Aging: Too Much Telomerase Can Be As Bad As Too Little

How do I knock off thirty years from my age?

Faust, the protagonist in Johann Wolfgang von Goethe's famous play, poses this question to Mephistopheles in the chapter *Hexenküche* (Witches' kitchen). Mephistopheles provides some pretty good advice – considering that he is the devil and this fictitious exchange takes place in the dark Middle Ages:

Begib dich gleich hinaus aufs Feld,

Fang an zu hacken und zu graben

Erhalte dich und deinen Sinn

In einem ganz beschränkten Kreise,

Ernähre dich mit ungemischter Speise,

Leb mit dem Vieh als Vieh, und acht es nicht für Raub,

Den Acker, den du erntest, selbst zu düngen;

Here is the paraphrased essence of the devil's advice: Seek out a life of moderation, stop being lazy, exercise regularly by ploughing the field and avoid unhealthy foods!

How does the great scholar and scientist Faust respond to these commonsense suggestions?

Thanks, but no thanks. Faust does not like manual labor and is quite happy with his current lifestyle, so he instead opts for plan B – a magic youth potion.

Nearly two centuries after Goethe's Faust was first performed, our quest for reversing the aging process continues. The magic potion which reverses aging continues to be as elusive as ever, but aging research has made substantial progress during the past few decades. One biological definition of aging is the gradual decline in function observed over time. Humans experience this age-related decline at a whole body or organ level such as memory loss or weakening of muscle strength, but aging also takes place in individual cells. Cellular aging or cellular senescence describes a form of "exhaustion" to the point where cells can no longer divide and a disruption of normal cellular activity. A substantial amount of scientific data suggests that the aging of individual cells plays a central role in the general decline of function in our muscle function, blood flow or metabolism which occurs when we grow older. But understanding cellular aging will not only unlock some of the mysteries of "healthy" aging, it may also help us understand and prevent certain age-associated diseases such as heart disease or cancer.

One of the central mechanisms responsible for the aging of cells is the shortening of telomeres. Telomeres are repetitive DNA sequences at the ends of chromosomes which act as protective caps. Every time a cell divides, its chromosomes undergo a doubling process so that the two daughter cells receive equal amounts of DNA. During the DNA replication and the separation of the newly formed chromosomes, small chunks of DNA are trimmed off at the end of the chromosomes. By having protective telomere caps, the shortening process only affects the telomeres and not the essential gene-encoding parts of the chromosome.

When cells in a tissue are damaged then their neighboring cells or reservoirs of regenerative stem cells and progenitor cells have to kick in, divide a replace the damaged cells. Having long telomeres would allow these regenerative neighbors to keep on dividing and restoring the tissue, whereas short-telomere cells would have to give up early on because their protective telomere caps would dwindle. Regenerative cells such as stem cells are frequently called upon to divide and this is why it is a good thing that these regenerative cells tend to contain high levels of an enzyme called telomerase which helps prevent the shortening of the telomeres. Telomerase thus acts as an anti-aging enzyme. The roles of telomeres and telomerase in cellular aging were first uncovered in the 1980s and 1990s by the pioneers Elizabeth Blackburn, Carol Greider and Jack Szostak, who all shared the 2009 Nobel Prize in Physiology or Medicine for "*the discovery of how chromosomes are protected by telomeres and the enzyme telomerase*".

At the 64th Lindau Nobel Laureate meeting, Elizabeth Blackburn reviewed the history of how she and her colleagues identified the role of telomeres and telomerase in the cellular aging process, but also presented newer data of how measuring the length of telomeres in a blood sample can predict one's propensity for longevity and health. It makes intuitive and theoretical sense that having long telomeres would be a good thing but it is nice to have real-world data collected from thousands of humans confirming that this is indeed the case. A prospective study collected blood samples and measured the mean telomere length of white blood cells in 787 participants and followed them for 10 years to see who would develop cancer. Telomere length was inversely correlated with likelihood of developing cancer and dying from cancer. The individuals in the shortest telomere group were three times more likely to develop cancer than the longest telomere group within the ten year observation period! A similar correlation between long telomeres and less disease also exists for cardiovascular disease.

Dr. Blackburn was quick to point out that these correlations do not necessarily mean that there is a direct cause and effect relationship. In fact, increasing telomerase levels ought to lengthen telomeres but in the case of cancer, too much telomerase can be just as bad as too little telomeres. Too much telomerase can help confer immortality onto cancer cells and actually increase the likelihood of cancer, whereas too little telomerase can also increase cancer by depleting the healthy regenerative potential of the body. To reduce the risk of cancer we need an ideal level of telomerase, with not a whole lot of room for error. This clarifies that "telomerase shots" are not the magical anti-aging potion that Faust and so many other humans have sought throughout history.

Why is that telomere lengths are such good predictors of longevity, but too much telomerase can be bad for you? The answer is probably that telomere lengths measured in the white blood cells reflect a broad

range of factors, such as our genetic makeup but also the history of a cell. Some of us may be lucky because we are genetically endowed with a slightly higher telomerase activity or longer telomeres, but the environment also plays a major role in regulating telomeres. If our cells are exposed to a lot of stress and injury – even at a young age – then they are forced to divide more often and shorten their telomeres. The telomere length measurements which predict health and longevity are snapshots taken at a certain point in time and cannot distinguish between inherited traits which confer the gift of longer telomeres to some and the lack of environmental stressors which may have allowed cells to maintain long telomeres.

What are the stressors which can affect cellular aging and shortening of telomeres? Blackburn listed a few of them such as stress hormones, oxidative stress and inflammatory stress. All of these stressors cause stress on a molecular level, which means they can damage proteins and other essential components of a cell. Oxidative stress, the excess production of reactive oxygen species oxidizes proteins, disrupting their structure and function to the extent that oxidized proteins become either useless or even harmful. Inflammatory stress refers to excessive inflammation which transcends the normal inflammatory response of cells from which they can recover. Prolonged inflammation, for example, can cause cells to activate a cell-death program. Recent studies in mice have shown that activation of inflammation pathways in the brain can suppress cognitive function, muscle strength and overall longevity. Blackburn also pointed out that stressors are often interconnected. Prolonged elevation of stress hormones or prolonged inflammation can increase oxidative stress. The higher the level of these stressors, the more prematurely cells will age. This means that the body of a person in their 30s or 40s exposed to high levels of inflammation or oxidative stress may already numerous cells showing signs aging.

How do these stressors lead to premature aging? Shortening of telomeres could be one answer. If cells are chronically inflamed due to autoimmune diseases or inflammation-associated diseases such as obesity and atherosclerosis then they have to be continuously replaced by cell division which shortens telomeres. However, telomere shortening is not the only route to cell aging. Aging research groups have uncovered multiple additional pathways which can accelerate the premature aging of cells without necessarily requiring the shortening of telomeres. Inflammation or oxidative stress can activate certain aging pathways such as the aging regulator p16INK4a. Our own work has shown that an inflammatory cytokine can convert highly regenerative blood vessel progenitor cells into aged cells which no longer replicate by activating p16INK4a, and that this occurs without affecting telomere length. Judith Campisi from the Buck Institute of Aging as well as several other researchers have uncovered an important vicious cycle: Once cells begin aging, they themselves release inflammatory proteins which in turn can activate aging in neighboring cells, thus setting a self-reinforcing cascade of aging in motion.

Where does this interaction of telomere-dependent and telomere-independent aging pathways as well as the influence of known (and many unknown) stressors leave us? The molecular understanding of cellular aging is progressing steadily, but the complexity of cellular aging and the even more complex question of how organs such as the brain and heart age requires a lot more work. There will be no single molecular switch which can reverse or halt aging and triple our lifespan, but most aging researchers do not this as their goal. Understanding specific aging pathways, as well as the genes and stressors which

activate them, will allow us to prevent and treat age-related diseases as well as one day be able to provide personalized advice to individuals on how to maximize their “healthspan”. For now, we can stick to some of the broad lifestyle interventions which were recommended by Mephistopheles: exercise and a healthy diet.

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