

Slowing down the central dogma rate for alleviating aging

Fang Cheng^{1,2} and Lei Wang^{1,3,*}

¹National Laboratory of Biomacromolecules, CAS Center for Excellence in Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, China

²Westlake Laboratory of Life Sciences and Biomedicine, School of Life Sciences, Westlake University, Hangzhou 310024, China

³College of Life Sciences, University of Chinese Academy of Sciences, Beijing 100049, China

*Correspondence: wanglei@ibp.ac.cn

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About 65 years ago, Francis Crick proposed the "central dogma" of molecular biology, outlining to the flow of genetic information from DNA to RNA, and ultimately to protein synthesis. Over the years, the discoveries of RNA editing, alternative splicing, epigenetic modification, and the retroviruses greatly enriched the content of the central dogma. This fundamental process still frame how we understand life. Aging is a highly complex biological process affected by multiple biological pathways, and some of which are intricately linked to DNA replication, transcription, and translation -- the core tenets of the central dogma. Emerging evidence points to a correlation between the pace at which each step of the central dogma operates and the aging process. It seems that slowing down the speed of these fundamental processes could offer a promising strategy for mitigating the aging process.

Here we highlight recent advancements indicating a connection between the speed of the central dogma and the aging process, providing new insights into the mechanisms and interventions of aging.

INCREASED DNA REPLICATION SPEED INDUCES GENOME INSTABILITY AND ACCELERATES AGING

Accurate DNA replication and efficient DNA repair are crucial for maintaining genomic stability, but can also potentially contribute to the aging process. As cells replicate, errors can occur during DNA replication. Additionally, DNA can be damaged by various environmental factors like UV radiation, chemicals, and metabolic byproducts. During the aging process, the accumulation of DNA damage becomes more pronounced as the cellular capacity to repair

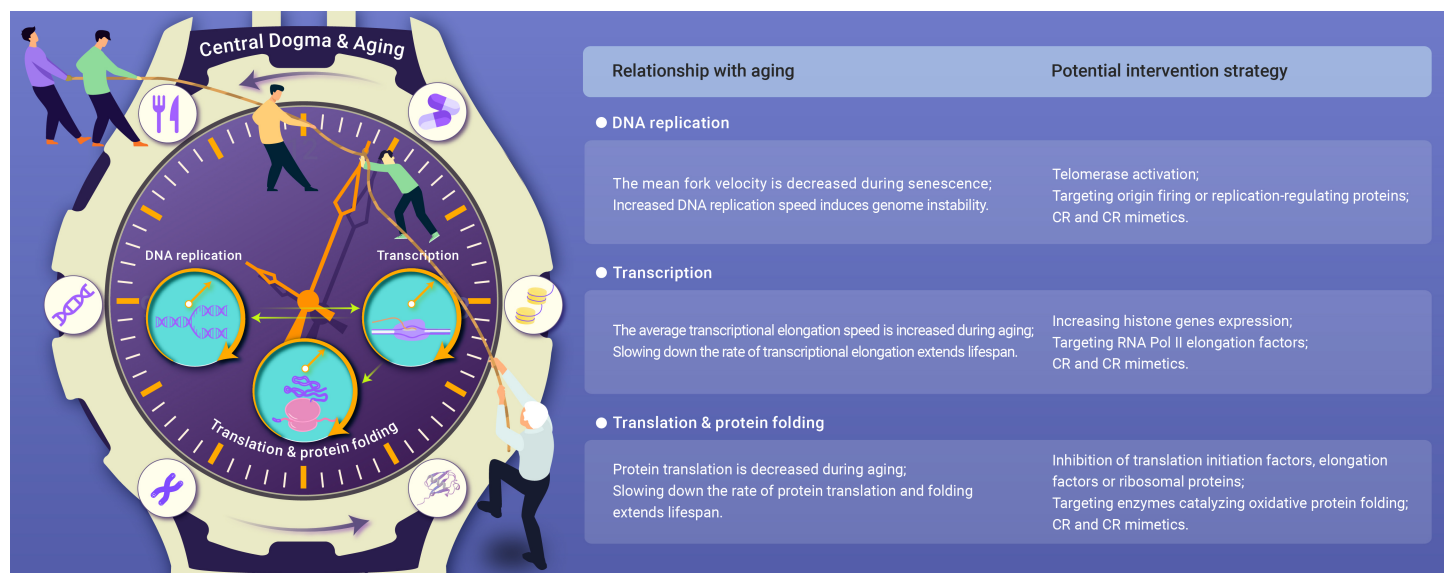


Figure 1. Slowing down the ticking of the 'central dogma' clock can alleviate aging The clock represents the aging process that governed by the central dogma. The flow of genetic information from DNA to RNA, and ultimately to protein synthesis is indicated by the arrows linking the three sub-dials. Slowing down the rate of each step of the central dogma by different interventions could be a promising strategy to alleviate aging.

this damage decreases, which leading to the persistence of DNA lesions and the genomic instability. However, questions about the primacy of mutations as a driver of aging have been raised recently, as elevated mutation rates do not consistently lead to premature aging, and old somatic cells can be used to clone mammals with normal lifespans.¹ Instead, the act of faithful DNA repair accelerates different aspects of aging, including advancement of the DNA methylation clock. Cellular responses to double-stranded DNA breaks erode the epigenetic landscape and the loss of epigenetic information accelerates mammalian aging, which can be reversed by epigenetic reprogramming.¹ Another recent study has shown that inhibition of poly (ADP-ribose) polymerase results in aberrant acceleration of the velocity of replication forks and does not cause fork stalling, leading to DNA replication stress and genomic instability.² Thus, high speed of DNA replication and repair above the tolerated threshold may induce the loss of genomic and epigenomic information, which may mutually reinforce aging. Another contributing factor for aging is the shortening of telomeres, which are protective caps at the ends of chromosomes. Telomeres undergo a substantial shortening that induces genomic instability and finally leads to cell senescence, which is part of the normal aging process. However, rapid and excessive cell division without

adequate telomere maintenance can lead to accelerated telomere shortening, which is associated with cell senescence.

It's important to note that the changes in DNA replication speed during aging are complex and can vary across different cell types and tissues. Due to the telomere shortening, cumulative DNA damage, lack of DNA precursors and energy limitation during aging, there is a decreased mean fork velocity during senescence. Slowing down the rate of DNA replication could reduce errors and increase fidelity, potentially enhancing genomic stability. As an example, telomerase activation has shown therapeutic effects to decelerate aging and treat aging-related diseases. Besides, the abundance of proteins associated with origin firing and the regulation of replication significantly influences fork progression, and the roles of these proteins in aging process need future study. The lifespan-extending interventions, such as caloric restriction (CR) or CR mimetics may reduce the DNA precursors and energy production, resulting in a reduced replication rate.

TRANSCRIPTIONAL ELONGATION RATE INCREASES WITH AGING AND CAN BE SLOWED DOWN FOR LIFESPAN EXTENSION

Decreased transcript quality and increased transcriptional errors during

aging have been demonstrated in various species. Transcriptional elongation is a critical step in gene expression, where RNA polymerase moves along the DNA template, synthesizing an RNA molecule that carries the instructions encoded in the DNA. Recent research has shown that the average transcriptional elongation speed (RNA polymerase II speed) increased with age across multiple invertebrates and mammalian species. Higher rate of transcriptional elongation is associated with changes in splicing and transcript quality, including elevated transcriptional noise (e.g., formation of circular RNAs) and increased numbers of mismatches with genome sequence. Strategies that slow down elongation rates such as RNA polymerase II mutation and increased nucleosome density can delay aging and extend lifespan.³ Although the molecular events driving RNA polymerase II speed increase remain unclear, it is known that various signals, including hormones, growth factors, and environmental cues, can influence the rate of transcriptional elongation.

Thus, slowing down the transcription elongation speed has been proposed as a strategy to enhance cellular maintenance and reduce the accumulation of errors that can lead to age-related decline. Indeed, the increased speed of elongation could be reverted under lifespan-extending interventions, such as CR and lowered insulin-IGF signaling.³ Besides, screening and characterizing the potent inhibitors targeting RNA polymerase II elongation factors could be a new strategy to slow down the rate of transcriptional elongation and to extend lifespan.

SLOWING DOWN THE RATE OF TRANSLATION AND PROTEIN FOLDING EXTENDS LIFESPAN

Reduced translational fidelity is known to correlate with shorter lifespan, given that mistranslation is the most erroneous step in gene expression. Thus, improving translation fidelity has been proposed as a potential strategy to extend lifespan. The rate of translation depends on various factors, including the availability of ribosomes, the abundance of tRNA, and the efficiency of ribosome movement along the mRNA template. Reduced protein synthesis, either by downregulation of initiation factors or ribosomal proteins, is a well-established anti-aging intervention. A recent study has shown that faster translation elongation also leads to impaired translational fidelity, while inhibition of eukaryotic elongation factor 2 (eEF2) by eEF2 kinase slows down elongation speed and improves translation fidelity. Interestingly, mTOR inhibition by rapamycin or CR, which interrupts anabolic metabolism, improves translation fidelity through activation of eEF2 kinase and extends lifespan.⁴ Slower protein translation could also reduce the load on other proteostasis machineries, such as the molecular chaperone and proteasome, therefore these machineries are freed up to process misfolded and aggregated proteins. Since protein translation is the largest consumer of cellular energy, reduced translation could allow energy to be diverted to cellular maintenance and repair processes.

Many proteins in the cell fold cotranslationally during their synthesis on ribosomes, which is influenced by the speed at which translation elongation occurs. Fast decoding rates are necessary when large amounts of protein are synthesized, such as during rapid cell proliferation. However, periods of slow decoding are believed to favor protein folding by providing enough time for each domain to acquire its native conformation, thus avoiding misfolding and aggregation. Interestingly, emerging evidence indicates that protein folding rate could also regulate the aging process. Oxidative protein folding is a unique process of protein folding, which is critical for the formation of disulfide bonds in most secretory and membrane proteins. In a recent study, we found that slowing down the rate of oxidative protein folding by depletion protein disulfide isomerase (PDI), a key oxidoreductase that catalyzes oxidative protein folding, alleviates senescence in various cell models of aging. Mechanistically, PDI deletion reduces the accumulation of hydrogen peroxide,

a byproduct of disulfide formation, thereby decreasing the expression of the senescence associated secretory phenotype.⁵

CONCLUSION

Aging is marked by a gradual decline in systemic integrity, leading to physiological decline and disease development. Deleterious age-related changes include DNA lesions, genomic instability, epigenetic aberrations, transcription errors, translation decline and loss of proteostasis. These changes in each step of the central dogma are usually regarded as causes or contributors to aging progression. However, recent studies have reported that slowing down the rate of central dogma could improve the fidelity of replication, transcription and translation, in a slower but safer manner, and eventually extend lifespan in multiple aging models (Figure 1). These findings raise a possibility that the changes of these molecular events could be an adaptive strategy for the cells and the body during aging. It is worthy to note that to slow down the speed of the central dogma for aging alleviation should depend on the cell types, species, and even the intervention time. Reducing the rate of DNA replication, transcription elongation, protein translation and folding could also lead to a shortage of critical cellular molecules and slower turnover. Further investigation is required to reveal how the paces change in each step of the central dogma in different cell types, aging models, and the stages of life by a comprehensive and integrated approach. Moreover, it will be important to investigate what are the effects of the lifespan-extending maneuvers, including CR and CR mimetics, on the speed of each step of the central dogma. In sum, we propose that as the fundamental framework that describes the flow of genetic information within a biological system, the running speed of the central dogma is tightly related to the aging process. The relationship between central dogma rate and aging is intricate and could be influenced by various genetic, environmental, and physiological factors. Maintaining the fidelity and economy of this system is critical for lifespan and healthspan extension. Future studies under this new theoretical framework will help us better understand the underlying mechanisms of how life is controlled by the central dogma and to develop potential interventions for healthy aging.

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DECLARATION OF INTERESTS

The authors declare no competing interests.