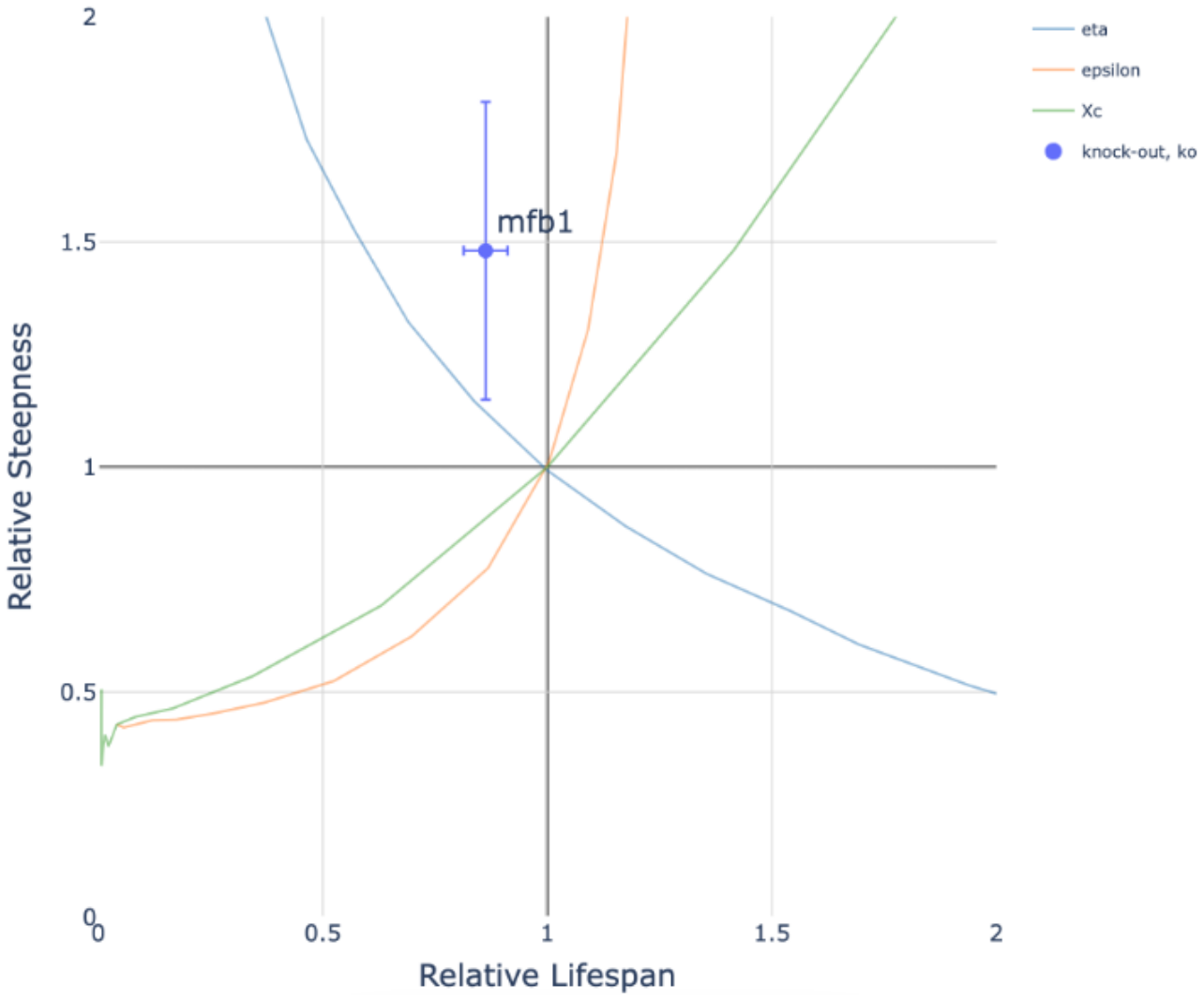

Repair
Double stranded break
H3
H4
H2A
H2B



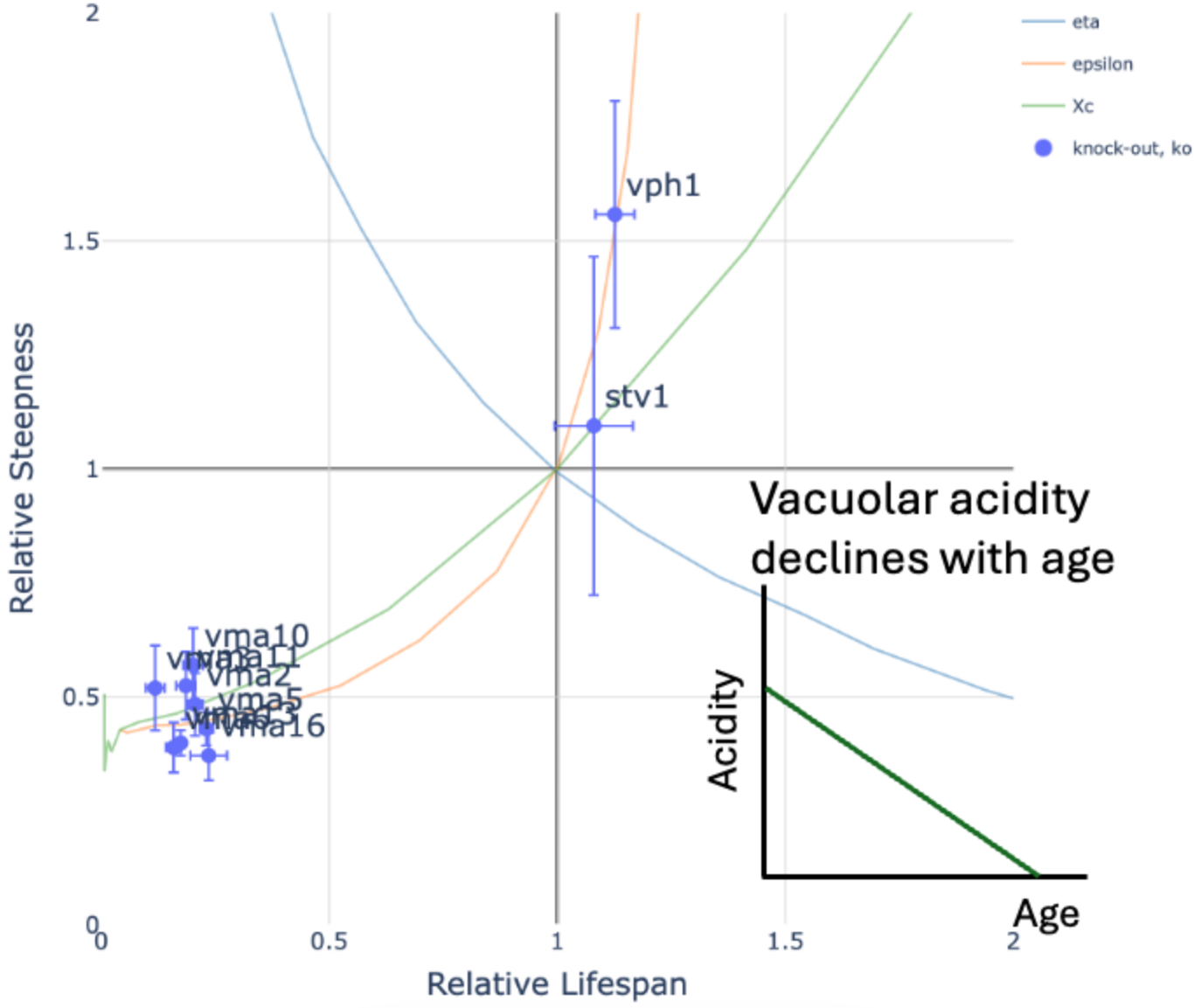
Protein pathway


Mother
Cell
Membrane
Mfb1
High quality
mitochondrion
TIM23
PHB
HOPS
Low quality
mitochondrion
Vacuole
V-ATPase
(proton pump)
H+
H+
H+
H+
H+
H+
Cysteine
H+
Cysteine
H+
ADP
+
P
ATP

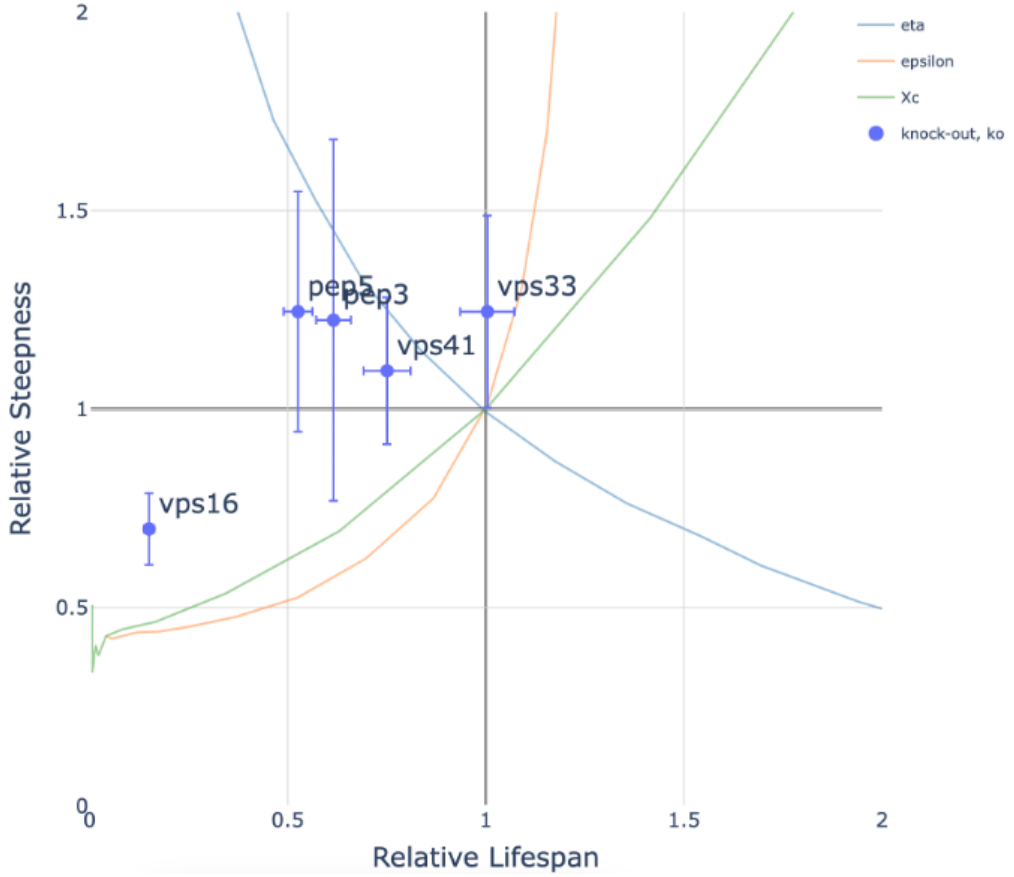
Mfb1 retains high quality mitochondria in the mother

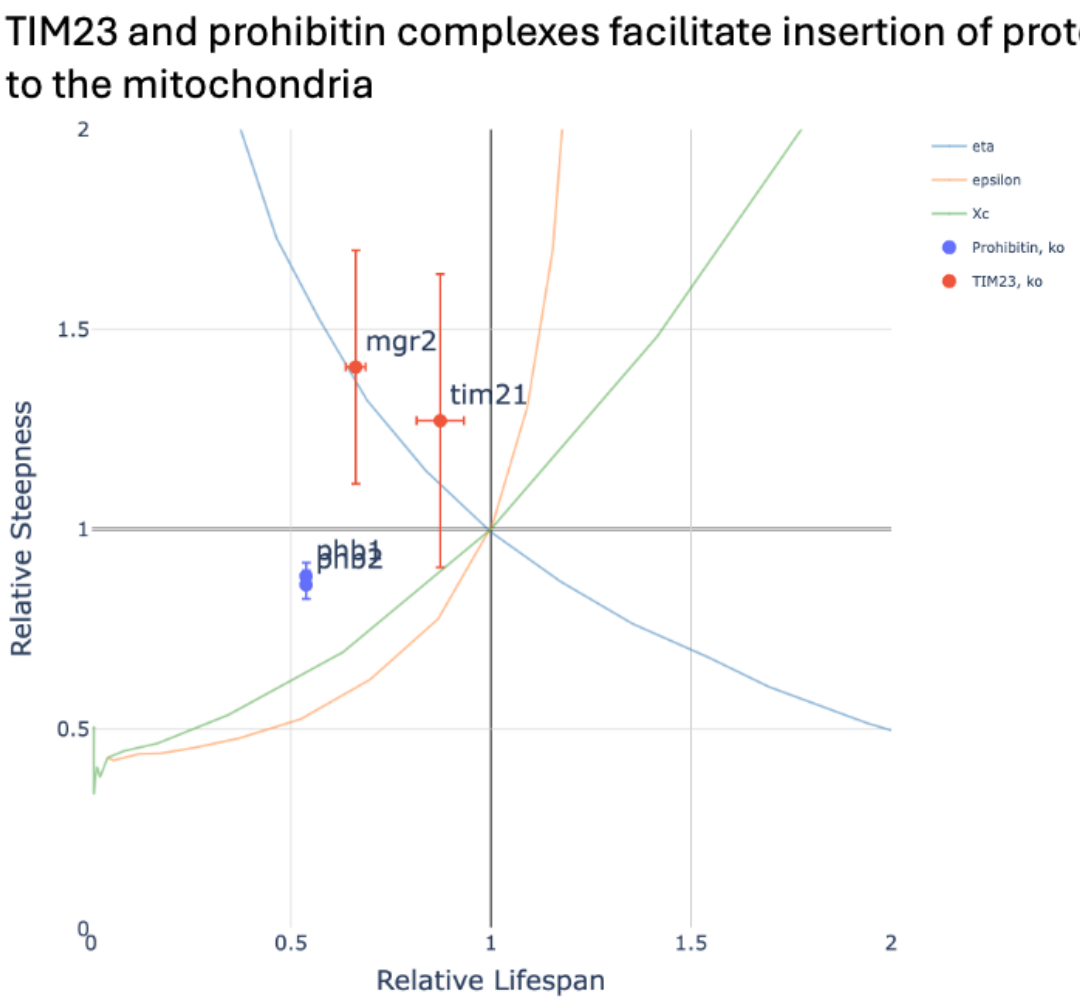


V-ATPase uses ATP to pump protons inside the vacuole



HOPS tethering complex links between the vacuole and mitochondria





Loss of vacuolar acidity triggers release of cysteine to the cytosol. Cytosolic cysteine limits the bioavailability of iron in the mitochondria. Thus, it impairs the function of the electron transport chain, which requires iron-sulfate clusters to function

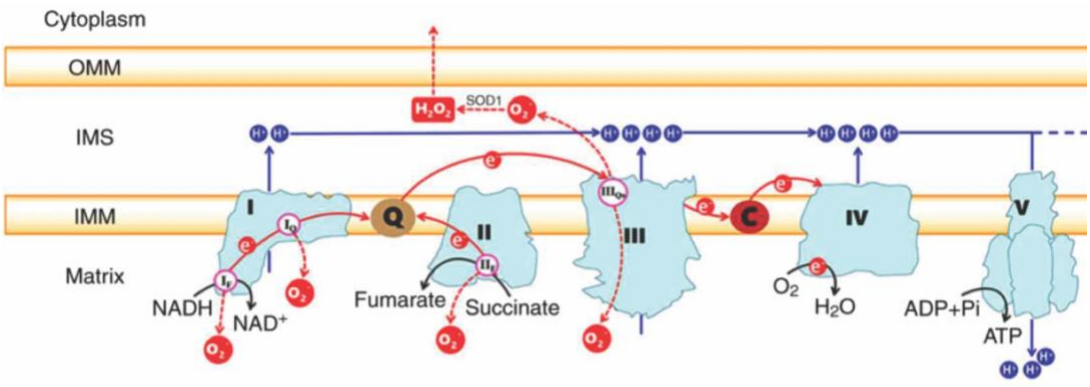
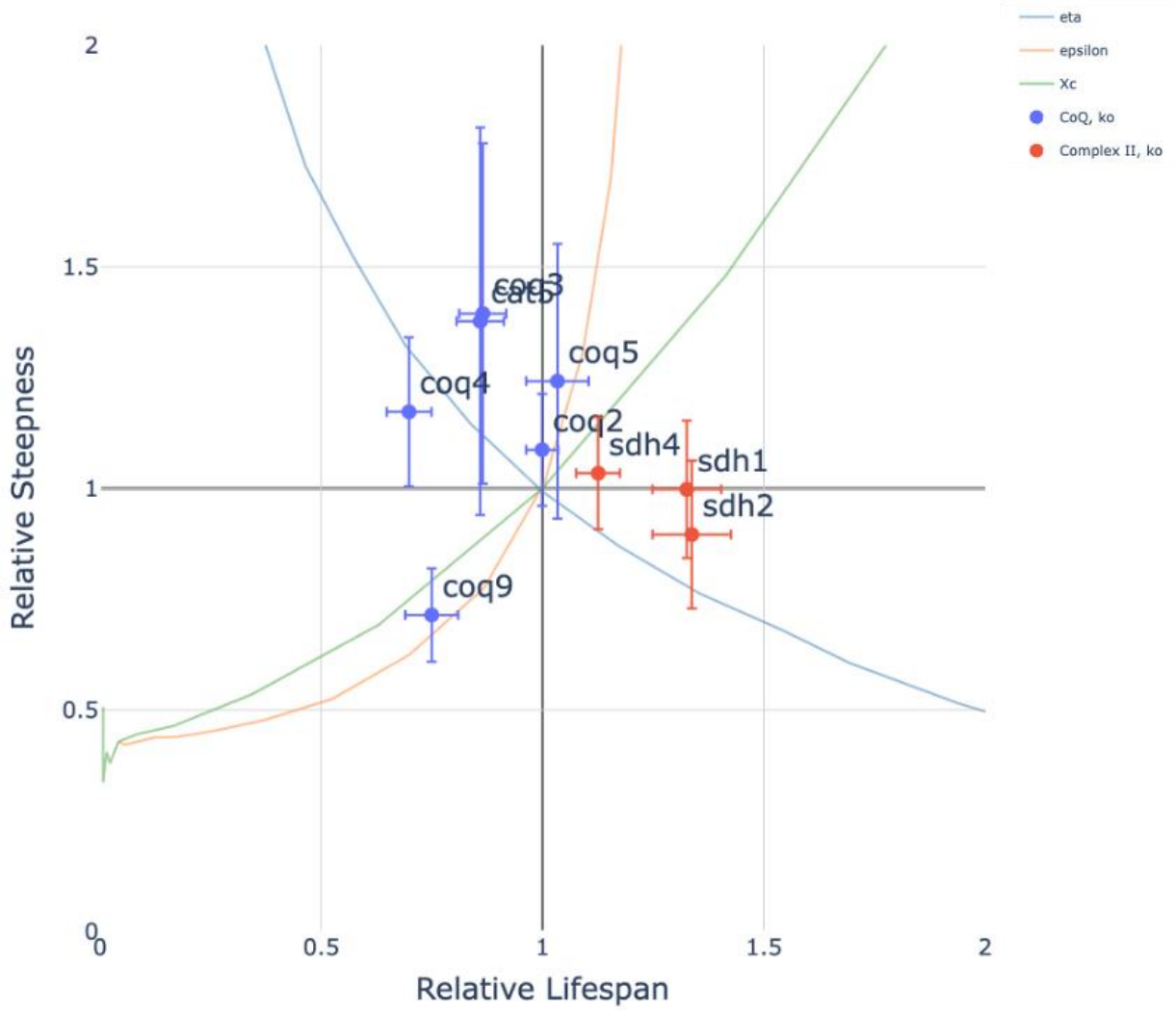
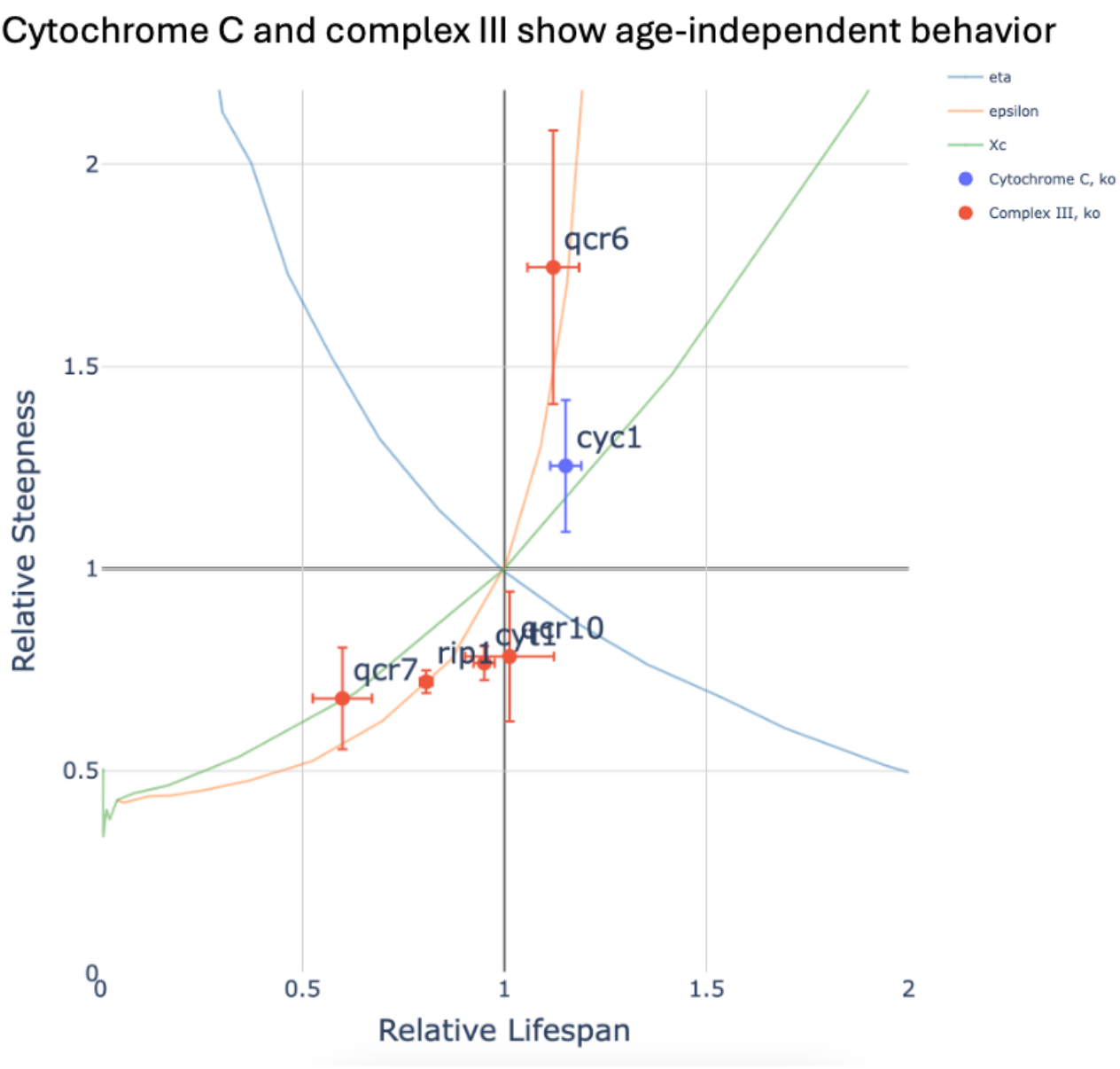


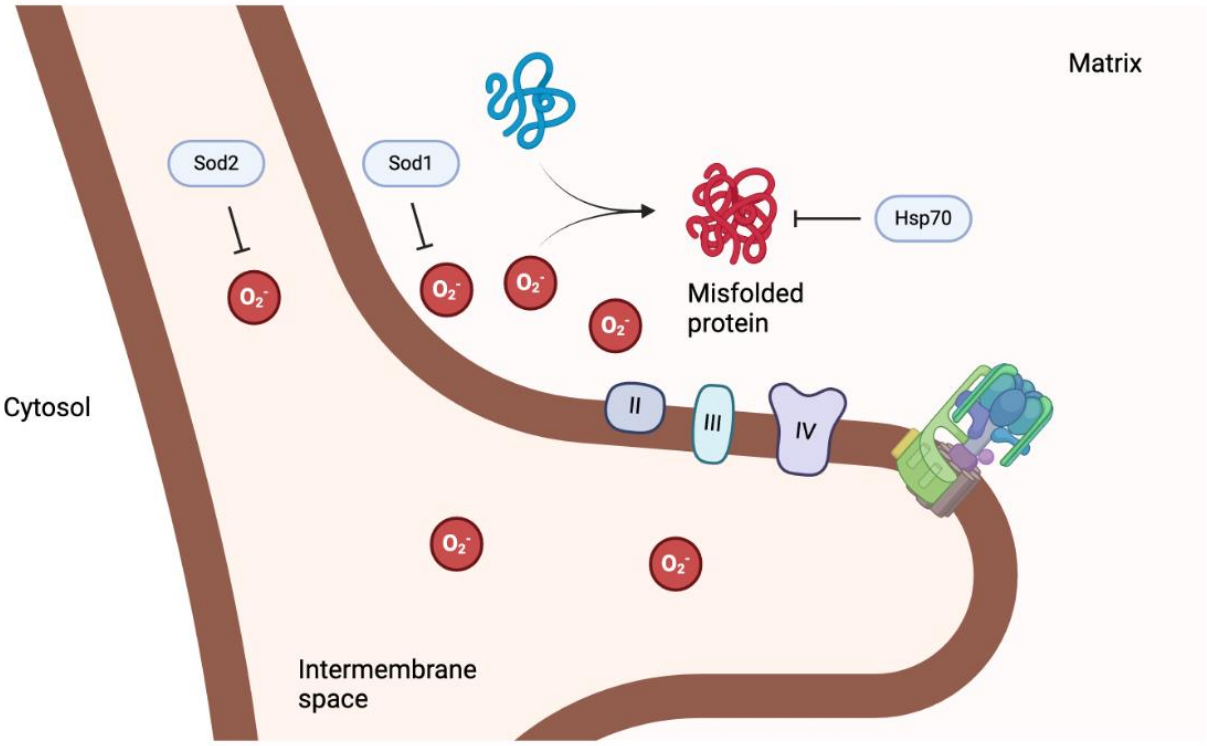
Figure from Ru-Zhou et al., International Journal of Molecular Medicine, 2019

Coenzyme Q and complex II show age-dependent behavior

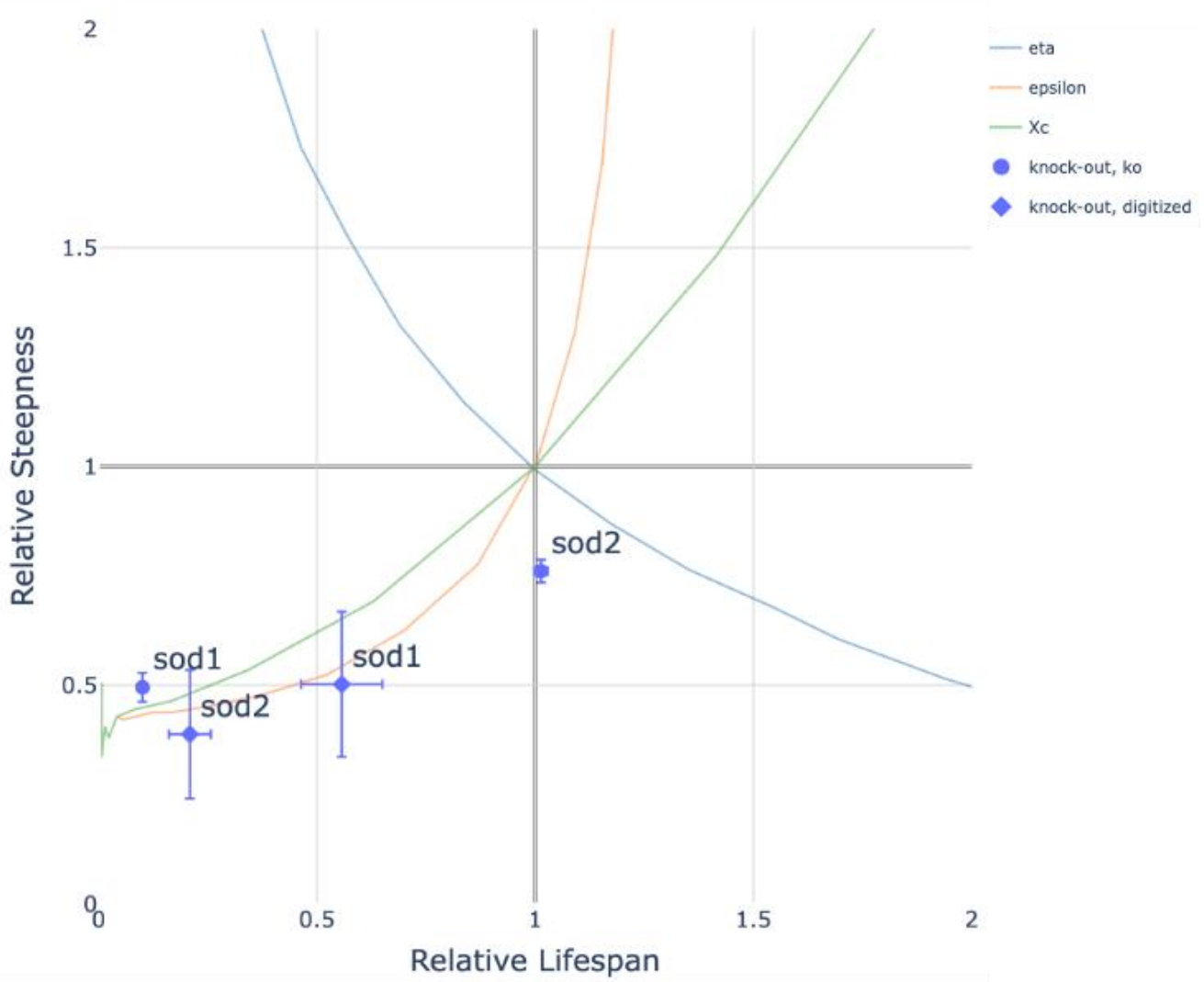




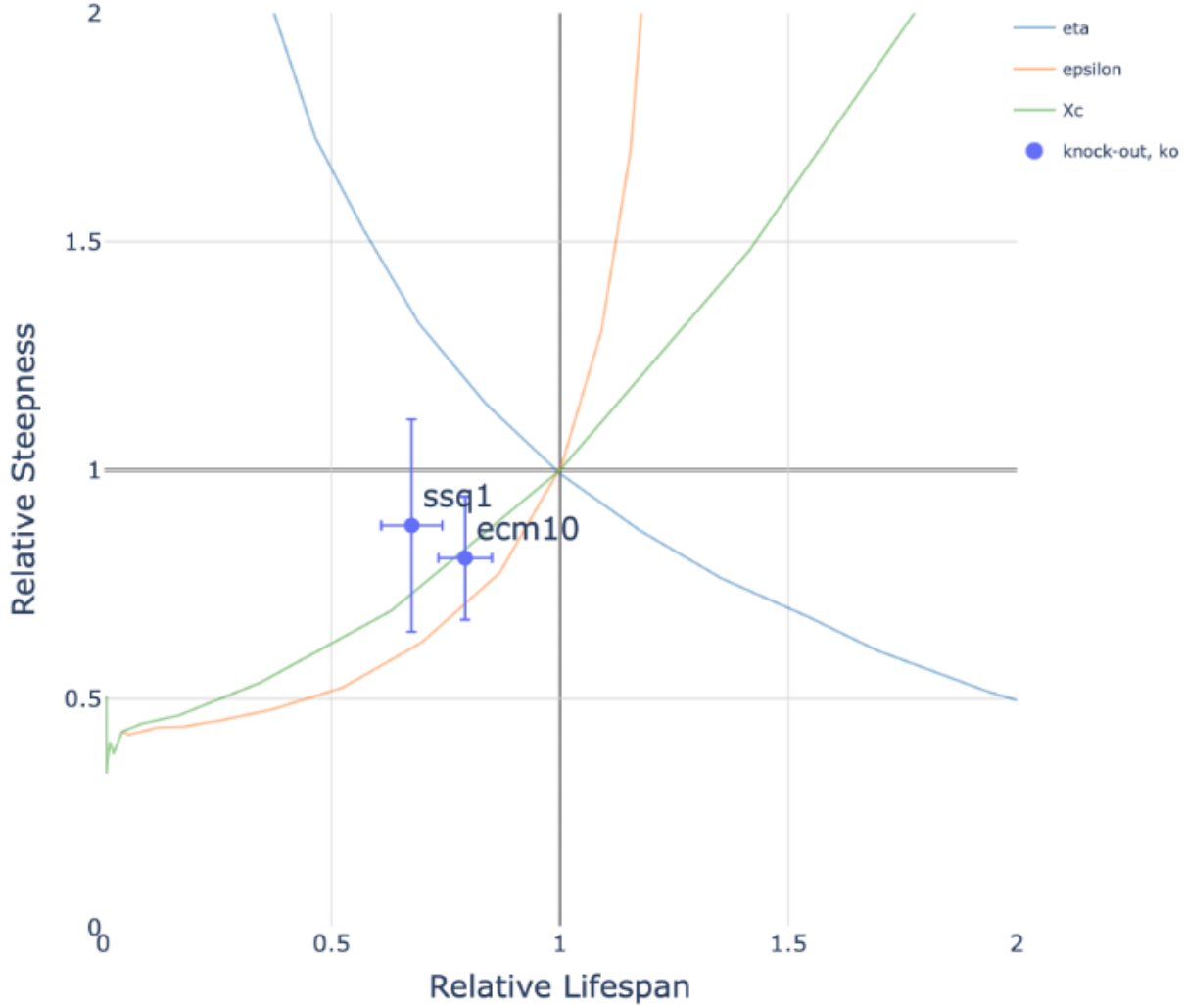
Matrix superoxide rises with age and causes damage to proteins and other components

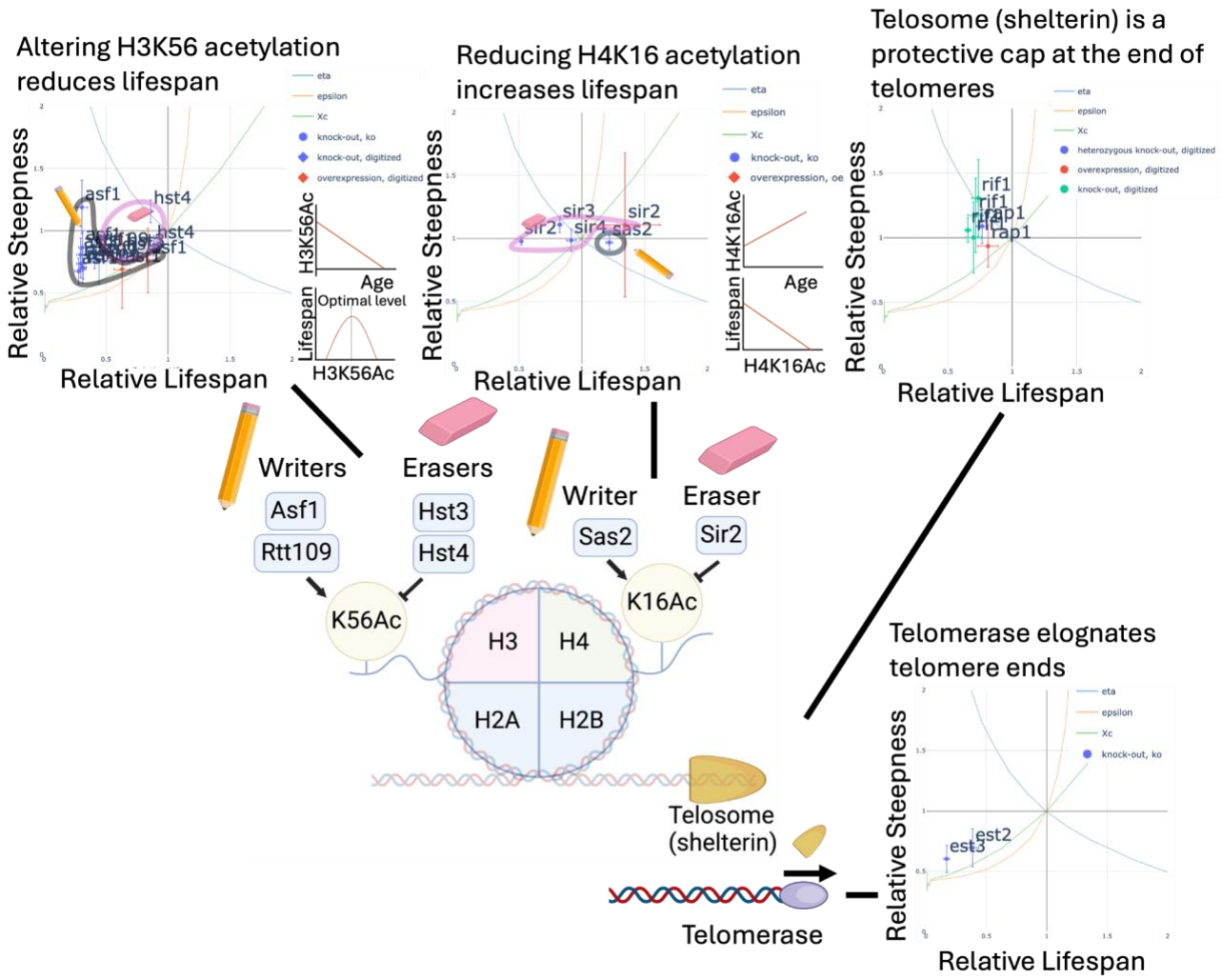

Matrix
Sod2
Sod1
Hsp70
Misfolded protein
Cytosol
II
III
IV
Intermembrane space

Sod genes remove superoxide

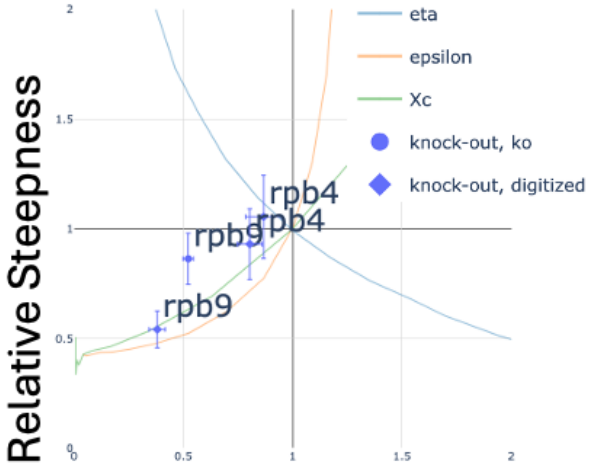


Hsp70 handles misfolded proteins in the mitochondria

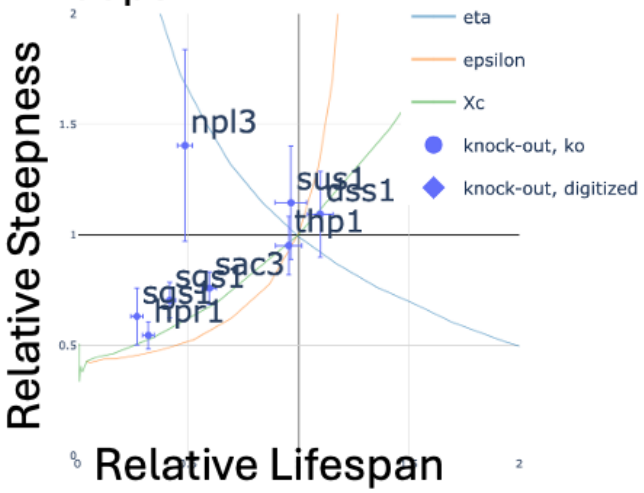



Altering H3K56 acetylation reduces lifespan
Relative Steepness
Relative Lifespan
asf1
hst4
eta
epsilon
Xc
knock-out, ko
knock-out, digitized
overexpression, digitized
H3K56Ac
Age
Optimal level
Lifespan
H3K56Ac
Reducing H4K16 acetylation increases lifespan
sir3
sir2
sir4
sas2
knock-out, ko
overexpression, oe
H4K16Ac
Age
Lifespan
H4K16Ac
Telosome (shelterin) is a protective cap at the end of telomeres
rif1
rif1
rap1
rap1
heterozygous knock-out, digitized
overexpression, digitized
knock-out, digitized
Writers
Asf1
Rtt109
Erasers
Hst3
Hst4
Writer
Sas2
Eraser
Sir2
K56Ac
K16Ac
H3
H4
H2A
H2B
Telosome (shelterin)
Telomerase
Telomerase elognates telomere ends
est3
est2
knock-out, ko

RNA polymerase transcribes RNA from accesible DNA

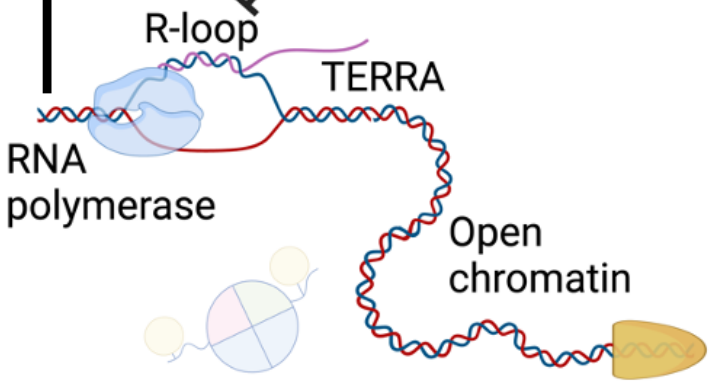


RNA escort complexes and DNA:RNA helicases resolve R-loops

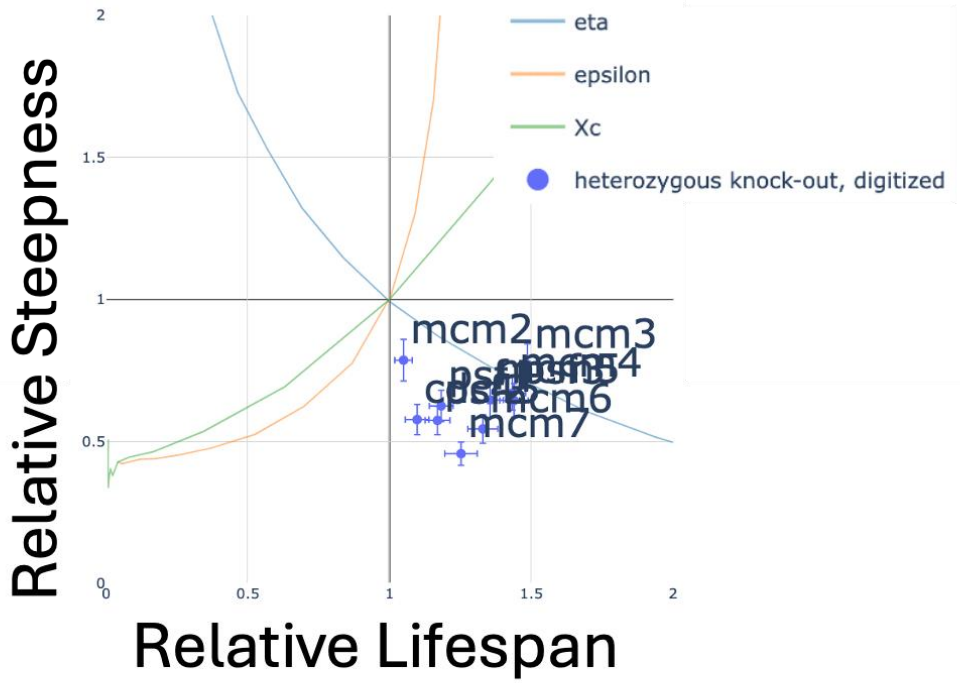


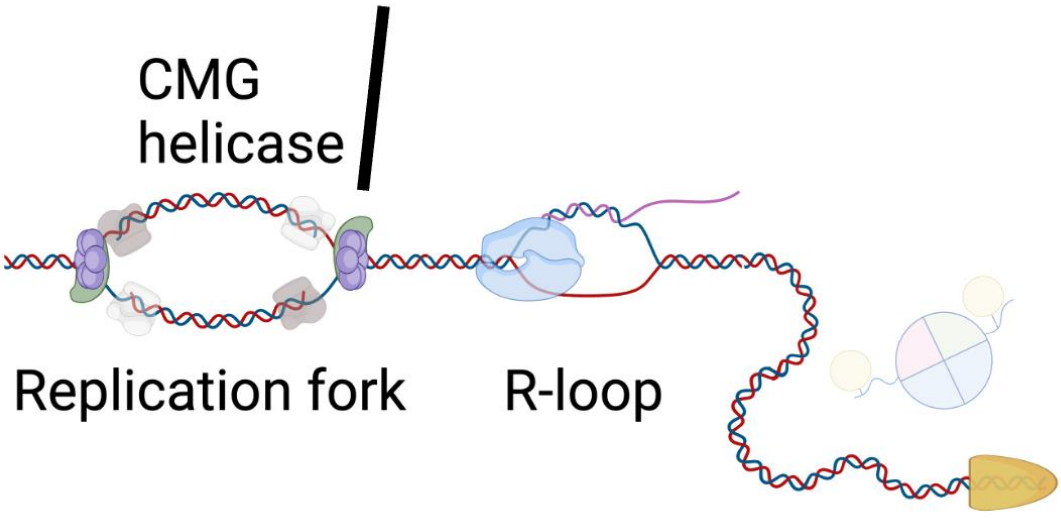
Npl3 Sgs1 = Werner & Bloom Syndromes

THO/TREX

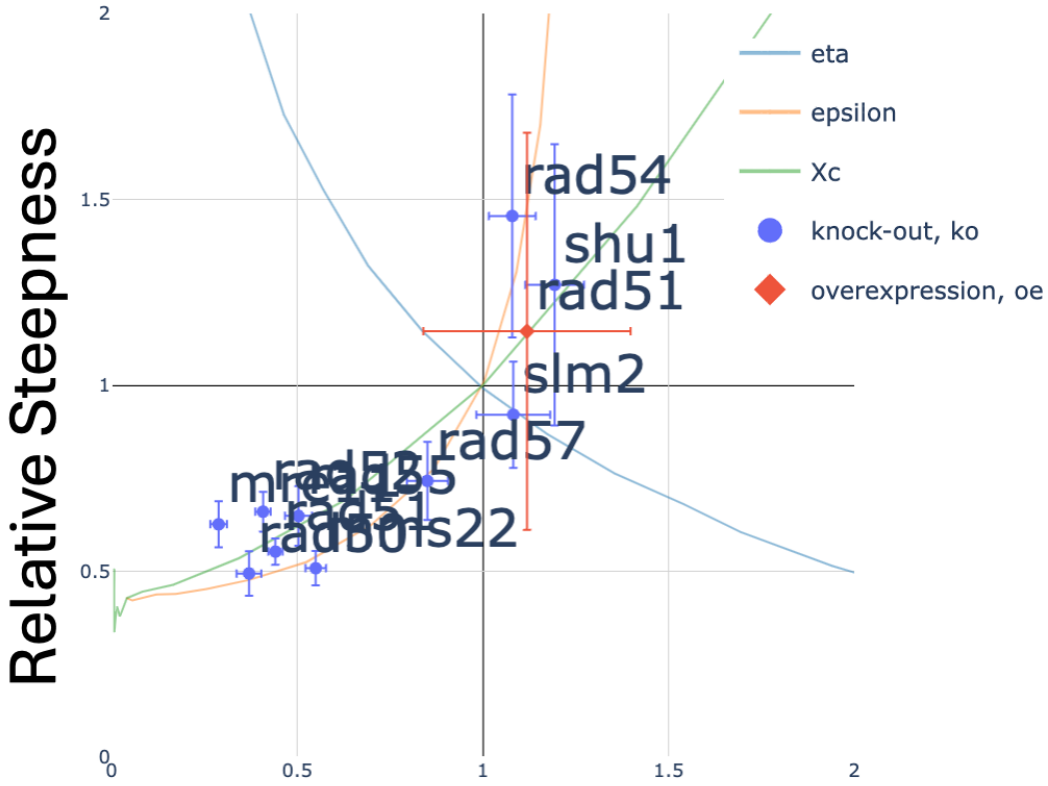


CMG helicase complex unwinds DNA double helix during replication



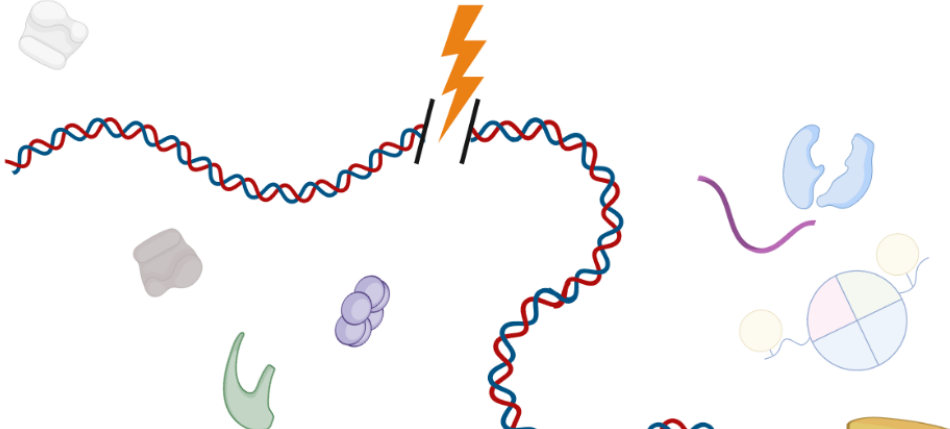


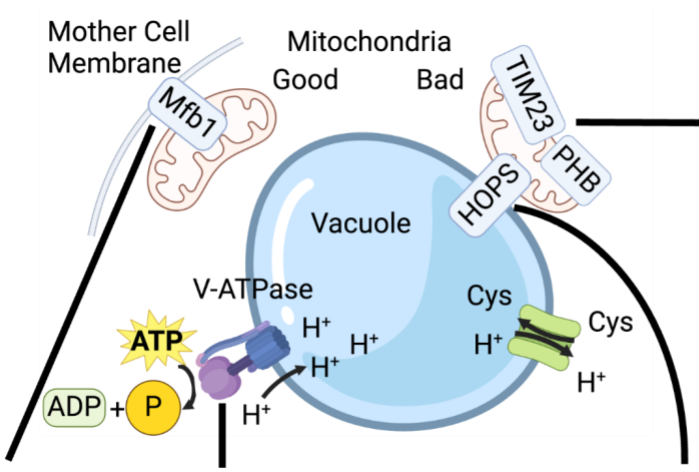
Double stranded break repair via homologous recombination



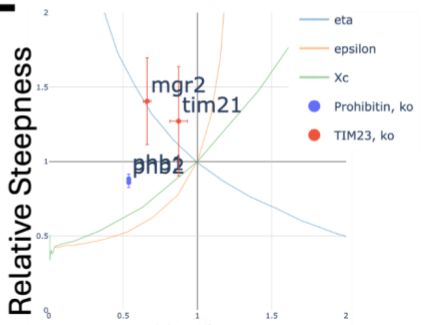
Repair

Double stranded break

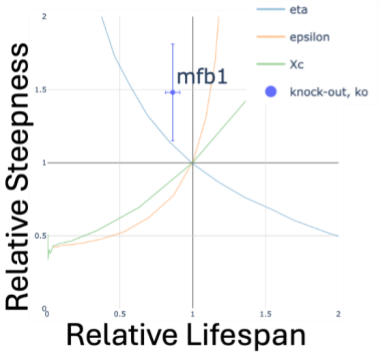




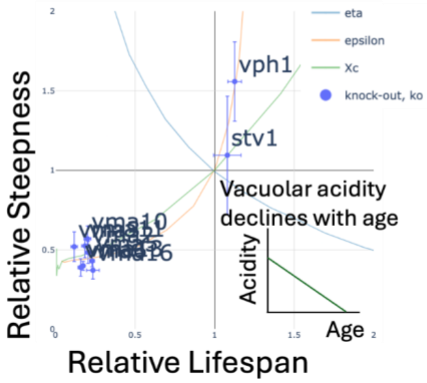
TIM23 and prohibitin complexes insert proteins to the mitochondria



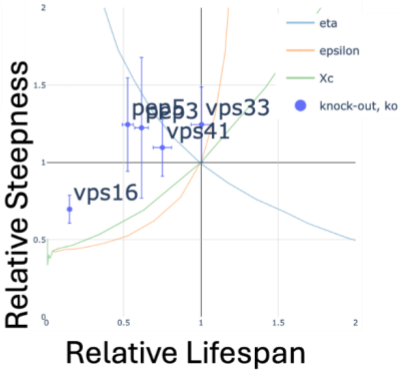
Mfb1 retains high quality mitochondria in the mother



V-ATPase uses ATP to pump protons inside the vacuole



HOPS tethering complex links between the vacuole and mitochondria



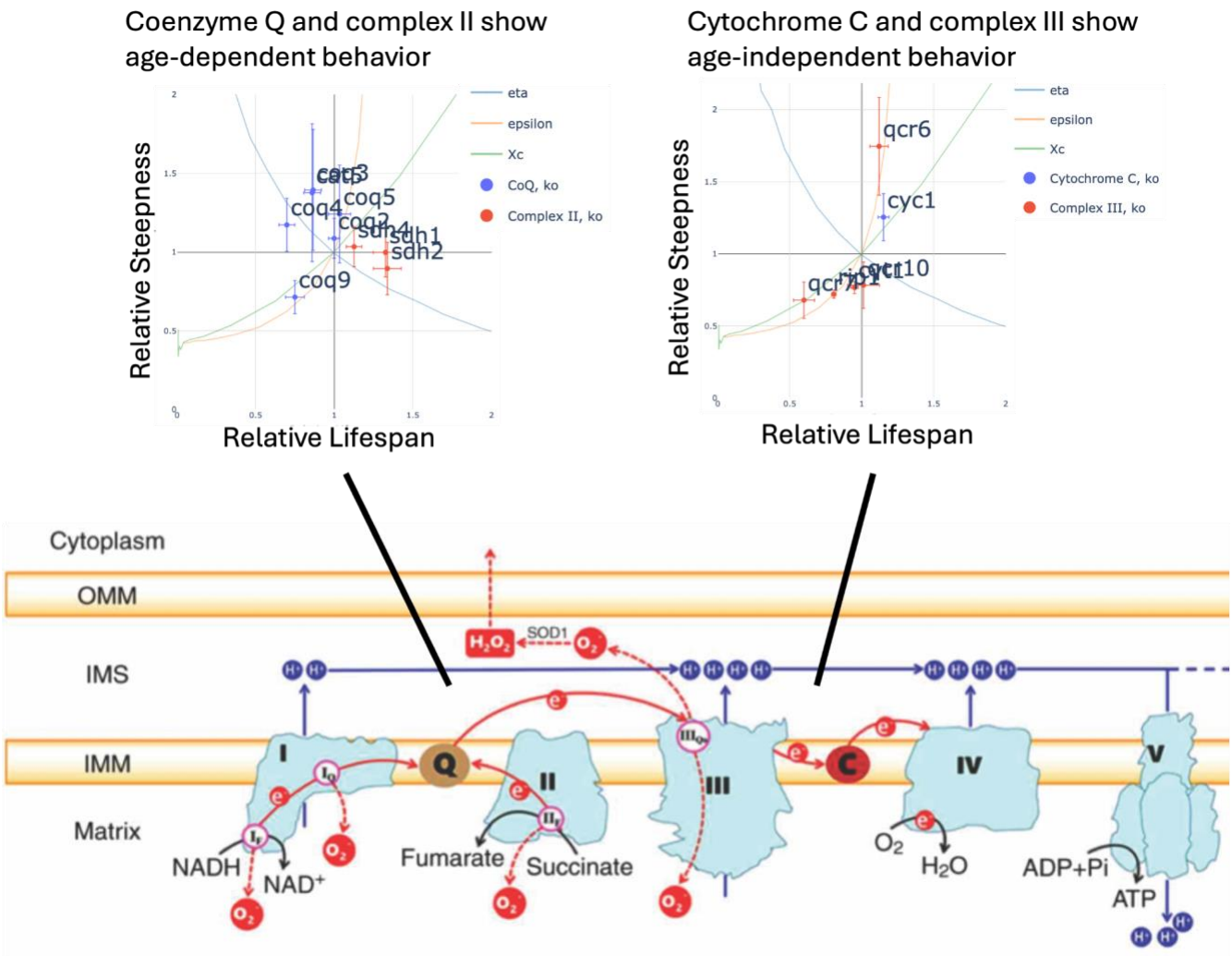


Figure from Ru-Zhou et al., Int. J. Mol. Med., 2019

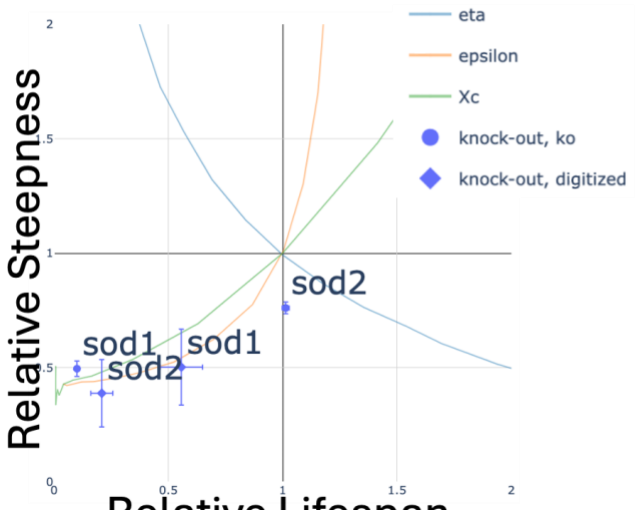
Yves Barre- disrupting complex 3 will generate ros. It's xc so ros is part of damage .

Cokayne syndrome shows disrupted transcription coupled nuclear excision DNA repair

Cockayne syndrome is a rare genetic disorder characterized by premature aging, growth failure, and neurological developmental delays. Individuals with Cockayne syndrome often exhibit short stature, photosensitivity, and a characteristic facial appearance with a small head and jaw. Neurological symptoms include developmental delays, intellectual disabilities, and progressive deterioration of motor skills. Unfortunately, life expectancy is significantly reduced, with many affected individuals not surviving beyond their teenage years.

The cause of Cockayne syndrome is mutations in the ERCC6 or ERCC8 genes. These mutations lead to impaired DNA repair, resulting in cellular damage and premature aging. Cockayne syndrome is inherited in an autosomal recessive manner, meaning that an individual must inherit two copies of the mutated gene, one from each parent, to develop the disorder.

Sod genes remove superoxide



Hsp70 handles misfolded proteins in the mitochondria