

HYPOTHESES

Telomeres and COVID-19

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Abstract

The medical, public health, and scientific communities are grappling with monumental imperatives to contain COVID-19, develop effective vaccines, identify efficacious treatments for the infection and its complications, and find biomarkers that detect patients at risk of severe disease. The focus of this communication is on a potential biomarker, short telomere length (TL), that might serve to identify patients more likely to die from the SARS-CoV-2 infection, regardless of age. The common thread linking these patients is lymphopenia, which largely reflects a decline in the numbers of CD4/CD8 T cells but not B cells. These findings are consistent with data that lymphocyte TL dynamics impose a limit on T-cell proliferation. They suggest that T-cell lymphopoiesis might stall in individuals with short TL who are infected with SARS-CoV-2.

KEYWORDS

COVID-19, lymphopenia, Telomeres, T cells

1 | INTRODUCTION

The following topics are briefly covered in this communication: (a) major features suggesting that telomere length (TL) is short in leukocytes of persons at higher risk of dying from COVID-19; (b) principles of hematopoietic cell TL dynamics relevant to the immune response in the face of SARS-CoV-2 infection; (c) the advantage of having a longer leukocyte TL (LTL) to mount an immune response against SARS-CoV-2 infection; (d) prescriptions for potential interventions; (e) ramifications stemming from the potential role of TL in COVID-19 outcome; and (f) contextualizing the pandemic from the standpoint of evolutionary forces shaping TL in humans.

2 | MAJOR FEATURES OF COVID-19

The majority of individuals who die from COVID-19 are elderly, adults with cardiovascular disease (CVD) and diabetes, and men.¹⁻³ In contrast, infants and children typically have a milder clinical course.⁴⁻⁷ At the population level, comparatively short telomeres in the elderly, persons with cardio-metabolic diseases and men⁸ may be the common thread linking the worse COVID-19 outcomes.

This conclusion is supported by another finding: the association of severe lymphopenia with fatal outcomes of COVID-19.⁹⁻¹¹ Lymphopenia also characterizes severe acute respiratory syndrome (SARS) and Middle East respiratory

Abbreviations: HSCs, hematopoietic stem cells; kb, kilobase; LTL, leukocyte telomere length; TL, telomere length.

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syndrome (MERS), two other diseases caused by *betacoronaviruses*.¹²⁻¹⁶ As described below, short LTL might partially explain the COVID-19-associated lymphopenia, which primarily reflects a decline in the number and exhaustion of T lymphocytes.¹⁷

3 | HEMATOPOIETIC CELL TL DYNAMICS AND ITS IMPORTANCE IN THE FACE COVID-19-ASSOCIATED LYMPHOPENIA

Leukocyte TL is a highly heritable human trait^{18,19} that displays wide inter-individual variation (range 3-4 kilo base [kb] after adjustment for age)^{20,21} and reflects mean TLs across all hematopoietic cells.²² Within every person, these cells, including the hematopoietic stem cells (HSCs) that top the hematopoietic hierarchy, show age-dependent telomere shortening.^{23,24} Although telomerase, the reverse transcriptase that maintains telomeres,²⁵ is active in subsets of hematopoietic cells, in most hematopoietic cells, this activity is insufficient to prevent telomere shortening that ultimately leads to cellular senescence, which culminates in cessation of replication.

Figure 1 depicts a model of hematopoiesis in the bone marrow under “steady state” conditions. Atop the hierarchy are a few HSCs with high proliferative capacity; they replicate approximately once a year.^{23,24} At the bottom of the hierarchy, multitudes of cells committed to specific lineages replicate approximately daily, producing ~350 billion cells

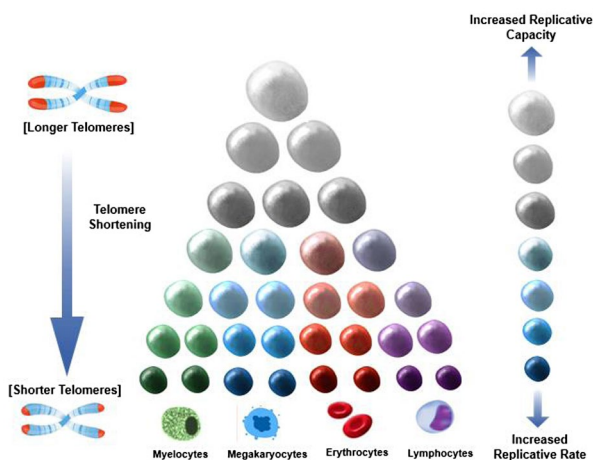


FIGURE 1 Replicative potential, replicative rate, and telomere shortening across the hematopoietic hierarchy. Larger cells denote more replicative capacity; darker cells denote faster replication. Cells atop the hierarchy replicate at a slow pace but have a high replicative capacity. Cells at the bottom replicate at a fast pace but have a lower replicative capacity. The length of telomeres (shown as the red caps at the end of the chromosomes) is progressively shorter toward the bottom due to the greater number of cell replications that occur moving down the hierarchy.

(erythrocytes and leukocytes) in adults.²⁶ Numerous mitotic divisions occur as cells are formed from top to bottom of the hierarchy; consequently, TL is shorter in unipotent cells at the bottom than cells at the top. Typically, about 3 months might elapse between the replication of HSCs and the release of their fully differentiated progenies into the circulation.²⁶ This hierarchal configuration of hematopoiesis, with its numerous unipotent cells with shorter telomeres at the bottom and progressively fewer cells with longer telomeres at the top, works efficiently to maintain homeostasis of blood cells not only in young persons with a longer LTL but also in older persons with a shorter LTL.²⁷

That said, hematopoiesis might stall in the face of a massive loss of circulating blood cells (non-steady state condition). When massive loss of cells happens, the fast-replicating unipotent cells at the bottom of the hierarchy (*first responding cells*) increase their replicative pace to offset the loss. Replication “waves” propagated up the hierarchy likely occur in tandem with the increased demand for replication of the cells at the bottom. Replications at the top, albeit slow, ultimately serve to replenish the ranks of more differentiated cells at the bottom. However, in response to massive loss of circulating cells, *first responding cells* will exhaust their TL-dependent replicative capacity and reach senescence more quickly in individuals with shorter LTL than those with longer LTL. This is because an individual's LTL (short or long) reflects TL across all cells of her/his hematopoietic hierarchy. The slow “refilling” of the stockpile of replicating cells at the bottom of the hierarchy would therefore stall hematopoiesis among individuals with a shorter LTL. Simply put, the recovery pace from a massive loss of circulating cells would be inversely related to LTL.

The kinetics of cell replication of the immune system are much more complex than the above model, which principally applies to cells, including lymphocytes, produced in the bone marrow. The development of lymphoid progenitors in the thymus during early life, maturation of lymphocytes and their production in secondary lymphoid organs add more layers of complexity to the model. We know little about the hierarchal configuration of human lymphopoiesis in lymphoid organs and in the circulation. However, we do know that lymphopoiesis is tightly linked to TL and telomerase, whose activity varies in different lymphocyte lineages. Both B and T cells show telomerase activity, which elongates telomeres in memory B cells.²⁸⁻³⁰ In contrast, telomerase fails to maintain TL in T cells and consequently TL is shorter and activation-induced proliferation is slower in memory T cells and in older persons.³⁰⁻³² Therefore, inter-individual differences in TL and the concomitant propensity of T cells to undergo senescence due to aging and in response of inherent factors (eg, genetically determined TL) might play a critical role in severe lymphopenia associated with COVID-19 and its often fatal outcome. Indeed, the lymphopenia associated with COVID-19 is marked by a reduction in CD4/CD8 cells, but not

B cells,^{17,33} consistent with their different TL dynamics during development and activation, that is, telomere elongation in B cells²⁸⁻³⁰ and telomere shortening in T cells.³⁰⁻³² Finally, in adults, TL is shorter by approximately one kb in lymphocytes than in granulocytes,³⁴ potentially explaining with an exception,³⁵ the absence of leukopenia^{9-11,33} in the majority of patients with COVID-19.

4 | THE ADVANTAGE OF HAVING A LONGER LTL IN THE FACE OF COVID-19 INFECTION

The average LTL at birth (in the US) is ~9.5 kb.²¹ Thereafter, LTL shortens by ~2 kb by the 3rd decade^{20,21} and by ~3.5 kb by the 9th decade of life.^{21,34} We know little about how much telomeres shorten per replication of hematopoietic cells in vivo. Estimates (~0.05-0.1 kb) rely on cultured cells.^{36,37} Still, consider a child whose LTL is only one kb longer than that of an adult. Based on the loss of 0.1 kb per replication, all else being equal, the TL-dependent replicative capacity of the *first responding cells* is 2¹⁰ larger for the child than the adult, meaning that the child has an enormous restorative advantage compared with the adult in the ability to respond to an acute and massive loss of circulating cells. Similarly, the average difference in LTL between adults without CVD versus those with CVD is ~0.3 kb.^{38,39} The TL-dependent replicative capacity of the *first responding cells* in adults without CVD would thus be 2³ larger than in those with CVD.

At present, the etiology of lymphopenia in patients with COVID-19 is poorly understood, but prompt recovery of the immune response requires massive lymphopoiesis, which is TL-dependent. The shorter telomeres of hematopoietic cells of the elderly, persons with cardio-metabolic disease, and men might impede their lymphopoiesis, particularly CD4/CD8 lymphopoiesis, in the face of COVID-19, increasing the risk of severe disease and a fatal outcome. In principle, all adults ranked in the lower part of the TL distribution, regardless of age, could be susceptible to severe COVID-19-associated drop in CD4/CD8 because their telomeres might be too short to sustain the speedy replicative response of these cells to acute and massive losses of lymphocytes.

5 | PRESCRIPTIONS FOR POTENTIAL INTERVENTIONS

A study sponsored by the National Institute of Allergy and Infectious Diseases has shown that remdesivir improves the outcomes of COVID-19.⁴⁰ Clearly, antiviral drugs might prove crucial for treating the infection. Reinforcing the immune response against SARS-CoV-2A by attenuating

lymphopenia might be helpful as well. The promoter region of the catalytic subunit of telomerase, hTERT, contains an estrogen transcription factor-binding site,^{41,42} but estradiol showed no effect at physiological dose on hTERT or telomerase activity in cultured peripheral blood mononuclear cells.⁴³ Still, (temporary) treatment of patients with severe COVID-19 with estrogen may, in theory, increase the activity of telomerase in vivo, thereby boosting T-cell lymphopoiesis. The telomerase activator TA-65 augmented telomerase activity and elongated telomeres in mice,⁴³ and increased telomerase activity and proliferation of cultured human T cells.⁴⁴ The oral intake of this compound was also shown to reduce the proportion of circulating senescent CD8⁺/CD28⁻ T cells in human volunteers.⁴⁵ The latest finding, however, warrants replication and caution, since the work was funded by the “anti-aging” industry.

6 | RAMIFICATIONS

The potential exists to diagnose clinically useful biomarkers of risk for severe COVID-19 based on the presumed LTL-COVID connection. Such biomarkers might help identifying persons in whom intensive management should be initiated sooner. Furthermore, the potential connection between LTL and the severity of COVID-19 raises a host of questions vital to public and global health. For instance, LTL in African Americans is ~0.2 kb longer than that of Americans of European ancestry,^{46,47} and in sub-Saharan Africans it is ~0.3 kb longer than in African Americans.⁴⁷ How can one reconcile the longer LTL of African Americans with their higher mortality rate from COVID-19,⁴⁸ assuming the finding holds after adjustment for age, sex, obesity, and demographic settings? The incidence of essential hypertension is higher⁴⁹ and the activity of the renin-angiotensin-aldosterone (RAAS) lower⁵⁰ in African Americans than in Americans of European ancestry. As mortality from COVID-19 is presumably higher in patients with essential hypertension¹⁻³ and given that angiotensin converting enzyme-2, which facilitates the intracellular entry of SARS-CoV-2, is a component of RAAS,^{51,52} different factors might influence the severity of COVID-19 in individuals of different ancestries. In this light, preliminary data, which require validation, suggest disproportionately less cases of COVID-19 in sub-Saharan regions.⁵³ Falciparum malaria—a disease that still kills numerous individuals, the majority of whom are sub-Saharan children younger than five years of age⁵⁴—causes massive hemolysis and often severe anemia in children.^{55,56} Might co-infection of infants and children with COVID-19 and malaria have a synergistic effect that greatly increases child mortality because of heightened telomeric demands for both lymphopoiesis and erythropoiesis?

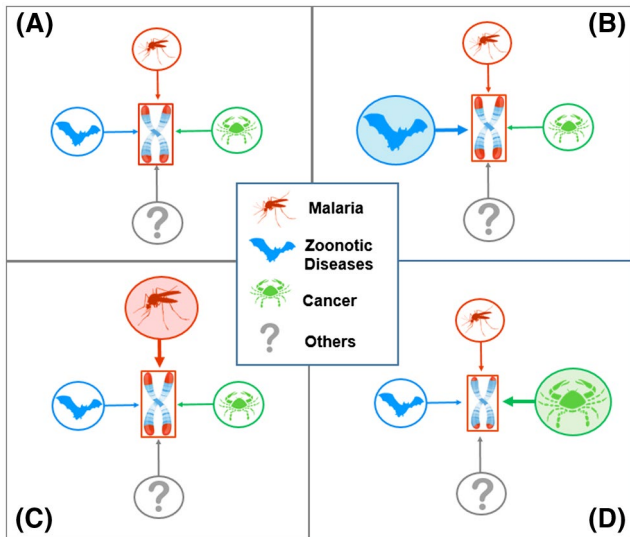


FIGURE 2 Evolutionary forces that regulate optimal TL (Model). Optimal TL is set by opposing factors that lengthen or shorten telomeres through natural selection. Displayed for illustration, are (compared to A) the effect of zoonotic viral diseases, for example, *betacoronaviruses*, which increases the demand for lymphopoiesis (B), and falciparum malaria, which increases the demand for erythropoiesis (C). Longer telomeres (red caps at the ends of the chromosomes) increase the chance of surviving these diseases. Therefore, repeated exposures to such diseases (B and C) in succeeding generations would lengthen telomeres. Cancer (D) might be an evolutionary force to shorten telomeres, because longer telomeres entail increased replicative potential and a higher cancer risk. Other factors (?) that increase demand for somatic repair through cell replication might lengthen telomeres.

7 | EVOLUTIONARY CONTEXT

Humans have been infected by zoonotic viruses, including *betacoronaviruses*, since the dawn of their evolution.^{57,58} Ever since the development of agriculture and settlements,^{59,60} they have also been exposed to *Plasmodium falciparum*, which causes the most lethal form of malaria. These infections unleashed powerful selective forces, explaining, for instance, the high prevalence of pleiotropic alleles that confer resistance to severe malaria among populations indigenous to malaria endemic regions. By increasing the turnover of lymphocytes and erythrocytes, *betacoronaviruses*, including SARS-CoV-2, *P. falciparum*, and other infectious and parasitic pathogens probably served to lengthen human telomeres through selection (Figure 2). Cancer, in contrast, has been a powerful evolutionary force to shorten telomeres in humans and other mammals (Figure 2).⁸ Human migration, endemic infections, and other exposures likely caused TL to fluctuate above and below an optimal value that maintained the balance between these and other selective forces⁶¹ that typically exert influence during the reproductive years. The majority of contemporary humans, however, largely experiences the lasting effects of such forces on TL in late

adulthood and old age.^{62,63} In this sense, the severe impact of COVID-19 on older individuals, persons with the cardio-metabolic syndrome, and men reaffirms the dictum: *Nothing in biology makes sense except in the light of evolution.*⁶⁴

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CONFLICT OF INTEREST

There is no conflict of interest.

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