Telomeres Hold the Key to Understanding Aging and Cancer

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In 1953, James Watson and Frances Crick described the structure of DNA and made history. However, just a few years later, a scientist from the other side of the world was conducting research in the field of molecular evolution that would shape our understanding of genetics. Susuma Ohno was born in Korea to Japanese parents in 1928. From a young age, he showed a love for animals, particularly horses, that would eventually take him to veterinary school. But rather than practicing as a vet, Ohno got pulled in a different direction: experimental science. As he was studying the chromosomes of mammals, he noticed that while there was great variation in the number of chromosomes in different species, the amount of chromosomal material (DNA bases) was the same. So whether there were 17 pairs of chromosomes in the creeping vole, or 84 pairs in the black rhinoceros, they shared the same amount of chromosomal material. This was not the case in lower phylogenetic species. Ohno hypothesized that there had been successive doublings of the amount of chromosomal material over evolutionary time, and recognized that most of the DNA in higher organisms did not contain coding sequences. He collectively called these regions 'junk DNA' (Beutler, 2002). We have since realized that there must be an evolutionary reason for its existence, but the name stuck.

> "Junk DNA *does* exist for a reason."

The term junk DNA is used nowadays to describe any DNA sequence that does not play a functional role in development, physiology, or some other organism-level capacity. However, junk DNA does exist for a reason. Highly repetitive DNA regions may play a role in gene regulation and chromosomal maintenance, while some transposable elements are thought to be remnants of defective viruses that now permanently reside in our genome (Palazzo & Gregory, 2014). A telomere is a special kind of repetitive nucleotide sequence found at each end of a chromatid that plays a role in protecting against degradation.

DNA polymerase, the enzyme that carries out DNA replication, can only synthesize new DNA in the 5' to 3' direction, so duplication cannot be carried out through the whole length of a chromosome. This is because in eukaryotic DNA replication, an RNA primer is required for each segment of DNA that is being replicated, so a primer cannot be placed at the very end. Thus, in each duplication, the end of the chromosome is shortened (Levy et. al., 1992). Telomeres therefore act as buffers to prevent genes from getting truncated. Over time, due to each cell division event, telomeres get shorter. Eukaryotic cells use the enzyme telomerase to elongate telomeres, but telomerase has not been detected in normal somatic cells. Therefore the typical response of cells to dysfunctional telomeres is to undergo a senescence growth arrest.

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Biologically, senescence is the phenomenon that occurs when telomeres reach a critically short length, and normal cells irreversibly stop multiplying and acquire a range of altered functions. Evidence suggests that the senescence response evolved as a failsafe mechanism to prevent proliferation of tumor cells, because as telomeres shorten, the chance that an actual gene may get truncated or mutated increases exponentially (Kim et. al., 2002). Therefore it is advantageous to halt the proliferation of these compromised cells rather than risk the multiplication of damaged cells. As senescent cells accumulate, their altered cellular functions may disrupt the surrounding tissue microenvironment crucial for suppressing the growth of oncogenic cells (cells with mutations in genes that have the potential to cause cancer).

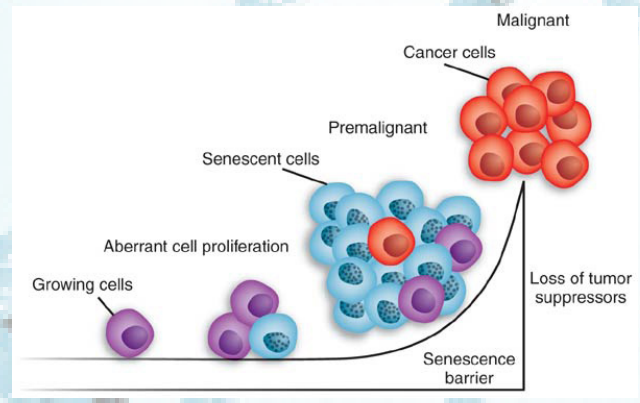

Figure #1. Cells that pass the senescence barrier may transform into malignant cancer cells.

Though telomerase activity can in theory compensate for short telomeres (which would reduce the amount of senescent cells, decreasing the likelihood of cancer), young healthy adults actually have very little telomerase activity (Buffstein, 2005). Even if we were one day able to take telomerase injections to keep our telomeres long and healthy, it turns out that, ironically, telomerase is more likely to promote cancer than suppress it (Kim et. al., 2002).

In an experiment measuring telomerase in mouse tissue compared with human tissue, somatic expression of telomerase was found to be higher in mice. When these values were standardized for differences in cell number, mice were found to be more cancer-prone than humans (Kim et. al., 2002). While telomerase expression itself doesn't cause a transformation, telomerase cooperates with potentially oncogenic changes to promote tumorigenesis, but "fixing" a cell that would have been senescent. A better understanding of telomerase function would suggest strategies for preventing cancer and other diseases, but as of now, it is clear that there is a definite link between telomere length and aging.

Generally, there are several theories that attempt to explain the phenomenon of aging. The evolutionary theory states that aging is a nonadaptive result of the declining power of natural selection to favor advantageous alleles, or to eliminate deleterious ones after sexual maturity. Mechanistic theories of aging attempt to illuminate processes involved in aging, implicating somatic decline with age. These include the rate of living theory, the telomere length theory, and others such as oxidative damage and membrane pacemaker theory (Buffstein, 2005). The hope, going forward, is that telomere length may serve as a biomarker of aging: a quantifiable parameter that reflects biological aging, and could potentially identify those at risk of age-related conditions and diseases (Mather et. al., 2011).

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There are many issues in trying to extend the human lifespan, the most logical one being that the only ones who will be able to afford life-extending medicine or treatments are those who are already privileged. Others make more philosophical arguments, claiming that humans miss the essence of life by focusing on the preservation of their "ego" (Pijnenburg & Leget, 2007). Even so, attempts have been made to extend the lifespan of cells.

In 2007, a health maintenance program launched a natural product-derived telomerase activator, TA-65. Low levels of TA-65 moderately activated telomerase in keratinocytes, fibroblasts, and immune cells in culture. However, the most striking effects were the declines in the percentage of senescent cytotoxic T cells and natural killer cells at 6 and 12 months following the dosage. The protocol lengthened critically short telomeres and remodeled the relative proportions of circulating leukocytes towards a more "youthful" profile (Harley et. al., 2011).

Such studies have shown promising results, implying that not only drugs, but also lifestyle changes, may be able to maintain long telomeres. Once we understand how we can manipulate telomere length and telomerase to predict aging, it is only a matter of time before research elucidates our understanding of cancer and age-related disease.

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