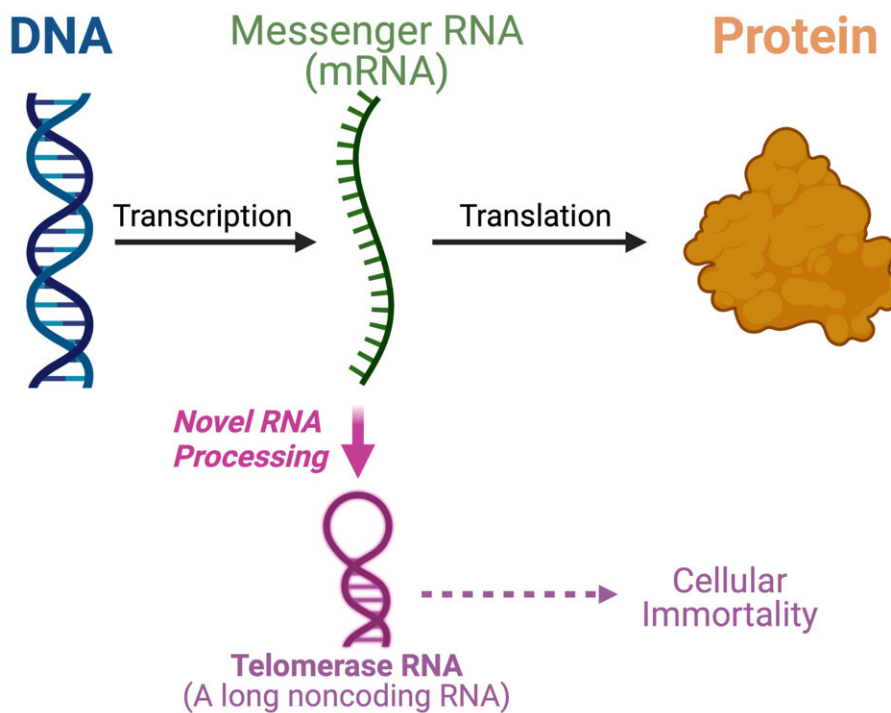


Scientists discover dual-function messenger RNA

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The central dogma of molecular biology showing what is happening in this study.
Credit: Julian Chen

For the very first time, a study led by Julian Chen and his group in Arizona State University's School of Molecular Sciences and the

Biodesign Institute's Center for the Mechanism of Evolution, has discovered an unprecedented pathway producing telomerase RNA from a protein-coding messenger RNA (mRNA).

The central dogma of molecular biology specifies the order in which genetic information is transferred from DNA to make proteins. Messenger RNA molecules carry the [genetic information](#) from the DNA in the nucleus of the cell to the cytoplasm where the proteins are made. Messenger RNA acts as the messenger to build proteins.

"Actually, there are many RNAs (ribonucleic acids) that are not used to make proteins," explained Chen. "About 70 percent of the [human genome](#) is used to make noncoding RNAs that don't code for protein sequences but have other uses."

Telomerase RNA is one of the noncoding RNAs that assembles along with [telomerase](#) proteins to form the enzyme telomerase. Telomerase is crucial for cellular immortality in cancer and [stem cells](#). In this study, Chen's group shows that a fungal telomerase RNA is processed from a protein-coding mRNA, instead of being synthesized independently.

"Our finding from this paper is paradigm-shifting. Most RNA molecules are synthesized independently and here we uncovered a dual function mRNA that can be used to produce a protein or to make a noncoding telomerase RNA, which is really unique," said Chen. "We will need to do a lot more research to understand the underlying mechanism of such an unusual RNA biogenesis pathway."

Basic research on the metabolism and regulation of mRNA has led to important medical applications. For example, several COVID-19 vaccines use messenger RNA as a means to produce viral spike proteins. In these vaccines, the mRNA molecules are eventually degraded and then absorbed by our bodies.

This new approach has advantages over DNA vaccines which run the potential risk of being deleteriously and permanently incorporated into our DNA. The discovery of dual-function mRNA biogenesis in this work might lead to innovative ways of making future mRNA vaccines.

In this study Chen's group discovered the unexpected mRNA-derived telomerase RNA in the model fungal organism *Ustilago maydis* or corn smut. Corn smut, also called Mexican truffle, is edible and adds a delicious umami effect to many dishes, for example tamales and tacos. The study of RNA and telomere biology in corn smut may provide opportunities for finding novel mechanisms for mRNA metabolism and telomerase biogenesis.

Why study telomerase RNA?

The Nobel Prize in Physiology or Medicine was awarded in 2009 "for the discovery of how chromosomes are protected by telomeres and the [enzyme telomerase](#)." Telomerase was first isolated from a unicellular organism living in pond scum. As it later turned out, telomerase exists in almost all eukaryotic organisms, including humans, and plays a crucial role in aging and cancer. Scientists have been scrambling to discover ways to utilize telomerase to make human cells immortal.

Typical human cells are mortal and cannot forever renew themselves. As demonstrated by Leonard Hayflick a half-century ago, [human cells](#) have a limited replicative life span, with older cells reaching this limit sooner than younger cells. This "Hayflick limit" of cellular life span is directly related to the number of unique DNA repeats found at the ends of the genetic material-bearing chromosomes. These DNA repeats are part of the protective capping structures, termed "telomeres," which safeguard the ends of chromosomes from unwanted and unwarranted DNA rearrangements that destabilize the genome.

Each time the cell divides, the telomeric DNA shrinks and will eventually fail to secure the chromosome ends. This continuous reduction of telomere length functions as a "molecular clock" that counts down to the end of cell growth.

The diminished ability for cells to grow is strongly associated with the [aging process](#), with the reduced cell population directly contributing to weakness, illness and organ failure.

Counteracting the telomere shrinking process is telomerase, the enzyme that uniquely holds the key to delaying or even reversing the cellular aging process. Telomerase offsets cellular aging by lengthening the telomeres, adding back lost DNA repeats to add time onto the molecular clock countdown, effectively extending the life span of the cell.

Telomerase lengthens telomeres by repeatedly synthesizing very short DNA repeats of six nucleotides—the building blocks of DNA—with the sequence "GGTTAG" onto the chromosome ends from a template located within the RNA component of the enzyme itself.

The gradual shrinking of telomeres negatively affects the replicative capacity of human stem cells, the cells that restore damaged tissues and/or replenish aging organs in our bodies. The activity of telomerase in adult stem cells merely slows down the countdown of the molecular clock and does not completely immortalize these cells. Therefore, [adult stem cells](#) become exhausted in aged individuals due to telomere length shortening which results in increased healing times and organ tissue degradation from inadequate cell populations.

Tapping the full potential of telomerase

Understanding the regulation and limitation of the telomerase enzyme holds the promise of reversing telomere shortening and cellular aging

with the potential to extend human life span and improve wellness of elderly individuals.

Human diseases that include dyskeratosis congenita, aplastic anemia and idiopathic pulmonary fibrosis have been genetically linked to mutations that negatively affect telomerase activity and/or accelerate the loss of telomere length. This accelerated telomere shortening closely resembles premature aging with increased organ deterioration and a shortened patient life span caused by critically insufficient stem cell populations. Increasing telomerase activity is seemingly the most promising means of treating these genetic diseases.

While increased telomerase activity could bring youth to aging cells and cure premature aging-like diseases, too much of a good thing can be damaging for the individual. Just as youthful stem cells use telomerase to offset telomere length loss, cancer cells employ telomerase to maintain their aberrant and destructive growth. Augmenting and regulating telomerase function will have to be performed with precision, walking a narrow line between cell rejuvenation and a heightened risk for cancer development.

Distinct from human stem cells, somatic cells constitute the vast majority of the cells in the human body and lack telomerase activity. The telomerase deficiency of human somatic cells reduces the risk of cancer development, as telomerase fuels uncontrolled cancer cell growth. Therefore, drugs that increase telomerase activity indiscriminately in all cell types are not desired. Small molecule drugs can be screened or designed to increase telomerase activity exclusively within stem [cells](#) for disease treatment as well as antiaging therapies without increasing the risk of cancer.

The study of telomerase RNA biogenesis in corn smut may unveil new mechanisms for telomerase regulation and offer new directions on how

to modulate or engineer human telomerase for innovations in developing antiaging and anticancer therapeutics.

This study, "Biogenesis of telomerase RNA from a protein-coding mRNA precursor," was just published in the *Proceedings of the National Academy of Sciences*. The ASU team includes first authors postdoc Dhenugen Logeswaran and former research assistant professor Yang Li, doctoral student Khadiza Akhter, former postdoc Joshua Podlevsky (currently at Sandia National Labs, Albuquerque, New Mexico) and two undergraduate students Tamara Olson and Katherine Fosberg.

Chen also commented on the caliber of the ASU undergraduate students, Tamara Olson and Katherine Fosberg, who were working in his lab for over a year. "They spent a lot of time in the lab and were fully involved in our research."

More information: Logeswaran, Dhenugen et al, Biogenesis of telomerase RNA from a protein-coding mRNA precursor, *Proceedings of the National Academy of Sciences* (2022). [DOI: 10.1073/pnas.2204636119](https://doi.org/10.1073/pnas.2204636119). doi.org/10.1073/pnas.2204636119

Provided by Arizona State University

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