Notes on "Lifespan: Why We Age and Why We Don't Have To by David A. Sinclair, PhD, with Matthew D. LaPlante"

Patrick Yin

July 21, 2021

1 Summary

In this book, Sinclair often refers to personal stories of his family and colleagues. He also provides rich historical context for the many topics that he discusses. I will be leaving these things out and only summarizing the bare bones essential information.

1.1 Why Do We Age?

1.1.1 Past Theories of Aging

1. **Nuclear DNA Mutations**: One hypothesis for aging is that it is caused by DNA damage and a resulting loss of genetic information. On a similar vein, the Error Catastrophe Hypothesis postulates that mistakes made during the DNA-copying process leads to gene mutations, including those needed to make the proteins that copy DNA. Eventually, more and more of a person's genome will be incorrectly copied. However, this theory is overturned because cloned animals live normal, healthy lifespans. The simplest explanation is that old animals retain all the requisite genetic information to generate an entirely new, healthy animal and that mutations are not the primary cause of aging.

2. **Free-Radicals**: This hypothesis blames aging on unpaired electrons within cells damaging DNA through oxidation, especially in the mitochondria where most free radicals are generated. This theory drives the popularity of antioxidants, which inhibits oxidation in cells produced by free radicals. However, this theory was overturned by scientists more than a decade ago. Research studies involving giving antioxidants to animals have all been disappointing in that antioxidants have not extended the maximum lifespan of animals tested. While free radicals do cause mutations, mutations are in abundance and do not explain aging.

1.1.2 Hallmarks of Aging

Today, researchers in the aging field have began to coalesce around a new model with multiple hallmarks of aging:

- Genomic instability caused by DNA damage
- Attrition of the protective chromosomal endcaps, the telomeres
- Alterations to the epigenome that controls which genes are turned on and off
- Loss of healthy protein maintenance called proteostasis
- Deregulated nutrient sensing caused by metabolic changes
- Mitochondrial dysfunction
- Accumulation of senescent zombielike cells that inflame healthy cells
- Exhaustion of stem cells
- Altered intercellular communication and the production of inflammatory molecules

1.1.3 Epigenetics

There are two types of information in biology: digital genetic information stored as DNA and analog epigenetic information stored in the chromatin. The epigenome consists of strands of DNA wrapped around spooling proteins called histones, which are bound up into bigger loops called chromatin, which are bound up in bigger loops called chromosomes. While all newly divided cells have the same genetic information, the epigenome instructs the cells what type of cell they should be (e.g. neuron or kidney cell).

1.1.4 Longevity Genes

Much research has been on "longevity genes" which demonstrate the ability to extend both the average and maximum lifespans of many organisms.

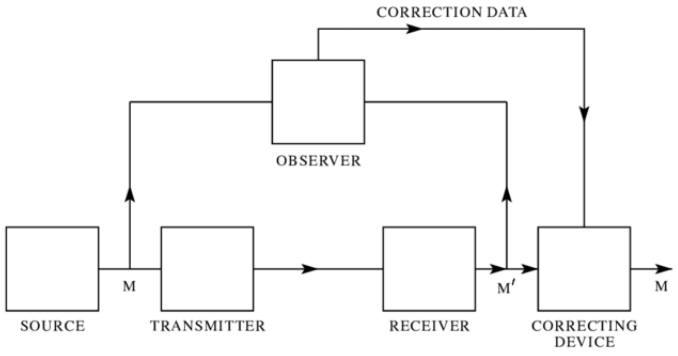
Sirtuins Sirtuins are enzymes that remove acetyl tags from histones and other proteins, which change the packaging of the DNA, turning genes off and on when needed. They tradeoff reproduction for repair and order our bodies to buckle down in times of stress and protect us against the major diseases of aging. They have evolved to require nicotinamide adenine dinucleotide (NAD), which decline with age. Sirtuins instruct the histone spooling proteins to bind up DNA tightly so that some genes stay silent while others can be accessed by DNA-binding transcription factors that turn genes on. Silent genes are in heterochromatin while accessible genes are in euchromatin.

Target of Rapamycin (TOR) TOR is a complex of proteins that regulates growth and metabolism. Called mTOR in mammals, they signal cells in stress to hunker down and improve survival by boosting DNA repair, reducing inflammation caused by senescent cells, and digesting old proteins.

AMPK AMPK is a metabolic control enzyme which evolved to respond to low energy levels.

1.1.5 The Information Theory of Aging

Despite all the hallmarks of aging, Sinclair believes there is a singular reason why we age: loss of epigenetic information. Epigenetic noise, Sinclair believes, is the root cause for all the hallmarks of aging. Sinclair's hypothesized universal model of life and death looks like this: Youth $\rightarrow$ broken DNA $\rightarrow$ genome instability $\rightarrow$ disruption of epigenome (i.e. packaging and gene regulation) $\rightarrow$ loss of cell identity $\rightarrow$ cellular senescence $\rightarrow$ disease $\rightarrow$ death. Wherever epigenetic factors (e.g. sirtuins) leave the genome to address DNA damage (e.g. radiation), the genes the should be off switch on and vice versa. Furthermore, wherever they stop on the genome, they must do the same and alter the epigenome. As a result, cells lose their identity, malfunction, and the chaos materializes as aging. In other words, aging is caused by overworked epigenetic signalers responding to cellular insult and damage. Sinclair proceeds to back this theory up with research done on mice and yeast. To summarize, Sinclair's Information Theory of Aging parallels Shannon's Mathematical Theory of Communication:



Here, the source of the information is the egg and sperm. The transmitter is the epigenome, transmitting analog information through space and time. The receiver is your body in the future. In order to "reverse" or "stop" aging, we need to restore the signal with an observer who records the original data, the original corrected data, and a correcting device to restore the original signal. This will be discussed in a later section called Yamanaka factors.

1.2 Aging is a Disease

Sinclair argues that trying to treat each individual disease (e.g. cancer, heart disease, etc.) separately is whack-a-mole medicine because surviving cancer or heart disease doesn't substantially increase the average human lifespan. This is because developing lethal diseases increases exponentially as we get older, so preventing one disease makes little difference. Instead, we should treat aging as a disease and try to treat this, which would prevent all these lethal diseases.

1.3 How to Live Longer?

1.3.1 Hormesis

Longevity genes are activated in response to biological stress. Hormesis are stressors that will activate longevity genes without damaging the cell. The little bit of stress that occurs when the genes are activated prompts the rest of the system to hunker down, conserve, and survive a little longer. The intuition here is that high nutrient signaling speeds up the biology clock of protein/lipid/dna damage, so by reducing this, we can slow down the process and thus reduce the degradation of our epigenome.

Calorie restriction (CR) CR without malnutrition has been shown to increase the lifespan of mice and other mammals. The intuition again is that calorie restriction limits nutrient signaling which slows down the normal biology process, leading to less protein/lipid/dna damage, and thus less epigenetic factors leaving the genome and ultimately causing epigenetic noise.

Intermittent Fasting (IF) In one study, participants undergoing IF had reduced body fat, lower blood pressure, and lower levels of a hormone made in the liver called insulin-like growth factor 1 (IGF-1) whose levels are closely linked to longevity.

Less Meat, More Vegetables Studies show heavily animal-based diets are associated with high cardiovascular mortality and cancer risk. Processed red meats are especially carcinogenic. Red meat also contains carnitine, which gut bacteria convert to trimethylamine N-oxide (TMAO), a chemical which is believed to cause heart disease. From a vitality perspective, meat contains all nine of the essential amino acids and a short supply of amino acids engages our survival circuits. Limiting intake of amino acids as well as caloric restriction limits mTOR activation, which forces cells to spend less energy dividing and more energy in the process of autophagy, which recycles damaged and misfolded proteins. We can't live without amino acids, but low levels are these correlate to increased lifespan.

Exercise Exercise raises NAD levels, which activates the survival network. AMPK, mTOR, and sirtuins are all modulated in the right direction by exer-

cise, building new blood vessels, improving heart/lung health, making stronger muscles, and extending telomeres. For example, the hormesis program puts SIRT1 and SIRT6 into action; they help extend telomeres and package them so they are protected from degradation. To engage our longevity genes fully, intensity does matter. You should sweat and be unable to say more than a few words without pausing for breath. This is the hypoxic response, inducing enough stress to activate defnses without permanent harm.

Cold Exposure Brown fat is a mitochondria-rich substance which decreases in amount as we age. Being a bit cold activates the mitochondria in your brown fat, which leads to a boost in sirtuin and thus lower rates of diabetes, obesity, and Alzheimer's disease. Goose bumps, chattering teeth, and shivering arms aren't dangerous conditions, but anything beyond is over the edge. Being hot is still unclear though. In *S. cerevisiae*, raising the temperature of the yeast turns on the PNC1 gene and boosts NAD production, leading to Sir2 proteins working much harder. However, humans are warm-blooded animals and haven't evolved a tolerance for large changes in temperature.

Prevent DNA Damage DNA damage is inevitable in our natural lifestyles, but we can try to reduce exposure to things to cause DNA damage, which force overworked sirtuins back to work. All the following can wreak havoc on our genomes:

- Cigarettes and second-hand smoking (which is worse than smoking)
- Second-hand smoke (from fires, cars, etc.)
- PCBs and other plastic chemicals (avoid microwaving as it releases more PCBs)
- Azo dyes (found in fireworks and yellow ink)
- Organohalides (in solvents, degreasers, pesticdes, hydraulic flauid)
- N-nitroso compounds found in food with sodium nitrate (e.g. beers, cured meats, cooked bacon)
- Radiation: UV, X-rays, gamma rays, and radon (second most frequent cause of lung cancer besides smoking)

1.3.2 Drugs and Compounds

Rapamycin Rapamycin lowers immune response enough to improve success of organ transplant acceptance. It inhibits the activity of mTOR and is one of the most consistently successful compounds for extending life. Mice with small doses of rapamycin live 9-14% longer.

Metformin Metformin is prescribed for treating diabetes due to it lowering blood sugar. It mimics aspects of CR and limits metabolic reactions in the mitochondria, slowing down the process by which they convert macronutrients into energy. This results in the activation of AMPK, which responds to low energy levels and restores the function of mitochondria. AMPK activation leads to more NAD made, activating SIRT1. Metformin inhibits cancer cell metabolism, increases mitochondrial activity, and removes misfolded proteins.

Resveratol Resveratol is an antioxidant found in very small amounts in red wine and many plants in times of stress. It is a known activator of SIRT1. Hundreds of studies have shown it protects mice against a dozen of diseases. One study showed the mice fed resveratrol lived 20% longer.

NAD Boosters Without sufficient NAD, sirtuins don't work efficiently: they can't remove acetyl groups from histones, silence genes, and extend lifespan. NAD levels also decrease with age. Nicotinamide riboside (NR) and NMN (nicotinamide mononucleotide) increase NAD in the body. NAD boosters are still being tested, and so far there are no signs of toxicity.

1.3.3 The Future

Sinclair talks about exciting new research being done, which could be in the frontlines of antiaging in the coming years.

Senolytics One of the key hallmarks of aging is the accumulation of senescent cells, cells which have permanently ceased reproduction. Short telomeres has been shown to cause senescence. A very short telomere loses its histone packaging, leading to the DNA to be exposed. The cell thinks it's a DNA break and tries to repair the DNA end, leading to hypergenome instability as chromosomes are shredded during cell division and fused again repeatedly, potentially becoming cancer. Otherwise, the exposed telomere causes epigenetic factors to leave their cells permanently to repair the damage but with no DNA end, cell replication is shut down. Senescent cells are called zombie cells because though they stop dividing, they continue to release tiny proteins called cytokines that cause inflammation and attract immune cells called macrophages to attack the tissue. Cytokines don't just cause inflammation, but also cause other tells to become zombies, possibly even becoming a tumor. Senolytics is a class of pharmaceuticals which create small-molecule drugs designed to kill senescent cells by inducing the death program. Two senolytic molecules, quercetin and dasatinib, eliminated senescent cells in lab mice and extended their lifespans by 36%.

Antiretrovirals Retrotransposons are a type of genetic component that jump out of the genome, break DNA, and reinsert themselves elsewhere. Without sirtuins to silence retrotransposons, cells start to transcribe these endogenous

viruses. As NAD levels decline with age, sirtuins are unable to silence retrotransposon DNA. Antiretrovirals, which are also used to fight HIV, won't stop aging at its source, but can prevent the DNA breaks and epigenome from degrading rapidly.

Yamanaka Factors In 2006, Japanese stem cell researcher Shinya Yamanaka discovered a set of four genes–Oct4, Klf1, Sox2, and c-Myc–which could induce adult cells to become pluripotent stem cells, or iPSCs. He showed that cellular age reversal was possible in a petri dish. These four genes are now called Yamanaka factors. Sinclair predicts that these and other switches can reset an entire body's epigenetic landscape (including sending sirtuins back to their origin). Mice with Yamanaka factors triggered two days a week remained young and lived 40% longer. The Yamanaka treatment is highly toxic as mice triggered for more than two days died due to teratomas, which are tumors made up of several type of tissue. By leaving out c-Myc which likely causes teratomas, the vision of regular old mice has shown to be restored. Sinclair believes the Yamanaka factors to be the biological correcting device. In terms of the backup set of data (i.e. molecular beacons) as well as the observer, researchers are not really sure. The correction data is likely to involve methyl tags on DNA, which are used to estimate an organism's age called the Horvath clock. The observer could be a specialized histone, transcription factor, or protein that latches onto methylated DNA which waits until a signal comes from a correcting device to restore the original information. The correcting device requires ten-elevent translocation enzymes, or TETs, which clip off methyl tags from DNA, the same tags that mark the passage of the Horvath aging clock. This indicates that the DNA methylation clock is a controller of age. How the TETs know to remove only recent methyls while preserving original ones (or else cells would turn into primordial stem cells) is a complete mystery.

1.4 The Future

Sinclair then goes on to hypothesize about the future as well as possible societal issues and benefits that come from individuals living longer. These chapters are more hypothetical and high-level.