Scientists Dramatically Extend Human Cell Lifespan by Shortening DNA's Telomeres

By [redacted]

Over the last two decades, scientists have honed in on some key causes of aging: ranging from DNA telomere length, DNA hyper methylation to mitochondrial DNA oxidation. And as scientists zero in on these structural changes to the human genome, the focus is shifting to how to fix them and reverse human aging. Last January for example, a research team at Stanford University School of Medicine figured out how to lengthen the telomeres in in human cells and increase their lifespan more than 10-fold.

The telomeres are the celebrated clocks of life, squiggly candle wicks of non-coding nucleotides that shorten at the ends of our DNA, as cells reproduce over time. Human telomeres are made up of thousands of repeated nucleotides in a TTAGGG pattern and protect the chromosomal ends of DNA strands from fraying, much like a shoelace cap. They also protect the DNA from chromosomal misalignment during replication. The telomeres are protected themselves by six proteins called the shelterin complex. A shortening of the telomeres in certain cells has been associated with numerous diseases and cell dysfunction including aging, aplastic anemia, cancer, dyskeratosis congenita, Duchenne muscular dystrophy, hypertension, atherosclerosis and endothelial cell death. Critically, short telomeres also destabilize adult stem cell differentiation, essential for tissue regeneration throughout the body.

This past January, in a study published in *The Journal of the Federation of American Societies for Experimental Biology* (FASEB), researchers at Stanford University's Baxter Laboratory for Stem Cell Biology, Department of Microbiology and Immunology, Institute for Stem Cell Biology and Regenerative Medicine and the Department of Mechanical Engineering, extended the telomere lengths of fetal lung fibroblast and 30 year old muscle myoblast cells by increasing their own production of a ribonucleoprotein called telomerase. Expressed by the h-TERT gene on chromosome 5, telomerase is responsible for replacing lost or damaged telomere nucleotides. Its production is limited however in non-stem cells and decreases over time.

To get the cells to increase telomerase production, the Stanford team inserted a messenger RNA (mRNA) encoding a TERT enzyme. TERT enzymes are part of the telomerase protein and initiate the replacement of telomere nucleotides. To create an immuno-acceptable mRNA encoding TERT, the researchers harvested a TERT coding RNA chain from a like plasmid DNA model. (Plasmids are extra DNA molecules that live outside the chromosomes of a cell) The modified mRNA was then infused into the fibroblast and myoblast cells via a standard lipid solution. Within 24 hours, the mRNA latched typically to the ribosome protein workbenches within the cells. Telomerase protein production increased significantly, peaked at 24 hours and then returned to baselines within 48 hours. After three mRNA infusions over four days, the fibroblast telomeres increased in length by 22%, equivalent to a 20-fold increase in their life span and the cells replicated 28 more times than the untreated control group. Myoblast telomere length increased by 12%, equivalent to a 10-fold increase in lifespan and replicated 3 and a half times more than their control group.

Critically, the telomeres resumed shortening at normal rates after the end of treatment. Equally important, the cell rate of replication remained the same as that of younger cells after treatment, and all of the cells eventually showed the natural markers of mortality reducing the concern of causing cancerous cells.

Over the last few years, much publicity, if not hype, has been given to the general systemic use of telomerase as a 'youth pill'. But excess telomerase production has been repeatedly linked to cancer. And while telomere shortening is undoubtedly linked to aging, not all cells are designed to produce the same amount of telomerase. In fact, telomerase is produced in only a select group of cells: stem, embryonic, white blood cells and others with a high rate of replication. Telomeres also naturally shorten at different rates in different cell types and in some cells, not at all, making general telomerase enhancement highly problematic. In most neuron cells, heart muscle, sperm and egg cells for example, telomeres retain their length until death.

So while telomerase might not yet be a one pill panacea for aging, the Stanford team's cell regeneration via mRNA infusion presents a compelling, safer and tailored advance towards reversing and seriously delaying aging. Adult stem cells for example, can weaken in their capacity to regenerate new tissue in large measure because their own telomeres shorten over time, damaging their chromosomal integrity. An insertion of cultured telomere intact stem cells however, and/or in combination with a pool of telomere intact tissue cells, might prove an effective in vivo method of significantly setting back the clock for any tissue with low telomere levels. Helen Blau, PH.D., who led the research at the Baxter Laboratory stated, "We have found a way to lengthen human telomeres by as much as 1,000 nucleotides, turning back the internal clock in these cells by the equivalent of many years of human life. This [also] greatly increases the number of cells available for studies such as drug testing or disease modeling."

Indeed, mRNA transfection also tackles the very real problem of low cell volume in cell culture tissue regeneration. Some adult stem cells for example, such as Endothelial progenitor cells, are difficult to harvest due to their low volume. By rapidly increasing the telomeres however, the Stanford research team achieved an increase in absolute fibroblast cell number of more than 10^{12} -fold, a substantial amount for tissue and organ regeneration.

The brevity of TERT mRNA treatment also averts the loss of stem cell phenotype specialization that can occur over time in culture.

Additionally, mRNA transfection presents a more natural approach to telomerase production since it is made from the cells' ribosomes, minimizing an auto-immune response. Other methods of somatic nuclear transfer, viral methods for gene delivery or the use of culture conditions that slow telomere shortening can often cause DNA mutations or an immune response.

Overall, the ability to quickly generate a large pool of telomere robust cells, without immortalizing them, is a tremendous step for regenerative medicine, it could have a huge impact on tissue rejuvenation as well drug screening to disease modeling: rejuvenating cell types that mediate certain conditions and diseases for example, such as hematopoietic stem cells or progenitors in cases of immuno senescence or bone marrow failure. And as our organs, bones and blood are replenished by longer telomeres, it will allow us to better understand the telomeres' overall chromosomal and chemical benefit to aging as well as its limitations—shifting our focus once again towards the next best ploy towards a younger age.