HOW DOES TELOMERASE REACTIVATION PROMOTE ANTI-AGING IN MICE, WHAT LIMITATIONS WERE OBSERVED IN HPGS MICE EXPERIMENT AND HOW CAN TRANSIENT ACTIVATION OF TELOMERASE USING HTERT RNA REJUVENATE AGED HUMAN CELLS WHILE AVOIDING PERMANENT TELOMERASE ACTIVATION?

Hadia Azeem,

Safa Fahad,

Sehar mujib

International School Lahore

Abstract

This research paper examines the studies in mice to determine how telomerase reactivation affects aging at the cellular and whole-organism level. The HPGS mouse experiment was given particular attention which demonstrated potential benefits of telomerase RNA treatment and also highlighted any limitations that should be considered for applications on humans. The results of these experiments were compared to the research using human cells to investigate whether transient activation of telomerase through hTERT RNA could restore telomere length and improve cellular function while also not maintaining telomerase activity permanently. Overall, it suggests that temporary telomerase activation may offer a promising approach to cellular rejuvenation while potentially reducing the risks associated with continuous telomerase activation, but further research is required to determine its safety, effectiveness, and feasibility as a future anti-aging strategy in humans.

I. INTRODUCTION

Humans have always urged to stay young and try to understand whether age related problems could be reversed. This research paper investigates whether restoring telomerase can repair age-related cellular damage, while also examining the limitations and safety problems that could prevent this from being used in humans.

Telomerase, the ribonucleoprotein enzyme that supports telomere length, has become a focus in aging research. [1]) While telomerase is inactive in most human somatic cells, helping cellular senescence and aging, recent studies show that telomerase reactivation in mice produces anti-aging effects including extended lifespan, improved tissue function, and reversal of aging [7]. However, the application of telomerase reactivation in humans faces biological barriers, especially the cancer risk that is associated with unlimited and uncontrollable telomere lengthening, which can eventually lead to cancer cells becoming immortal. Experiments are chosen to be done on mice as they are one of the most widely used in biomedical research. Along with that, they also share a large proportion of their genes and many fundamental biological processes; their cells undergo similar processes such as DNA replication, cellular senescence, and telomere maintenance. Additionally, mice have relatively short lifespans, so researchers can study aging and lifespan effects much faster than in humans. They can also genetically modify mice to turn telomerase on or off and directly study its effects.

The process of aging is complex and is controlled by many different biological factors. Aging can be influenced by different molecular mechanisms, which can be seen by the fact that even closely related species can have very different lifespans. The most important mechanisms that affect aging are discussed below.

II. TELOMERASE REACTIVATION AND ANTI-AGING EFFECTS IN MICE

The main idea is that a major operator of age-related tissue degeneration is linked with telomere dysfunction, not just with aging and that restoring telomerase activity could be beneficial in anti-aging therapies.

To examine whether the damage caused by the telomere dysfunction particularly due to DNA mutations, could actually be reversed rather than merely paused. The researchers engineered mice carrying a special TERT-ER knock-in allele, a bioengineered version of the TERT gene combined to an Estrogen Receptor domain, allowing the enzyme to remain inactive until specifically switched on under control of the natural TERT promoter.

III. Methods of Telomerase Reactivation

In the study "[7]" by Prof. Ronald Depinho it was found that this engineered protein could be activated when the mice received 4-hydroxytamoxifen (4-OHT, a modified form of tamoxifen that binds to the engineered estrogen receptor and activates the otherwise inactive TERT-ER protein), providing the scientists accurate control over when telomerase was turned back on. It was discovered that reactivating telomerase in these old, severely aged mice, resulted in the telomeres extension, DNA damaged signalling decreased, cellular checkpoint pathways were switched off, previously inactive cells began dividing again, and damaged tissues across multiple organs-including the testee, intestines on anti-agings, spleen, and intestines-regenerated in mice. {9}

Another study suggested, scientists looked at what happens when they permanently add an extra working copy of the TERT into mice before they are born. The method used was unlike other past studies where the TERT gene was temporarily delivered using viruses. These researchers inserted the TERT into a safe location in the mouse genome called the Rosa26 locus (a DNA site commonly used to add genes without disrupting other important genes) and used embryonic stem (ES) cells to create these genetically modified mice. The EF1α promoter acted like an "on switch" to keep the TERT gene active in many tissues throughout the body.

IV. Factors resulting from telomerase reactivation

These are the results from earlier studies on tests conducted on mice showing the effectiveness of telomerase reactivation.

A. Metabolomic and Systemic Rejuvenation

In a study by [9] metabolic profiling has provided evidence that telomerase reactivation reverses aging at a systemic level in mice. In this study, 117 wild-type mice of different genetic backgrounds were determined, ranging from 8 to 129 weeks of age, which was used by researchers to determine a robust metabolic signature that reliably predicted biological age to independent age.

The result of the study found that in telomerase-deficient mice, the metabolic profiles were equivalent or more than the predicted for older ages than their chronological age, while in mice which over-expressed telomerase showed metabolic profiles corresponding to younger ages than expected. ([9] When telomerase was reactivated in old mice using TERT gene therapy, their metabolic profile shifted to resemble that of younger mice, which suggests that telomerase can

reverse many age-related changes throughout the body, not just in individual cells.

B. Tissue-Specific Rejuvenation and Longevity Extension

This study looked at what happens when scientists permanently add an extra working copy of the TERT gene (the procedure has been described in Section 2.1).

The result of the experiment showed the modified mice had a higher telomerase activity, longer telomeres, and an overall increase in lifespan compared to normal mice.[2]) It was also noted that this increase in telomerase activity did not lead to higher levels of DNA damage or cancer, which is a major concern in these conducts.[2])

The mice also demonstrated improved healing abilities in addition to the lifespan. They were able to repair skin wounds more quickly, which was linked to increased production of key factors such as FGF7 (which stimulates skin cell growth), VEGF (which promotes the formation of new blood vessels), and collagen.[2])

The study also examined how these mice responded to disease. Scientists induced Intestinal inflammation (colitis) using DSS, a chemical commonly used to model inflammatory bowel disease, the TERT-modified mice showed significantly greater resistance to the disease and those mice also exhibited reduced expression of the genes associated with inflammation.

C. Brain empowerment

In research conducted by Tian-Yi Zhu , the mice were genetically engineered. Most importantly, the brain also recovered. $Sox2^+$ neural progenitor cells (stem-like cells expressing the transcription factor Sox2, which maintains their ability to self-renew and generate new nerve cells), Dcx^+ newborn neurons (immature neurons expressing Doublecortin, a protein that marks newly formed neurons during neurogenesis), and $Olig2^+$ oligodendrocyte lineage cells (cells expressing the transcription factor Olig2 that develop into oligodendrocytes, the cells responsible for producing myelin-the insulating sheath surrounding nerve fibers that allows rapid electrical signal transmission) all increased after telomerase reactivation. Because these neural progenitor cells originate in the subventricular zone (a stem-cell-rich region lining the brain's lateral ventricles that continuously produces new neurons throughout adult life) and migrate to the olfactory bulb (the brain region responsible for processing smells), restoring neurogenesis improved hyposmia (a reduced ability to smell) and restored normal instinctive smell-avoidance behaviors. ([10] [11]

V. How can transient activation of telomerase using hTERT RNA rejuvenate aged human cells while avoiding permanent telomerase activation?

This research tested whether putting back telomerase into the bodies of mice with progeria, a disease that causes them to age rapidly, making their cells live longer. Hutchinson-Gilford Progeria Syndrome (HGPS) is a rare genetic disease caused by mutations in the LMNA gene (gene encoding lamin A), which produces a strange protein called progerin (an unusual form of lamin A that disrupts the nucleus). Progerin gathers around the nuclear membrane and makes it structurally unstable. Progerin affected cells showed DNA damage, impairment in their morphology, increased inflammation, telomere deterioration, when compared to their parent cells.Moreover, HPGS cells were discovered with cellular senescence. [25]

Hence, researchers used human Progeria cells[3]), and tested using hTERT and mRNA. The hTert is a catalytic subunit of the telomerase and In-vitro-transcribed hTERT mRNA is a genetically modified RNA encoding human telomerase reverse transcriptase and introduced into transient transfection. They used mRNA rather than specifically inserting the TERT gene into the cells, and the treatment was transient(temporary) because the mRNA would eventually be broken down[.(22)]

When the cell receives hTERT mrRNA, it translates into TERT protein for a while, allowing telomerase to become more active, and increasing telomere length. This is significant because telomeres can activate mutations in DNA and contribute to cellular senescence. Researchers therefore tested much more than telomere length: they examined SA-β-galactosidase(a biological marker used to identify aging) which markes the cellular senescence, cell proliferation, nuclear structure, inflammation and telomere-associated proteins such as DNA-PKcs, Ku70 and Ku80. Following the hTERT treatment, the Progeria cells showed significant improvement in overall anti-aging by increasing telomere length, improved proliferation, and reduced scenesense, suggesting that telomerase activation was not simply making telomeres longer but was helping the cells function more normally. (21)

Using this same treatment, they subsequently investigated IPSC-derived endothelial cells (endothelial cells produced from induced pluripotent stem cells, which are reprogrammed cells that can be converted into different cell types) from HPGS, because vascular dysfunction is a major feature of Projeria.[(19)] The results showed that IPSC endothelial cells could not replicate and faced DNA mutations, inflammation signaling , erosion of telomeres and abnormal cell morphology. They compared treated cells with untreated cells and measured telomere lengths using 2 methods. First, MMqPCR (monochrome multiplex quantitative PCR) and second qFISH (quantitative fluorescence in situ hybridization, a technique that uses fluorescent probes to measure telomeres directly in individual cells). To make the cells less senescent, they also calculated β-galactosidase, DNA-mutations and inflammatory signaling. Importantly, they also tested endothelial function, including nitric oxide production, angiogenesis and lDL uptake.[13]

In order to test the treatments conducted on human cells, they moved to testing the treatments on Progeria mice after obtaining results from human cells and used mTERT which was delivered through a lentiviral vector. The mice received two treatments through the tail vein, and this increased their lifespan by approximately 20%[10], while also reducing DNA damage markers, inflammatory and thrombosis-related signals and increasing SIRT1 in blood vessels and other organs. They then began looking for a safer and more clinically realistic way to deliver TERT RNA without depending on a viral vector. They came up with lipid nanoparticles, or LNPs, which are tiny fat-based particles that can protect RNA and transport it into cells.[4]) To test this delivery system out, they first used luciferase mRNA (mRNA encoding luciferase, an enzyme that produces detectable light) instead of TERT. This acted as a reporter system (a tracking method that allows researchers to see whether delivered RNA reaches cells and becomes active): if the cells received the luciferase mRNA, they produced luciferase and generated detectable light, allowing the researchers to determine where the RNA was delivered. It was found that the LNP system could safely deliver RNA throughout the body, with particularly strong activity in the liver, supporting the possibility of using LNPs to deliver therapeutic TERT RNA.[5]) [4] [10]

However, this opened a new curiosity that ordinary linear mRNA is temporary and can be devalued very quickly, so it shows repetitive treatment would be necessary. This opened a new chapter to investigate TERT circular RNA which is TERT circRNA, an RNA molecule which forms a closed circular structure with close ends).

Because circular RNA can be better at degradation than linear RNA, researchers then had to hypothesize that TERT circRNA could produce TERT for longer while still avoidant of permanent modification of the genome. [[6])

The researchers hypothesized that TERT circRNA could produce TERT for longer while still avoiding permanent modification of the genome. In a 2025 study [6] researchers tested TERT circRNA directly on human endothelial cells from patients with Progeria and compared its effects with linear TERT mRNA. A single treatment with TERT circRNA led to strong telomere extension and reduced several signs of cellular aging, including the activity of proteins associated with cellular senescence. It also reduced the levels of progerin, the abnormal protein responsible for many of the effects of Progeria, as well as several molecules involved in inflammation and DNA damage. [6])Along with these changes, the treated cells showed healthier nuclear structure and were able to proliferate more effectively. Their ability to produce nitric oxide and form new blood vessels also improved, suggesting better endothelial function. The treatment also improved mitochondrial function by reducing harmful reactive oxygen species and improving mitochondrial membrane , which is an indicator of how well mitochondria are producing energy. Interestingly, TERT circRNA produced stronger effects than linear TERT mRNA in several of these measurements. [(20)]

VI. Side effects

A. Inflammatory reactions

LNP can cause inflammation, fever, tiredness or temporary immune activation [16]. This could

happen if your immune system recognizes it as foreign and reacts to it. This depends on the composition of the LNP. So researchers need to develop a way to deliver the mRNA without causing an excessive immune response.

B.Repeated-dose effects

For an anti-aging treatment, 1 dose may not be enough so repeated doses may be necessary. However, repeated doses may change the way your body reacts to this treatment, and could increase the possibility of other side effects. This creates a challenge because researchers need to determine how often the treatment can safely be given while still maintaining its effectiveness. Long-term and repeated-dose studies would therefore be important before applying this approach to humans.

C. Liver accumulation

LNPs can accumulate in the liver naturally after entering the bloodstream [17], which means that a large amount of the treatment may reach the liver rather than being equally distributed throughout the body. This can be a limitation if the TERT needs to reach other tissues as well.

D..Liver toxicity

This can also cause Hepatotoxicity, which basically means stress or damage to the liver.

Importantly, this is an avoidable effect of LNPs. According to an experiment from it was found that C12-200 LNPs caused greater liver toxicity than formulations such as ALC-0315, SM-102 and D-Lin-MC3-DMA. Scientists can monitor possible liver damage by measuring ALT and AST, since increased levels of these enzymes in the blood can indicate liver injury. Therefore, a suitable LNP for TERT therapy would need to deliver mRNA effectively while minimising liver toxicity.

E. Local and Systemic Immune Cell Infiltration

LNPs can cause immune cells to gather in the tissues where they are delivered, and this reaction may become more noticeable over time rather than immediately after treatment. In studies using C12-200 LNPs, immune cells including neutrophils, macrophages and T cells were found to accumulate at injection sites several days after administration. The amount and type of immune-cell infiltration differed between LNP formulations, showing that the composition of the LNP affects how strongly the immune system reacts. For TERT mRNA therapy, excessive immune-cell infiltration could cause inflammation and damage to the treated tissue, making it important to develop LNPs that cause a weaker unwanted immune response.

F.Inflammatory Cytokine Elevation

LNPs can also activate the immune system by increasing the levels of pro-inflammatory cytokines [16], which are signalling proteins involved in inflammation. Some LNP formulations were found to increase cytokines such as IL-1β, IL-6, GM-CSF, TNF-α and IFN-γ in tissues and blood. For example, GM-CSF can help stimulate the production and movement of neutrophils, increasing the inflammatory response. However, this effect depends on the LNP formulation: SM-102 and ALC-0315 showed much less cytokine increase than more strongly immunogenic formulations. This suggests that choosing and optimising the LNP composition could reduce excessive inflammation during TERT delivery.

G. Off-Target Organ Accumulation and Biodistribution

When LNPs are given throughout the body, they may accumulate in organs other than the intended target, including immune-related organs such as the spleen. This is a problem because the LNP may then release its mRNA in cells that were not supposed to receive it. In the case of TERT mRNA, unwanted expression in other tissues could potentially increase side effects and reduce how precisely the treatment works. The relationship between where LNPs travel in the body, where the mRNA becomes active, and the immune response is also not yet fully understood. Therefore, improving the ability of LNPs to reach the correct cells and avoiding unnecessary accumulation in other organs is an important barrier for future human treatment.

VII. Conclusion

Therefore, the research has progressed from simply asking whether telomerase can lengthen telomeres to a question: can we temporarily activate telomerase in human cells and use it to reverse multiple characteristics of cellular aging without permanently changing the genome? Overall, telomerase reactivation shows promising anti-aging effects in mice and human cells. Transient hTERT RNA activation may rejuvenate aged cells while avoiding permanent telomerase activation, but further research is needed to establish its safety in humans.

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