

Telomeres and Telomerase in Renal Health

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ABSTRACT

The role of telomeres and telomerase in human biology has been studied since the early 1990s because telomere attrition is implicated in various diseases including cardiovascular dysfunction, carcinogenesis, and the progression of acute kidney injury. Telomeric length is a reliable indicator of intrinsic biologic age and a surrogate for the mitotic clock. Because the prevalence of chronic kidney disease increases with age, telomere length and telomerase activity may play a role in its progression.

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Most human cells have a limited lifespan that is controlled by cell cycle progression and the mitotic clock.^{1,2} Because of the inability of DNA polymerase to fully replicate lagging chromosome strands, there is a loss of 50–100 bp of DNA with each successive cell division.^{3,4} Telomeres, which ultimately determine the organism's biologic age, comprise tandem TTAGGG repeats of 5000 to 15,000 bp that normally reside at the ends of chromosomes as protective caps.^{5,6} The nuclear role of telomeres is to prevent chromosome ends from being identified as double strand breaks in DNA, thus limiting chromosome shortening and recombination. The length of telomeres is regulated by telomerase, which catalyzes the addition of telomeric repeats to the 3' ends of chromosomes to preserve their integrity.³

Telomerase was discovered in 1989; however, the cellular pathways involved in its biosynthesis and recruitment are still unclear.⁷ The structure of human telomerase was identified in 2007 and comprises two primary components: telomerase reverse transcriptase and telomerase RNA.⁸ The telomerase reverse transcriptase protein catalyzes the addi-

tion of deoxynucleotide triphosphates, whereas telomerase RNA encodes the complementary telomere template. Telomerase is active throughout embryogenesis but is downregulated during tissue differentiation, leaving the majority of mature human cell types with a limited response. Consequently, mature telomeres tend to progressively shorten with every cell division, eventually resulting in nuclear instability followed by senescence or apoptosis.⁹

Cellular senescence is a state of growth arrest in which cells remain metabolically active but refractory to mitogenic stimuli. Replicative senescence can be accelerated by oxidative stress, which induces telomeric attrition.¹⁰ As telomeres reach a critically short length, they are recognized as damaged chromosomes, activating tumor suppressor protein p53 and cell cycle inhibitor p16^{INK4a}.¹¹ The activation of p53 leads to overexpression of the cyclin-dependent kinase (CDK) inhibitor, p21. The p21 protein binds to and inhibits the activity of CDK2/4, resulting in cell cycle G₁-phase arrest. Similarly, p16^{INK4a} inhibits CDK4 to prevent recurrent cellular proliferation. Among people over the age of 60, the expression levels of p53 and p16^{INK4a}

are elevated, with serious implications for repair and regeneration of vital organs, including the kidneys.^{1,11,12}

The decline of renal function in the elderly is well documented and characterized by multiple phenotypes including decreased GFR, increased vascular resistance, decreased renal blood flow, and a 20 to 25% loss of renal mass (Table 1).¹³ During aging, telomere length decreases more rapidly in the renal cortex than in the medulla, contributing to the cortical scarring and glomerular senescence observed in aging kidneys.¹⁴ Aging also associates with multiple diseases, including stroke and congestive heart failure, which are comorbid with kidney failure.¹⁵ Patients with heart failure have significantly shorter telomeres, suggesting it may be one factor affecting the sensitivity of the kidney to injury.¹⁶ In addition to age-dependent telomere shortening, factors such as oxidative stress and dysregulation of the renin-angiotensin system (RAS) can decrease telomere length and increase the intrinsic biologic age.¹⁷ Whereas the RAS regulates BP and ion balance and is critical in maintaining renal physiology,¹⁸ the dysregulation of RAS results in oxidative stress and inflammation,¹⁹ which contributes to de-

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Table 1. Renal dysfunctions with a telomeric contribution

Renal senescence
↓ glomerular filtration rate
↓ urinary concentrating/diluting ability
↓ urinary acidification
Impaired potassium clearance
Glomerular senescence
Renal cysts
Fibrosis
Glomerulosclerosis
Renal cell carcinoma

creased telomere length and renal fibrosis.²⁰

Impaired immunity is a predictor of morbidity and mortality in elderly populations, and inflammation also contributes risk for chronic kidney disease.²¹ Unlike the majority of somatic cells, the cells of the immune system are highly proliferative and therefore require maintenance of telomere length. Lymphocytes have the ability to upregulate telomerase activity, thereby prolonging their lifespan.²² Aging, oxidative stress, and chronic inflammation can cause lymphocyte telomeres to shorten, resulting in immune cell senescence and compromised T-cell function. This immunosuppression can increase susceptibility to kidney infection and injury. Alternatively, persistent immune cell activation engages fibroblasts, resulting in excess collagen deposition, renal fibrosis, and pathologic tissue repair.²³ When telomere length diminishes in lymphocytes, a potential outcome is a decreased T-cell response. This may ultimately contribute to kidney diseases, such as glomerulosclerosis, and impede renal regeneration.¹⁴

The relationship between telomere shortening and decreased renal repair and regeneration after injury is an area of increasing study.²⁴ The progression from renal injury to end-stage kidney disease is more prevalent in the elderly than in young people and is likely caused by a decrease in repair responses with aging. Westhoff *et al.*¹² reported that, compared with wild type, mice lacking functional telomerase have marked reductions in renal function and regeneration 7 to 30 days after ischemia-reperfusion injury.

This study suggested that shortened telomeres contribute to increased renal injury and decreased recovery after insult. As stated above, telomere attrition causes chromosome instability, cellular senescence, and apoptosis, all of which prevent normal cell function and contribute to disruption of organ homeostasis.^{2,9}

As telomeres become shorter, chromosomes become compromised, and cells assume more unstable phenotypes. Although this instability typically triggers senescence, the loss of tumor suppressor genes through the acquisition of mutations can result in an extended life span,²⁵ potentially leading to cancer initiation and progression.⁴ To acquire their unlimited potential for proliferation, tumor cells must attenuate the pressure on telomere shortening, thereby avoiding perpetual instability and cell death.²⁶ Telomerase activation is one mechanism by which tumor cells overcome successive telomere shortening. For example, low or undetectable telomerase activity is seen in most normal tissue or be-

nign tumors, whereas 90% of human cancers are telomerase positive.²⁷ This observation has led to the use of telomerase levels as a tumor marker for both early detection and prediction of clinical outcome. In a 2001 study of telomerase activity in urologic malignancy, telomerase levels were elevated in 90% of bladder, 80% of prostate, and 69% of renal carcinomas.⁴ Elevated telomerase activity was also detected in the urine samples of these patients, suggesting it may be used as an early marker for bladder cancer.

The impacts of telomere length and activity on human health will continue to receive attention as the elderly population increases. This is of particular concern in vulnerable organs of the cardiovascular system. In addition to aging, lifestyle choices such as high stress and poor diet correlate with decreased telomere length and detrimental health outcomes.²⁸ Pharmacologic activation of telomerase has been suggested as a treatment for certain diseases and as a nutritional supplement to delay the aging process.

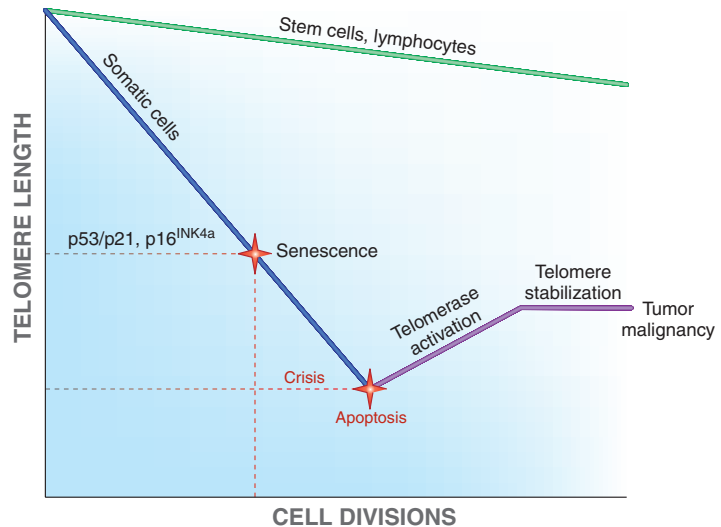


Figure 1. Changes in telomere length with successive cell divisions.²⁹ In somatic cells, a portion of the telomere is lost during each progressive cell replication. Eventually the telomeres become critically short, resulting in the activation of p53 and p16^{INK4a}. Activation of p53 leads to the overexpression of p21. Both p21 and p16^{INK4a} are cyclin-dependent kinase inhibitors that prevent continual cell proliferation and cause senescence. Inactivation of p53 and/or p16^{INK4a} enables cells to bypass senescence, which results in continued telomere attrition and genetic instability, eventually leading to cell crisis and apoptosis. Cells able to survive crisis by activating telomerase can stabilize telomere length and continue to replicate indefinitely, thus risking malignant transformation. Stem cells and highly proliferative cells like lymphocytes normally have some telomerase activity, allowing them to maintain telomere length for a longer period of time.

However, there is significant concern about the carcinogenic effects of these potential remedies; the inhibition of telomerase activity is considered a viable treatment for preventing tumor malignancy. Although promising for the treatment of some tumors, anti-telomerase therapy does have potential deleterious effects on highly proliferative cell types such as lymphocytes. This paradox highlights the conflict between the ability of telomerase to minimize biologic aging versus increasing cancer risk (Figure 1).²⁹

Nonpharmaceutical interventions are another potential solution to prevent telomere attrition. Activities such as moderate exercise and caloric restriction¹⁹ decrease the speed of premature telomere shortening, possibly because of a decrease in oxidative stress and an increase in antioxidant defenses.³⁰ Ultimately, telomere length and telomerase activity may be modifiable factors with the potential to substantially improve renal health outcomes.

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DISCLOSURES

None.

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