Review

Telomeres and Telomerase as Promising Targets for Malaria Therapy: A Comprehensive Review

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Review

Telomeres and Telomerase as Promising Targets for Malaria Therapy: A Comprehensive Review

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Simple Summary: Malaria infection continues to exert a huge public health burden mainly due to the resistance phenomenon. In the face of multiple challenges, including resistance agains conventional antimalarials and insecticides, finding new ways to combat this global challenge is highly essential. This review explores targeting the telomeres/telomerase system, an essential component crucial for chromosome maintenance. It has recently been reported that the malaria parasite utilizes an unusual chromosome maintenance mechanism and that once in the host, it accelerates telomere shortening leading to cellular senescence and aging. Our aim is to understand how malaria parasites exploit telomeres and telomerase and devise strategies to evade the human immune system while improving their survival tactics. We conclude that targeting the telomerase system shows promise for innovative malaria therapies. These findings not only offer hope for advancements in malaria therapy but also present opportunities for tackling age-related diseases

Abstract: Infection with the malaria parasite Plasmodium, remains a major cause of illness and death world-wide. The development of evasion strategies by the parasite from host immunity and its adaptability to antimalarial drugs has raised the urgency for developing new strategies to combat this disease. One promising avenue is targeting telomeres – sequences found at chromosome termini– and telomerase – the enzyme that catalysis synthesis of telomeres using an intrinsic RNA template. As telomeres shorten critically, cells undergo replicative senescence or apoptosis. Plasmodium, lacking telomerase activity in its human stages, exploits alternative mechanisms, accelerating telomere shortening, aging, and immune evasion. Chemical telomerase inhibitors show promise as antimalarials. In this review, we examine the potential of targeting this system in malaria therapy, with telomerase inhibitors offering a novel approach. A systematic search on PubMed using Boolean techniques identified 246 relevant articles from 1985 to March 31, 2024. After filtering, 43 articles met inclusion criteria, supplemented by snowball sampling. The telomerase inhibitor drug strategy is widely applicable against cancer. However, given the druggability of telomerase and the absolute requirement for active telomere maintenance in the vast majority of parasites including plasmodium, telomerase and telomere maintenance could well represent the Achilles heel of the parasite.

Keywords: malaria, telomeres maintenance, plasmodium, therapeutic target

Introduction

Malaria infection poses a significant public health burden, affecting over half of the population worldwide. The disease, transmitted by female Anopheles mosquitoes and caused by the Plasmodium parasite, persists as a formidable threat. Plasmodium falciparum and Plasmodium vivax, among the five identified parasites causing human malaria, pose a substantial public health threat and economic burden [1]. In 2022, a total of 249 million malaria cases and 608,000 deaths were reported globally across 85 countries. The Sub-Saharan African area experiences the greatest impact of malaria, accounting for 94% of instances (equivalent to 233 million cases) and 95% of fatalities (amounting to 580,000 deaths), with roughly 80% of these deaths occurring in children under the age of 5. [2,168]. The years coinciding with the peak of COVID-19 pandemic, added an extra burden to

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malaria control efforts, with a distressing increase in new cases and deaths during this period [3,4]. The African region, particularly countries like Nigeria, Congo, Tanzania, and Mozambique remains the hardest hit, accounting for over half of the global cases [1,2,5]. According to GBD 2016 Healthcare Access and Quality Collaborators, 2018, these challenges are partly due to limited resources and inadequate healthcare systems.

Over the years, numerous malaria control measures have been implemented to lower disease incidence and mortality rates, including the development of better healthcare systems, increased funding, use of vector-repellent bed nets, Indoor residual sprays (IRS), and artemisinin combination treatments (ACTs), the challenges of malaria control measures keep increasing in sub-Saharan Africa [7,8].These statistics emphasize the urgent need for sustained efforts to combat malaria, especially in heavily affected regions. One of the underexplored areas that provide new avenues for malaria therapy is the mechanistic pathways of genomic stability of both plasmodium and humans during host-parasite interaction [9,10]. The telomere-telomerase system which composed of cellular elements that play essential role in maintaining genomic integrity and regulating cellular aging, offers innovative possibilities in targeting malaria [11–14]. Telomeres are specialized repetitive DNA sequences at linear chromosome ends, act as protective chromosomes ends from degradation [15,16]. Together with its associated proteins, telomeres prevent the loss of genetic information during cell division and protect chromosome ends from degradation and fusion. The DNA sequences of telomeres typically consist of tandem repeats of short nucleotide sequences, such as TTAGGG in humans, extending for hundreds to thousands of base pairs (Figure 1).

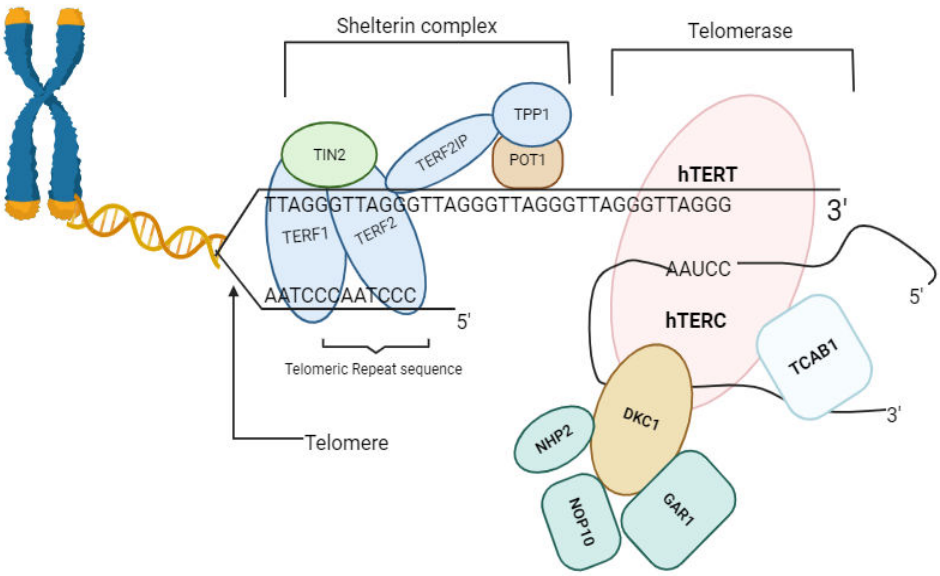

Figure 1. Telomere primary structure scheme. Figure by T. N. WAKAI, design was done in BioRender.com, and ideas adopted from [17].

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hTERT: Human Telomerase Reverse Transcriptase; telomere elongation, maintaining chromosome stability. **hTERC**: Human Telomerase RNA Component; template for telomere synthesis, enabling telomerase action.

POT1: Protection of Telomeres 1, **TPP1**: Adrenocortical Dysplasia Homolog (ACD) Protein or TINT1; telomerase recruitment to telomeres. **TERF1**: Telomeric Repeat-binding Factor 1; telomere protection. **TERF2IP**: Telomeric Repeat-binding Factor 2 Interacting Protein; stabilizes telomeres against chromosome end fusions. **TIN2**: TRF1-Interacting Nuclear Factor 2; Mediates interactions between telomere proteins, maintaining telomere integrity. **DKC1**: Dyskerin Pseudouridine Synthase 1; Modifies telomerase RNA, facilitating telomerase complex assembly. **NHP2:** Nucleolar Protein 2; Aids in telomerase complex assembly, crucial for telomere elongation. **NOP10**: Nucleolar Protein 10; Essential for telomerase stability and function in telomere maintenance. **GAR1**: Guide to the Function of NHP2-like Protein 1; Maintains telomerase RNA stability, ensuring proper telomerase function. **TCAB1**: Telomerase Cajal Body Protein 1; Guides telomerase to nuclear compartments.

This repetitive nature allows telomeres to cap the chromosome ends, shielding them from DNA breaks repair enzymes and preventing degradation or fusion with neighbouring chromosomes [18,19]. Telomeres undergo shortening with each round of cell division. This is as a result of a phenomenon of the end-replication problem, where the lagging strand cannot replicate to full length [20–22]. As a result, telomeres gradually erode over time, contributing to cellular aging and senescence [23]. Ultimately, as telomeres reach a critical threshold, cells enter a state of replicative senescence or apoptosis, constraining their ability to proliferate and contributing to tissue aging and overall decline in organismal health [24–26].

To counteract telomere shortening, some cells express an enzyme called telomerase [27,28]. Telomerases are a specialized ribonucleoprotein complexes that add repetitive DNA sequences at the ends of telomeres, thereby maintaining or even lengthening them. Telomerase consists of a catalytic protein subunit, which carries out the synthesis of telomeric DNA, and an RNA component that serves as a template for telomere extension [29,30]. The activity of the enzyme telomerase is typically high in embryonic cells, germline, and certain stem cell populations, but is typically repressed in most somatic cells [31]. However, aberrant activation of telomerase or alterations in telomere maintenance mechanisms can contribute to various diseases, including cancer, where unchecked telomere elongation enables unlimited cell proliferation [32,33]. Understanding the dynamics of telomeres and telomerase is crucial for elucidating the mechanisms underlying cellular aging, disease development, and potential therapeutic interventions aimed at modulating telomere dynamics to promote health and longevity [24,28,34,35].

While telomere shortening is linked to aging and diseases like cancer, Plasmodium parasites possess active telomerase, allowing them to evade cell death [36–38]. Targeting telomeres and telomerase emerges as a promising strategy for malaria therapy, with studies indicating that inhibiting telomerase activity can kill Plasmodium parasites [14,39,40]. Telomerase activity is crucial for maintaining telomere length and enabling unlimited cellular proliferation, a characteristic shared by both cancer cells and many single-cell eukaryotic pathogens [32,41,42]. While telomerase's role in cancer has been extensively studied, its significance in human parasites remained largely unexplored. These parasites, like cancer cells, depend on a continuous enzyme activity of telomerase to sustain their proliferative ability within their hosts [42–44]. Studying telomerase dyanamics in human parasites could reveal insights into their biology and identify new therapeutic targets for treating parasitic diseases. [45].

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Telomeres and Telomerase implication in Health and Disease

Telomeres are structures that function as "caps" on the tips of linear chromosomes to maintain genomic stability. They prevent chromosome degradation and fusion by safeguarding the internal regions of the chromosomes [16]. These complexes of nucleoproteins are made up of repetitive DNA sequences and accompanying proteins, that shield and safeguard chromosome ends, preventing them from being identified as DNA damage [46]. Telomerase is a ribonucleoprotein that act as an enzyme for catalysing the replenishing of these sequences which are gradually lost each time a cell undergoes division [47]. This enzyme activity is typically elevated in germ line, embryonic cells, and certain stem cells that are constantly dividing [48]. Nevertheless, the enzyme's function is suppressed in most somatic cells [31]. Dysregulation of mechanisms responsible for maintaining telomeres, including shifts in telomerase enzyme activity or alterations in the normal length of telomeres, plays a significant role in the development of several diseases [24,27].

In various host-parasite interactions, specific telomere processes are involved in gene regulation. For the highly proliferative human pathogen *P. falciparum*, telomerase plays a dual role. It not only supports telomeres maintenance but also involve in repairing of damaged chromosome ends [37,49]. Telomere length (TL) is influenced by both genetic inheritance and environmental factors, such as reactive oxygen species (ROS) [49–51] and inflammation [52–54] through different mechanisms as highlighted in Figure 2. Other lifestyle factors contribute to telomere length alterations including nutrition [55–58].

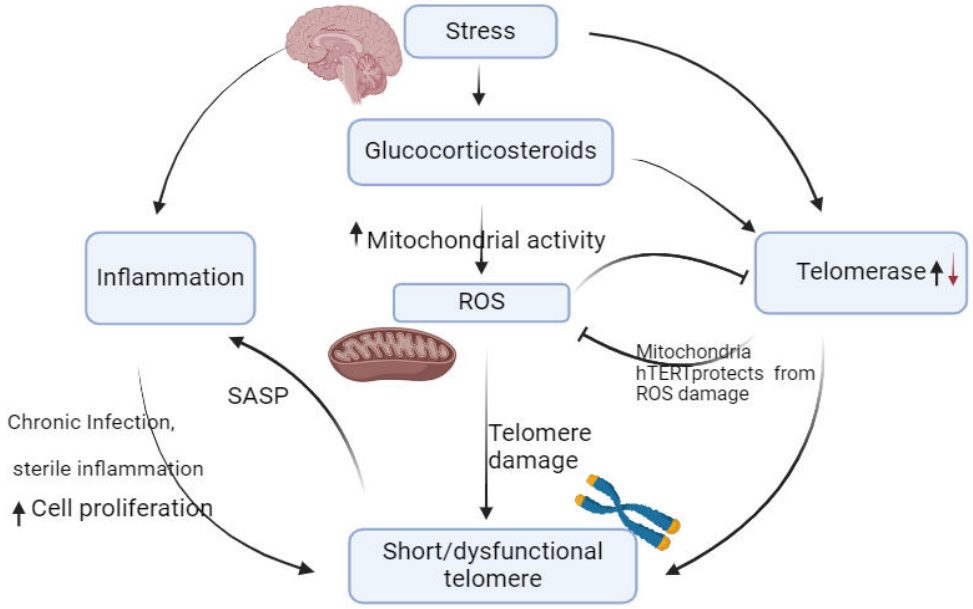

Figure 2. The Role play by psychological Stress in Telomere Shortening and Dysfunction. *Figure by T. N. WAKAI, designed was made in BioRender.com, and ideas adopted from* [49].

Numerous pieces of evidence, including observational data indicate that individuals who have been exposed to infectious diseases tend to exhibit shorter telomeres [59]. As such, the implication infectious diseases exert on telomere/telomerase dynamics is increasingly recognized as a critical aspect of host-pathogen interactions and disease progression [60]. Evidence from human observational studies indicates that chronic viral infections and inflammatory liver diseases correlate with telomere attrition [61,62] in specific cells potentially compromising immunocompetence and longevity. Moreover, individuals with telomerase deficiency due to rare genetic disorders exhibit heightened vulnerability to infectious diseases, and other complications [63,64]. This supports the notion that telomerase plays a crucial role in immune function and disease resistance. In vitro experiments reveal that acute antigen exposure initially boosts telomerase activity in T lymphocytes [64,65], but repeated encounters lead to its decline, suggesting a link between immune activation and telomere dynamics [66]. Studies with telomerase-deficient mutant mice further supports the

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significance of telomerase in immune cell proliferation and function, as well as organ regeneration following injury [63]. Decreased telomere length has been implicated in viral infections including HIV [67], Hepatitis [62], and HPV [61].

Other research works agree on the concept that exposure to infectious agents could expedite telomere shortening, contributing to immunosenescence and cellular aging process. Notably, research in avian species highlights that encounters with pathogenic infections lead to telomere shortening in blood cells and multiple tissues [12,68]. Other studies provided evidence that long-term exposure to infection can reduce telomere length which in turn modulate the host's response to inflammatory signals throughout life [53,60,69].

Telomere Length and Telomerase dynamics in Malaria

Malaria mostly affects children, especially those below the ages of five (WHO, 2023). However, elderly people experience higher rates of morbidity and mortality from infectious diseases than young people, at least in part because of age-related declines in immune function that make them more vulnerable to infections [70,71]. Changes in both genes and environment contribute to the aging process. Many age-related diseases may originate in cellular aging [56], which is defined as a decline in cellular function, growth, and division. Infections have been linked to premature aging [72–74]. Recent progress in aging research indicates a reciprocal relationship between biological age and susceptibility to disease, suggesting that exposure to infectious diseases can expedite cellular aging [68,75]. Moreover, research has illustrated that telomeres undergo gradual erosion with cell division, eventually leading to cellular senescence or programmed cell death (Figure 4), unless they are sufficiently restored by telomerase [24,52].

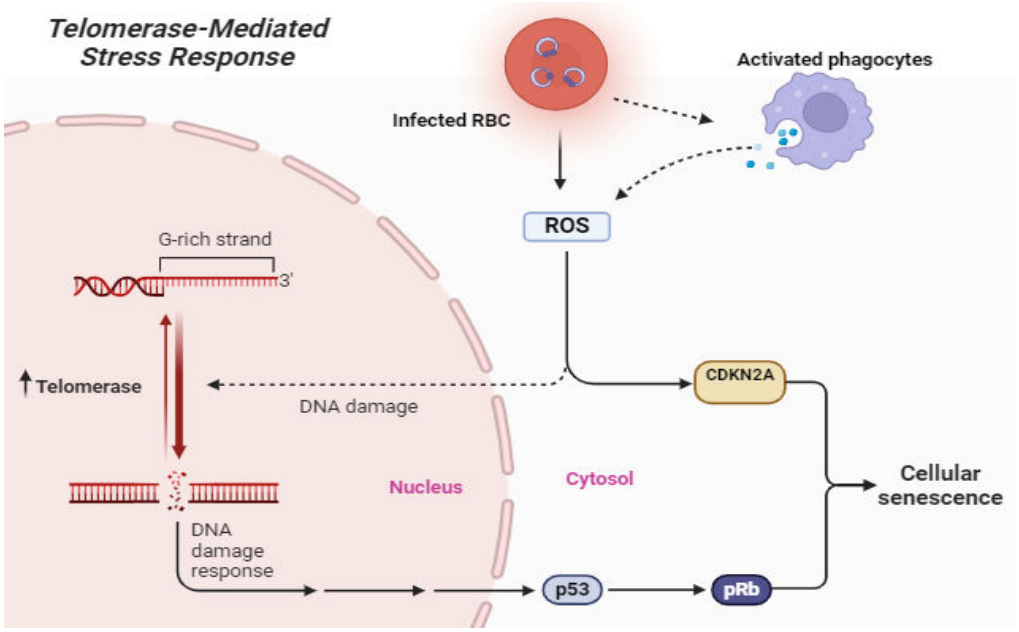

Figure 4. Schematic representation of possible Telomerase-mediated stress response during malaria. *Figure by T. N. WAKAI, designed in BioRender.com.*

Cellular stress orchestrated by parasite infection and immune response can lead to DNA damage and TL shortening. Telomerase helps restores telomeres which are vital for cell cycle, apoptosis, and cellular maintenance. Impaired telomerase enzymatic activity can precipitate aging, cellular senescence and immune function impairment [49]. The telomeres of *Plasmodium* parasites have attracted great interest from aging biologists. Telomere regulation has been implicated in a number of host-parasite interactions [14], including the promotion of telomere maintenance and chromosome end repair processes [37]. *P. falciparum* has been observed to accomplish the process of linear chromosome replication, thereby elucidating the parasites' ability to persist despite their high replication rate [76]. Additionally, disease severity depends on parasite load in the host species

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[77,78]. In *P. falciparum*, the telomere-associated sequence (TAS), which is 15–30 kb in length, precedes each of the 14 linear chromosomes of the parasite [79,80].

The telomere-associated sequence (TAS) on each chromosome consists of six distinct blocks of telomere-associated repeat elements (TAREs) [37,81]. Within the TAS region, the genes encoding the virulent var and rifin genes in *P. falciparum*, as well as the vir gene in *P. vivax*, are located [82–84].This region of the Plasmodium genome also contains telomere-associated silent information regulator 2 (Sir2), which plays a role in chromatin silencing. Sir2 is thought to bind to upstream promoter region of var genes, effectively silencing them. This results in regulation of expression of antigenic genes [85,86]. However, the aberrant lengthening of telomeres caused by Sir2A deficiency and its relationship with telomerase-mediated telomere length homeostasis and the regulation of virulence genes in *P. falciparum* are yet to be understood [44]. The telomerase of Plasmodium parasites could be targeted to prevent their multiplication and cell survival, opening novel malaria prevention strategies.

Interestingly, recent studies have reported a potential link between telomere length, telomerase activity, and malaria infection [72–74,87,88]. Other studies have reported an elevated telomerase activity in many cancers, while in malaria, telomerase may play a role in parasite development and virulence (Asghar *et al*. 2016b; Mohanty, Gupta, and Bhatnagar 2015; Religa *et al*. 2014). Recent research (past decade) demonstrates eukaryotic telomere transcription resulting in TERRA, a G-rich RNA molecule [91]. *Plasmodium* species, during their complex life cycle, infect both human and mosquito hosts, leading to chronic infections and repeated invasion of red blood cells (Figueiredo and Scherf 2005). This repetitive infection cycle places substantial stress on the telomeres of both parasite and host cells, necessitating the maintenance of telomere length for survival and propagation [92].

In recent years, research has revealed that eukaryotic telomeres undergo transcription, generating a G-rich RNA known as TERRA. Initially, it was thought that TERRA solely served a structural role and did not contain any protein-coding sequences [91]. However, the discovery of two novel signaling proteins encoded by telomeres may provide a new biomarker for biological age, and a simple blood test for these proteins may provide an early warning of cancer, inflammation, and malaria infection [93,94]. Further research on telomerase in malaria is imperative due to its pivotal role in controlling telomere length, which is linked to the advancement of these diseases. Understanding telomerase's function and activity may facilitate the creation of improved diagnostic methods and targeted treatments for malaria and cancer, potentially enhancing patient outcomes and survival rates [93,95].

Diagnostic and Prognostic Potential of Telomeres and Telomerase in Malaria

Recent research has explored the diagnostic potential of telomere and telomerase dynamics in malaria [73,88]. Studies highlight that TL in lymphocytes of infected patients is quite shorter as compared to uninfected cells [96,97], and that telomerase enzyme activity can be measured in serum of malaria patients [93]. It has been demonstrated that variations of TL in malaria parasites correlates with disease severity and treatment outcomes [72]. Other reports have revealed correlations between diminished immune function and reduced telomere length in blood samples [69,89]. However, changes in TL may be considered as a biomarker of disease and not the underlining cause [98]. Additionally, quantification of telomerase activity has already shown promise as a biomarker for detecting malaria infection and monitoring treatment response [74].

Research has firmly established that reduced telomere lengths in leukocytes serve as a predictor of poor prognostic outcomes, suggesting compromised immune functions and heightened susceptibility to diseases and infections, including malaria [98,99]. Additionally, TL attrition has been linked with risk of overall mortality [100]. Moreover, advanced molecular techniques like qPCR and LAMP has been shown to enhance the detection and measurement of telomeres and telomerase enzyme activity in clinical samples [38,77,101,102].

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Telomere Length Regulation in Malaria Parasite

Telomerase systems in *Plasmodium* and humans differ significantly. Table 1 summarizes the key differences between the two systems [37]. In Plasmodium parasites, telomerase exhibit an essential role in the preservation of TL. This enzyme comprises two integral components: telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC) [29,90,103]. The TERT protein possess the catalytic functions of the enzyme, while TERC RNA is a template to be used the synthesis of new telomeric sequences [37]. The TERT protein in *P. falciparum* has an N-terminal extension that is absent in human TERT, and TERC RNA lacks the conserved template region found in human TERC [104,105]. This contrast extends to telomerase activity regulation, as Plasmodium maintains stable telomere length through tight regulation, whereas human telomerase is generally repressed, leading to gradual telomere shortening [88,106].

Table 1. Key variations in *Plasmodium* and human telomerase systems.

Feature	*Plasmodium* telomerase system	Human telomerase system
Telomere repeat sequence	TTAGGG	TTAGGG
Telomerase RNA template	TER1	TER1
Telomerase reverse transcriptase	TERT	TERT
Accessory proteins	TRF2, TPP1	TIN2, Pot1
Regulation	Unknown	Complex, regulated by multiple factors, including cell ty pe, differentiation state, and stress

Interestingly, Plasmodium telomeres exhibit rapid elongation and recombination-based exchange, which distinguishes them from the dynamics observed in human telomeres. Although telomerase is not normally expressed in most somatic cells, it has been shown to be overexpressed in some adult stem cells, embryonic stem cells, and cancer cells [107].

It has been reported that inhibition of telomerase enzyme activity in *Plasmodium* can result to gradual loss of telomere function and, ultimately, cell death [44]. Human telomerase, hTERT is typically expressed only in few stem cells and cancer cells, whereas in *Plasmodium* species, telomerase is constitutively expressed throughout the parasite life cycle [108,109]. The telomeres of *Plasmodium* parasites are generally much shorter than those of human cells. For instance, while human somatic cells typically have telomeres ranging from 5-15 kb, those in P. falciparum are notably shorter, measuring only approximately 1-2 kb on average [36,88]. One other key difference that characterize the human telomerase is that it is primarily responsible for maintaining telomere length, while in *Plasmodium* parasites, telomere maintenance involves a combination of telomerase-mediated extension and recombination-based mechanisms [13,44]. Although telomerase activity is not essential for replication in most human cells, it has been shown to be very crucial for *Plasmodium* replication [44,110].

In addition, *Plasmodium* telomerase activity is regulated by both cell cycle molecules and telomere-associated proteins, while hTERT is modulated by a complex network of factors, including telomere-binding proteins, epigenetic modifications, and signalling pathways [35,111] . The telomerase system in *Plasmodium* species has evolved independently from that in humans, and

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appears to have undergone extensive diversification and adaptation to the unique requirements for the parasite's life cycle [112,113]. Telomerase enzyme of *Plasmodium* species may have roles in evading host immune responses. For example, it has been suggested that telomerase-mediated telomere maintenance in Plasmodium may help the parasite avoid detection and destruction by the host immune system [88,114].

Furthermore, the differences between the Plasmodium and human telomerase systems have made telomerase an attractive target for the development of new antimalarial drugs [36,40,45,115]. Several telomerase inhibitors have been identified that specifically target *Plasmodium* telomerase have shown promise as potential therapeutic agents. Linear DNA replication presents a challenge due to incomplete copying at the 5' ends, resulting in 3' overhangs rich in guanine (G-overhangs) on both strands. strands [116]. Consequently, these overhangs necessitate protection from cellular enzymes to prevent the loss of genetic information [117,118]. Cells have evolved two primary mechanisms to safeguard their chromosomal termini and prevent DNA loss [119,120].

One of these mechanisms involves telomeres. These repetitive DNA sequences were initially considered nonessential for gene expression, telomeres gradually shorten with each cell division [23] as depicted in Figure 5. When telomeres shortens, the cell gradually loses its capacity to divide, ultimately leading to cell death [121,122].

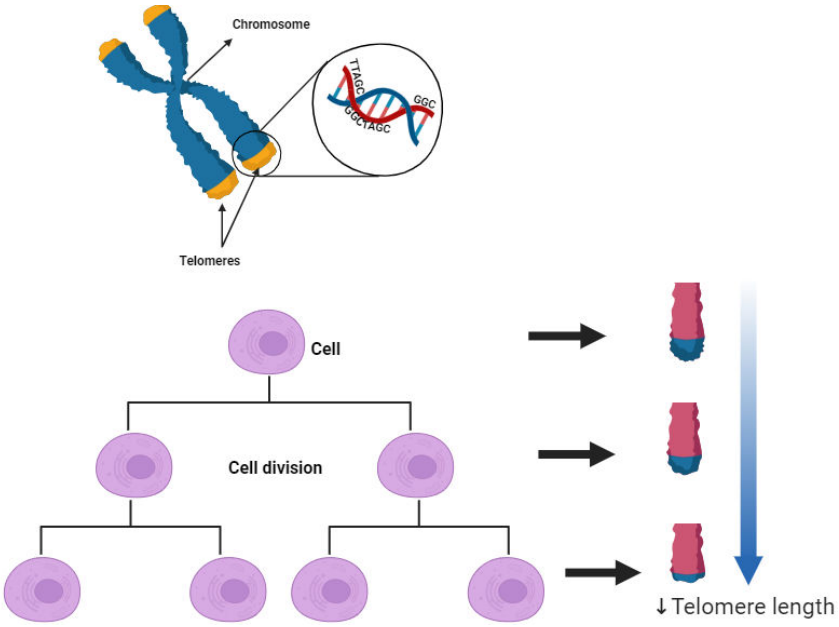

Figure 5. Depletion of Repetitive DNA at Chromosome Ends Due to Telomere Shortening. *Figure by T. N. WAKAI, designed in BioRender.com* with ideas adopted from [35].

The second crucial component of this protective system is telomerase. This protein enzyme is used for maintaining TL [123]. This is achieved by adding specific DNA repeat sequences to the chromosome termini. Notably, telomerase exhibits activity in specific cell types, such as stem cells and germ cells, while remaining inactive in most other cell types [124].

In humans, telomere shortening has been associated with cellular aging and contributes to the development of various diseases. This phenomenon leads to a state known as cell senescence, characterized by irreversible growth arrest. In contrast, cancer cells often reactivate telomerase, allowing them to evade cell senescence and continue unchecked proliferation [125]. The prospect of targeting telomeres and telomerase holds promise as a strategy for developing novel treatments for cancer and other diseases. However, it is essential to emphasize that telomerase also plays a crucial role in the normal functioning of certain cells, such as stem cells. Consequently, any efforts to target telomeres and telomerase must be designed with precision to ensure their safety and effectiveness in preserving the functionality of these critical cell types [40,126,127].

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In humans and other mammals, telomere sequences gradually shorten with each replication cycle until they reach a critical point called "Hayflick limit," after which cells enter into replicative senescence, see Figure 6 [107]. This process of telomere shortening serves as a protective mechanism against uncontrolled cell proliferation, including tumour cells [107]. However, what was originally conceived as a protective mechanism soon became problematic, as it can lead to various aberrations in cellular processes, such as the loss of telomere G-overhang, resection of the C strand, increased recombination frequency at chromosome ends, chromosome fusion, genome instability, altered gene expression patterns, growth arrest, and cell death [121,128].

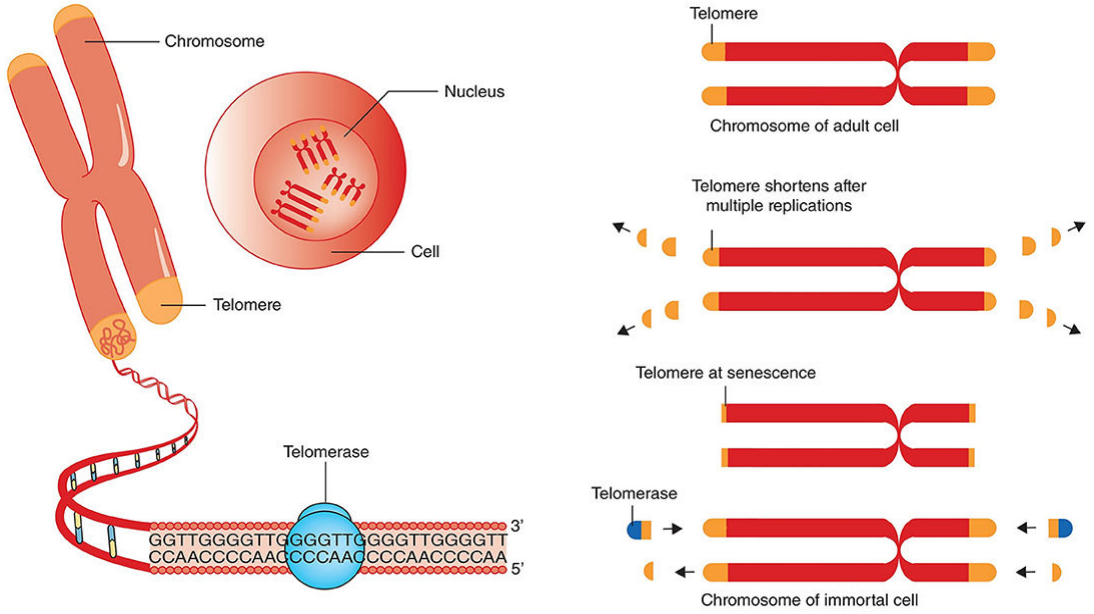

Figure 6. Telomere Attrition and Telomerase-Mediated Extension [94].

Telomerase activity is subject to tight regulation but is expressed in highly proliferative cells to preserve telomere length and prevent cell death and growth arrest [35,124]. Researchers have reported traditional methods of protecting human cells against disease through antioxidant protection using specific diet [129], treatment of Hemolytic and inflammatory diseases [130,131]. However, the efforts have not been enough to protect cellular senescence and death in malaria. The mechanisms governing telomere length maintenance are currently under active area of research, as aberrations in these mechanisms have been associated with variety of human ailment, including cancer [132,133], cardiovascular and nervous disorders [125], and malaria [72,73,89]. Notably, the *Plasmodium* parasite employs telomerase to maintain the length of its telomeres during replication [13,37]. This presents an opportunity to target the telomerase enzyme, disrupting the parasite's ability to replicate and cause disease [134].

Telomeres and Telomerase-Targeting Drugs

The persistent global challenge of malaria, primarily attributed to the Plasmodium species necessitates the continuous exploration of innovative therapeutic targets [135,136].Telomeres and the enzyme telomerase have attracted significant attention of scientists in the field of oncology due to their roles in cellular senescence and immortality [137,138]. The exploration of telomeres and telomerase-targeting strategies extends beyond cancer research. They are also implicated in the pathogenesis of infectious diseases, notably malaria [59,60,89]. Recent insights suggest that these components also play essential role in the survival and proliferation of Plasmodium parasites, presenting a unique target for antimalarial intervention [37,42,134]. Telomerase, particularly its TERT

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and TERC, is essential for telomere elongation, facilitating the parasite's replication and immune evasion within the host [88,103,114,139].

Malaria parasites exploit this telomere-telomerase system to replicate within the host cells [92,140]. This essential system plays a pivotal role in preserving the stability of the parasite's chromosomes during replication, facilitating continued replication, and inducing damage to the host's red blood cells [134,141]. Targeting this system emerges as an attractive focus for both diagnostic and therapeutic applications against Plasmodium parasites, offering the potential to disrupt parasite replication and control its spread [39,106,120,120]. In the quest for innovative antimalarial interventions, strategizing for targeting telomeres and telomerase could present a promising avenue for tackling this disease. While telomerase remains a widely explored target for disease treatment, there hasn't been a successful development of a telomerase-targeted inhibitor that has advanced to late-stage human clinical trials [142]. Given the pivotal role of telomerase in maintaining telomere length and genomic stability in Plasmodium parasites, efforts are underway to exploit this vulnerability for therapeutic purposes [34,120]. Efforts to target telomerase in Plasmodium parasites aim to selectively target telomerase in parasites and disrupt their ability to maintain telomere length, leading to genomic instability and cell death while sparing host cells [143].

There are several approaches that are currently explored, one of them include the design of inhibitors that specifically target telomerase activity in Plasmodium parasites [36,40,144]. Additionally, gene editing technologies such as CRISPR-Cas9 may offer a means to disrupt telomerase function in these parasites, potentially leading to new avenues for anti-malarial drug development [145–147]. A spectrum of telomere-telomerase targeting approaches which have been demonstrated in cancer, is illustrated in Figure 8.

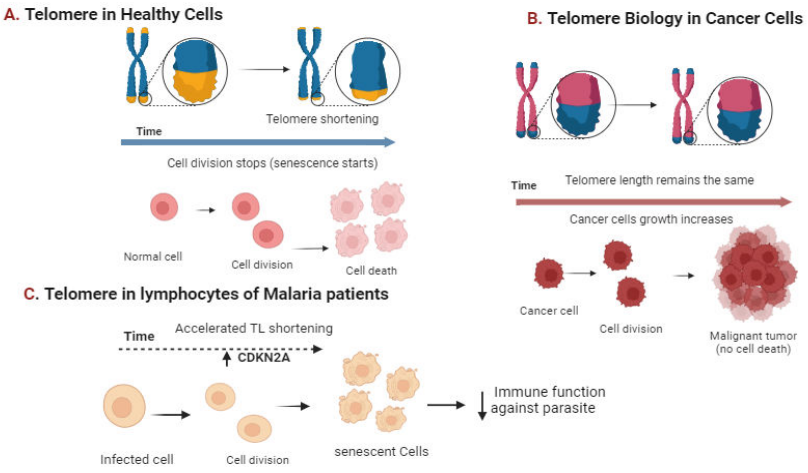

Figure 8. Telomere shortening in Healthy (A) and Diseased cells(B and C). *Figure by T. N. Wakai, designed in BioRender.com.*

GRN163(L), DN-TERT, and BIBR1532

GRN163(L), DN-TERT, and BIBR1532 are three distinct compounds that have demonstrated the ability to directly inhibit telomerase activity. These compounds exert their effects by targeting key components of the telomerase enzyme, such as the telomerase reverse transcriptase (TERT) or the telomerase RNA component (TERC). By of telomerase, these compounds interfere with the enzymatic function by disrupting its ability to extend telomeres, As a result, cells, including cancer cells, are unable to maintain their telomeres' length, leading to instability of the genome and ultimately cellular senescence and death [148–150].

BRACO19, RHPS4, and Telomestatin

BRACO19, RHPS4, and Telomestatin represent a class of compounds that have garnered significant attention for their ability to induce the formation of G-quadruplex structures at telomere termini (Figure 7). These structures, composed of guanine-rich sequences, are stable secondary DNA

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structures that can interfere with telomerase activity and impede telomere elongation. By promoting the formation of G-quadruplexes, BRACO19, RHPS4, and Telomestatin disrupt the normal function of telomerase, ultimately leading to telomere shortening and cellular senescence or apoptosis [151]. This approach has shown promise as a potential anticancer strategy, as cancer cells, which often exhibit high telomerase activity, are particularly vulnerable to telomere disruption. The development and optimization of compounds that target G-quadruplex formation at telomeres offer new avenues for the design of innovative cancer therapies aimed at selectively targeting telomere maintenance mechanisms.These compounds have been shown to induce G-quadruplex structural formation at telomere termini [152–154].

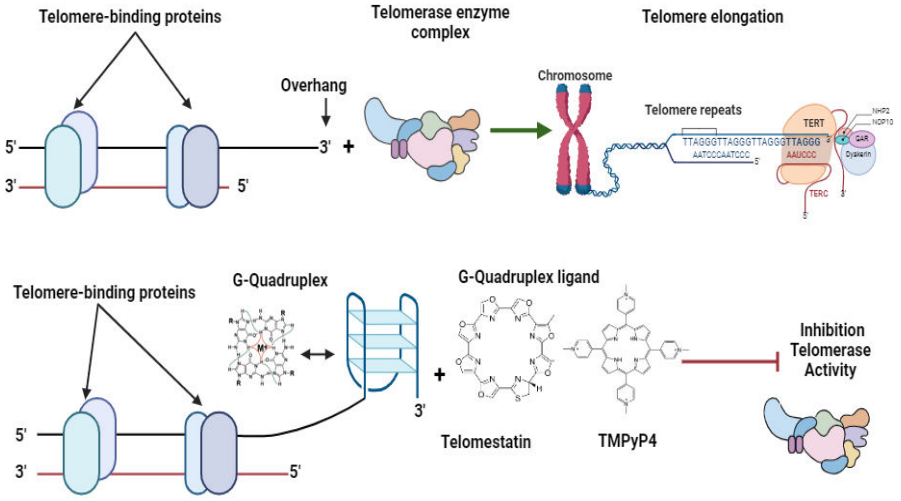

Figure 7. Inhibition of telomerase by G-quadruplex ligands Figure by T. N. WAKAI, designed in BioRender.com, adopted from [45].

T-Oligo

T-oligo, a synthetic oligonucleotide, acts as a mimic for dysfunctional telomeres, thereby initiating cellular responses that culminate in the arrest of cell cycle process and senecence. This compound exerts its effects by activating ATM/ATR-mediated pathways, key regulators of DNA damage responses [155]. Upon exposure to T-oligo, cells perceive the presence of dysfunctional telomere-like structures, triggering a cascade of signaling events modulated by ataxia telangiectasia mutated(ATM) and ataxia telangiectasia and Rad3-related(ATR) protein kinases. These kinases orchestrate the activation of downstream effectors involved in DNA damage repair, cell cycle checkpoint control, and cellular senescence induction (Figure 8). Consequently, T-oligo-induced activation of ATM/ATR pathways halts cell cycle progression and promotes the establishment of a senescent phenotype, rendering cells incapable of further proliferation [148,156–158].

Immunization Involving Peptides Derived from TERT or the Introduction of TERT mRNA into Dendritic Cells

Immunization strategies utilizing peptides derived from TERT or the inoculation of TERT genes into dendritic cells offer innovative approaches to harnessing the immune system's potential in combating cancer [159]. Peptides derived from TERT, when administered as part of an immunization protocol, serve as antigens capable of activating both T and B cells. Upon exposure to these TERT-derived peptides, dendritic cells process and present them to T cells via major histocompatibility complex (MHC) molecules (Figure 8). This presentation triggers the activation and proliferation of T cells, including cytotoxic T lymphocytes (CTLs) and helper T cells, which play crucial roles in antitumor immunity [160]. Furthermore, B cells can recognize TERT-derived peptides as antigens, leading to the production of TERT-specific antibodies that contribute to the immune response against cancer cells expressing TERT. Alternatively, the introduction of TERT mRNA into dendritic cells serves as a means to directly activate the immune system. Dendritic cells transfected with TERT

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mRNA can express TERT protein, which is then presented to T cells, eliciting an immune response against cancer cells expressing TERT. This activation of T and/or B cells enables the recognition and elimination of cells expressing high TERT levels, thereby bolstering the immune system's ability to target and eradicate parasitic cells [45,66,157].

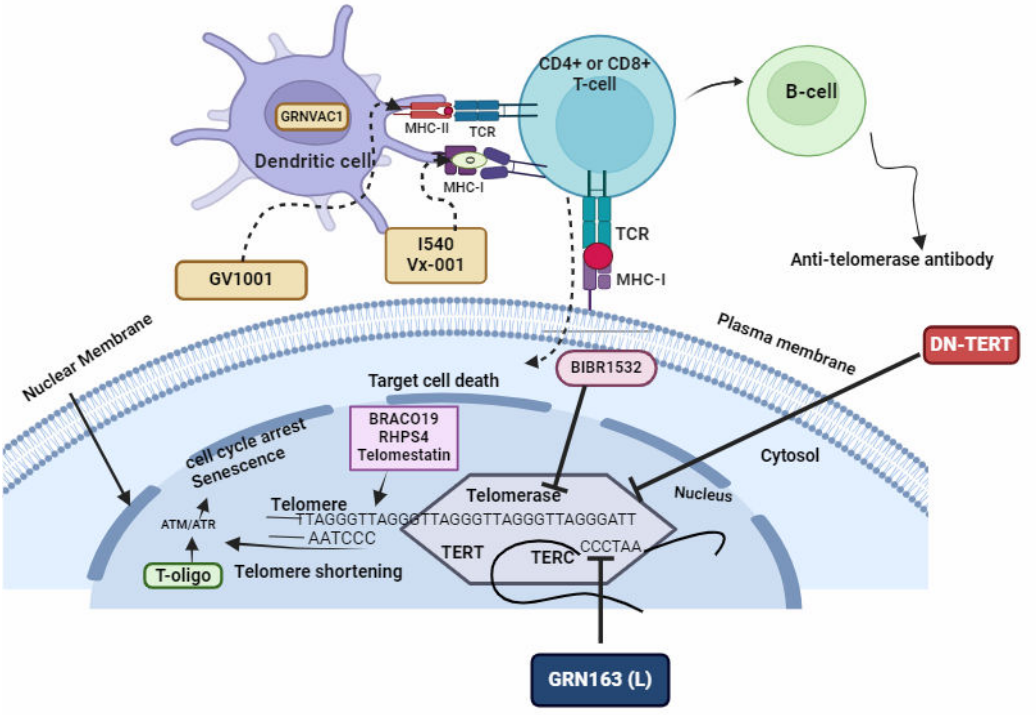

Figure 8. Drugs Targeting Telomeres and Telomerase. *Figure by T. N. WAKAI, designed in BioRender.com*, adopted from [157].

Several compounds have shown potential as telomere-targeting agents based on their ability to interact with telomeric DNA or disrupt telomere function [19,161]. However, drugs specifically designed to target telomeres and telomerase in malarial parasites have shown promising results [106]. However, they are still in the early stages of research, with no clinical drugs currently available [142,144,162,163].

Scientists have developed approaches aimed at developing drug targets against telomeres in malaria parasites (Table 2). These approaches can be classified into three: Firstly, the use of telomestatin analogs and G-quadruplex ligands: G-quadruplex ligands and analogs bind to G-quadruplex structures within the parasite's telomeres, stabilizing them and inhibiting telomerase function [14,115,151] (Figure 7). Secondly, the disruption of telomere maintenance system by synthesising compounds that interefere with telomere-associated proteins causing genomic instability and parasite cell death [92]. and thirdly, by synthesising compounds that induce telomere dysfunction through oxidative stress mechanisms [50,164]

Table 2. Selected Compounds Targeting Telomeres and Telomerase in Malarial Parasites.

Compound	Mechanism of action	Reference
Bis{N-[(pyrrolo[1,2-a]quinoxalin-4-yl)benzyl]-3-aminopropyl}amine derivatives	Disrupts telomere maintenance by Stabilizing *Plasmodium*	Guillon *et al.*, 2017
TMPyP4 (5,10,15,20-Tetrakis-(N-methyl-4-pyridyl)porphine)	Inhibition telomerase and parasite growth	[45]

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Dideoxy GPT	Inhibition of telomerase activity and promotes p cell senescence in vitro	[36]
17-AAG (Radicicol)	Depletion of Pfsir2 protein,deacetylation of Histone, shields telomerase access to telomeres	[42]
Imatinib	Inhibition of Plasmodium kinase PfPK5 and dyregulation of parasite cell cycle progression	[144,166]
Berberine	Inhibition of Telomerase activity in *P. falciparum* in stage specific manner	[167]

Conclusion and Future Perspectives

Over the years, malaria control measures have aimed to reduce the global disease burden, but challenges persist, especially in sub-Saharan Africa, where effectiveness is hindered by drug-resistant parasites and insecticide-resistant mosquitoes. Identifying new drug targets and vaccines is crucial to enhance control efforts. Telomerase has garnered interest as a potential drug target for various diseases, including malaria. Recent studies have explored telomeres and telomerase in Plasmodium, revealing the parasite's unique mechanism for chromosome end maintenance. Plasmodium parasites exhibit high telomerase activity, making them vulnerable to inhibition, which disrupts telomere maintenance, leading to cell death. Despite possessing the genetic machinery for telomere synthesis, Plasmodium cannot elongate telomeres due to absent telomerase in asexually replicating stages in the human host. Malaria infection has been demonstrated to accelerates telomere shortening in humans, avian and rodent population. This shortening correlate with disease severity and treatment outcomes, including cellular senescence and accelerated cellular aging in malaria patients. Telomere length measurement and telomerase enzyme activity quantification may serve as an infection diagnostic and prognostic biomarker. Understanding how malaria induces telomere shortening and cellular senescence could offer insights for effective intervention. While telomerase-based therapies are in development, Plasmodium's unique telomerase system presents a promising avenue for future antimalarial drug discovery.

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