How Aging Works and How to Stop it

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Intro

Aging is a concept familiar to all of us. It claims the most lives yearly and weakens us severely as we get older. Aging itself does not “kill” people, rather, it weakens our immune systems until they stop working well enough to protect us from diseases. This is why conditions like Alzheimer’s or dementia become much more deadly at old age. Currently, modern medicine is working on fixing the problems caused by aging, but not aging itself. But by stopping the aging process, many diseases such as Alzheimer’s, cardiovascular disease, and dementia would be solved in the process as well. In addition, staying youthful also has the benefit of being less susceptible to diseases that aren’t related with age, as your body and immune system are overall stronger. With recent scientific breakthroughs, new potential therapies in the fight against aging have been discovered.

How exactly do we age?

Aging is an accumulation of changes over time. Our health mechanisms decline as we get older and as a result we become more susceptible to diseases. Our senses, respiration, digestion, and other bodily functions also deteriorate as the years go on. Studies have shown that activities such as exercise, having a good diet, and restricting calorie intake by a third or a half can all increase life expectancy (Covarrubias et al.). Meanwhile, smoking, stress, or lack of sleep can decrease our life expectancy. This has been shown across most mammals from humans to dogs to mice, and its effects are increased the sooner you start it in your life (Mercken et al.). For example, the effects smoking will have on your life are worse the earlier it begins . The same goes with healthy activities like having a good diet, which also benefit you more the sooner you start. However, the reasons activities like exercise or eating healthy make us live longer is because they produce a certain molecule crucial to many of our cell functions.

The importance of NAD+ in aging

NAD+ (Nicotinamide adenine dinucleotide) is a coenzyme used in redox reactions (a chemical reaction where electrons are transported between the 2 reactants in the process), and can influence many key cellular processes like DNA repair, chromatin remodeling (it allows transcription proteins to access genomic DNA and in turn control gene expression), and immune cell function. NAD+ is required for around 500 different enzyme reactions, and is found in the cytoplasm, but can also be in other parts of the cell. NAD+ is in a constant state of synthesis, degradation, and recycling, so its levels are never stable, rather it fluctuates up and down (Covarrubias et al.). However, NAD+ also has a very important role in aging. The aforementioned activities that make people healthier also increase NAD+ levels, hence why people live longer by participating in them (Imai and Guarente). A study has shown that people

who are regularly active contain much higher NAD+ levels than those who aren't, and shows that more active older adults contain about the same amount of NAD+ as active young adults (Okabe et al.). Meanwhile, older adults with the same level of physical activity as the younger adults had a considerable difference in their NAD+ levels. NAD+ levels also increase when food consumption is reduced by around half and when consuming foods such as milk, vegetables, or grains. That's because those foods contain NMN (nicotinamide mononucleotide) and NR(nicotinamide riboside) in them, which breaks down into NAD+ when inside the body (Okabe et al.). Furthermore, all lifeforms tested with NAD+ supplementation from mice to worms to yeast benefited. As for restricting food intake, most studies agree that caloric restriction works, however no one seems to know why. But NAD+'s main use in aging is to provide fuel for a certain set of proteins that are essential to our life.

Sirtuins and why they are important

The first of these proteins are sirtuins. Sirtuins are a class of proteins that regulate our health and lifespan, and use NAD+ as a fuel (Imai and Guarente). Studies show that decreases in NAD+ also have an accompanying decline of sirtuins along with them. NAD+ has its own benefits like energy management and maintaining healthy brain function, but its use as a fuel for SIRT-2 is an important part of why it's beneficial for aging. There are also many other classes of sirtuins that help with general body functions. Decreases in SIRT-1, the most commonly studied sirtuin in mammals, can worsen our circadian rhythm, which controls our internal sense of time (Imai and Guarente). SIRT-3 helps with protection against oxidative stress, and SIRT-6 helps keep the tips of our chromosomes healthy (Verdin). The benefits of NAD+ supplementation appear to work because they reactivate sirtuins and allow them to work more. Sirtuins play an important part in aging, but there are two other NAD+ consuming proteins that are crucial as well.

The role of CD38

CD38 is the second of this dynamic trio. CD38 is a NAD+ consuming protein that essentially acts as a flare to bring immune cells to help with problems going on in the body (Covarrubias et al.). CD38 along with sirtuins and PARPs use NAD+ as a fuel, but there is one detail that differentiates them from sirtuins. What makes CD38 stand out is that as we get older, we produce more CD38 which in turn lowers our levels of NAD+, and is one of the reasons why we age in the first place (Chini et al.). Meanwhile, levels of sirtuins drop as time goes on, and they're also the protein that helps us stay young and healthy (Imai and Guarente). An experiment has shown that CD38 increase in white adipose tissue (WAT), decreased NAD+ levels, while inflammation in the tissue caused CD38 levels to rise (Chini et al.). There are theories on why CD38 levels increase over time. One theory is that CD38 increases are most

likely a countermeasure to inflammation or stopping other diseases, while another is that the degradation of the thymus over time causes more CD38 to be produced. Although sirtuins also consume NAD+, CD38 levels are increased drastically as time goes on while sirtuins levels drop (Wang et al.). Meanwhile, reduction of CD38 does not seem to cause any bad side effects and, along with the addition of more NAD+, it protects you people from metabolic inflexibility, diet-induced obesity, and fatty liver and glucose intolerance (Sultani et al.).

PARPS and their use in aging

PARPs (poly ADP-ribose polymerases) are a family of 17 proteins essential for our survival. They have important uses such as repairing DNA and expressing genes. PARP inhibitors (PARPi) are often used in anti-cancer treatment, inhibiting DNA repair while also exploiting a defect in DNA repair to kill the cell (Sachdev et al.). PARPs, like the other proteins mentioned here, use NAD+ (Rajman et al.). However, PARPs are similar to another NAD+ protein: CD38. As DNA damage accumulates over time, PARP activity increases and it often competes with sirtuins for NAD+. As a result, SIRT-2 and the other sirtuin classes have less NAD+ to help with keeping ourselves healthy, decreasing the overall pool of NAD+ available but still providing a crucial role in our life nonetheless.

What telomeres do

However, there is another important piece of aging that indirectly benefits from NAD+. Telomeres are the caps at the end of chromosomes. They act like the tips of a shoelace and protect the chromosomes from external damage. Sometimes when the cell replicates itself, a bit of the telomere is lost. When too much is lost, the cell can no longer divide.
One of the ways cancer cells keep replicating is that they keep their telomeres long, so they continue replicating long beyond when a normal cell would have died (*Telomerase: Definition, Function, Structure and Cancer | Biology Dictionary*). However, telomeres are also important to aging. This shouldn't come as much of a surprise considering that we rely on our cells to live, but when telomere lengths get too short, important parts of DNA are lost through cell division. Calling back to sirtuins, SIRT-6 helps to keep our telomeres healthy by producing a ribonucleoprotein called telomerase, that helps regenerate the ends of our telomeres. NAD+ supplementation has increased telomere length and can also be correlated to SIRT-6 being more active (Verdin). However, it should be noted that artificially boosting telomerase with certain substances doesn't have much of an effect, with the only benefits being to people whose telomere lengths were already very short (*Telomerase: Definition, Function, Structure and Cancer | Biology Dictionary*). Furthermore, having too much or too little telomerase can make you more susceptible to cancer, so it's important to find a sweet spot that we can maintain (*Aging: Too Much Telomerase Can Be as Bad as Too Little - Scientific American Blog Network*). Telomeres are crucial to the problem of aging because they keep our DNA safe and can also be

used as the target in certain anti-aging medications. However, telomere experiments could be controversial, as scientists are unsure whether it could increase or decrease the chances of cancer. While rejuvenated telomeres could protect our DNA from errors in cell replication, in cells that have already mutated from other types of DNA damage, the rejuvenated telomeres might have a damaged cell stay alive when it should have died (Callaway). Overall, their role in the fight against aging is important, and telomeres will be an important factor when considering how to deal with the problem of aging.

The progress so far with experiments regarding aging

There have been several successes in recent years concerning aging, most notably David Sinclair's NAD+ supplementation on mice in 2020 (Lu et al.). In this experiment, mice that had previously suffered from poor vision now had their retinas fixed to see clearly again. Sinclair and his team treated mice with NMN, which turns into NAD+ when processed inside of the body. The mouse treated with NMN was also much more athletic and overall healthier compared to the one that hadn't been treated with the supplement. Sinclair has also done other studies, including one where his team had successfully aged a newborn twin. Side by side, although both mice were born at the same time, one was old and frail while the other was young and healthy. These studies have shown the importance of NAD+ in aging, and is why NAD+ is one of the most central components in aging studies. Furthermore, experiments reducing CD38 in mice have proved successful with NAD+ levels rising and having other protective roles in cardiac diseases such as ischemia, cardiac hypertrophy, and lipid overload-induced heart injury. However, there are some downsides to these revelations. Currently, anti-aging pills only increase our health span for a few years, so they won't drastically increase your life. The tests with CD38 are also important to know, but there is a big difference between testing on animals rather than humans, so although we have found breakthroughs in mice, it might be decades until we see the results in humans. That being said, current anti-aging experiments are still in early stages, and we've learned so much that it's plausible that our generation might be the first group of people to beat aging.

Conclusion

With experiments surrounding NAD+ production already taking place, it seems we could see an end to aging soon. However, current experiments have been limited to mice and what works for them vastly differs for humans. For example, we can treat most cancers in mice but we have yet to find a cure for cancer that works on humans. Furthermore, new medications go through a vigorous process of testing different animals before the first human test can take place. That being said, anti-aging technology has taken off recently and it's likely that in the near future, we will have some way of protecting ourselves from aging. Solving aging also fixes a lot of other diseases humans have been struggling to deal with, such as alzheimers, dementia, and

types of cardiac diseases that all become more likely as we get older. Furthermore, anti-aging will also make our immune system, mental, and physical body much healthier and increase our healthspan drastically, giving us the ability to be free of burdens we would carry in our 70's or 80's. Although the prospect of anti-aging is relatively new, the future looks bright, and an end to aging could arrive sooner than we think.

Bibliography

Aging: Too Much Telomerase Can Be as Bad as Too Little - Scientific American Blog Network. https://blogs.scientificamerican.com/guest-blog/aging-too-much-telomerase-can-be-as-bad-as-too-little/. Accessed 11 Sept. 2022.

Callaway, Ewen. "Telomerase Reverses Ageing Process." *Nature*, Nov. 2010, doi:10.1038/news.2010.635.

Chini, Claudia C. S., et al. "CD38 Ecto-Enzyme in Immune Cells Is Induced during Aging and Regulates NAD+ and NMN Levels." *Nature Metabolism*, vol. 2, no. 11, Nov. 2020, pp. 1284–304, doi:10.1038/s42255-020-00298-z.

Covarrubias, Anthony J., et al. "NAD+ Metabolism and Its Roles in Cellular Processes during Ageing." *Nature Reviews. Molecular Cell Biology*, vol. 22, no. 2, Feb. 2021, pp. 119–41, doi:10.1038/s41580-020-00313-x.

Imai, Shin-ichiro, and Leonard Guarente. "NAD+ and Sirtuins in Aging and Disease." *Trends in Cell Biology*, vol. 24, no. 8, Aug. 2014, pp. 464–71, doi:10.1016/j.tcb.2014.04.002.

Lu, Yuancheng, et al. "Reprogramming to Recover Youthful Epigenetic Information and Restore

Vision." *Nature*, vol. 588, no. 7836, Dec. 2020, pp. 124–29, doi:10.1038/s41586-020-2975-4.

Mercken, Evi M., et al. "Of Mice and Men: The Benefits of Caloric Restriction, Exercise, and Mimetics." *Ageing Research Reviews*, vol. 11, no. 3, July 2012, pp. 390–98, doi:10.1016/j.arr.2011.11.005.

Okabe, Keisuke, et al. "Implications of Altered NAD Metabolism in Metabolic Disorders." *Journal of Biomedical Science*, vol. 26, no. 1, May 2019, p. 34, doi:10.1186/s12929-019-0527-8.

Rajman, Luis, et al. "Therapeutic Potential of NAD-Boosting Molecules: The In Vivo Evidence." *Cell Metabolism*, vol. 27, no. 3, Mar. 2018, pp. 529–47, doi:10.1016/j.cmet.2018.02.011.

Sachdev, Esha, et al. "PARP Inhibition in Cancer: An Update on Clinical Development." *Targeted Oncology*, vol. 14, no. 6, Dec. 2019, pp. 657–79, doi:10.1007/s11523-019-00680-2.

Sultani, G., et al. "NAD+ : A Key Metabolic Regulator with Great Therapeutic Potential." *Journal of Neuroendocrinology*, vol. 29, no. 10, Oct. 2017, doi:10.1111/jne.12508.

Telomerase: Definition, Function, Structure and Cancer | Biology Dictionary. https://biologydictionary.net/telomerase/. Accessed 29 Aug. 2022.

Verdin, Eric. "NAD^+ in Aging, Metabolism, and Neurodegeneration." *Science*, vol. 350, no. 6265, Dec. 2015, pp. 1208–13, doi:10.1126/science.aac4854.

Wang, Ling-Fang, et al. "CD38 Deficiency Alleviates D-Galactose-Induced Myocardial Cell Senescence Through NAD+/Sirt1 Signaling Pathway." *Frontiers in Physiology*, vol. 10, Sept. 2019, p. 1125, doi:10.3389/fphys.2019.01125.