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# The potential of interferon-gamma in the regulation of hTERT expression: insights into telomere dynamics and immune activation in malaria

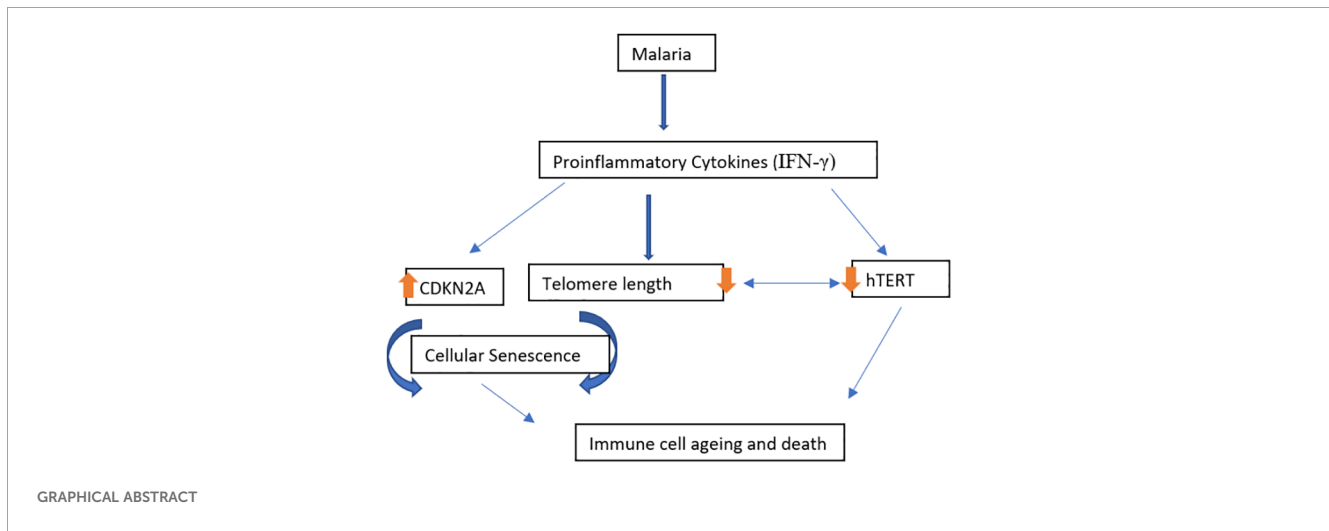
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Malaria remains a significant burden to public health, causing an estimated 282 million new cases in 2024 alone. Recurrent infections and increasing antimalarial resistance contribute to weakening immunity, a process that includes accelerated cellular ageing in immune cells, associated with telomere shortening. Increasing evidence suggests a link between *Plasmodium* infection and accelerated telomere shortening, as well as immune cell senescence. hTERT, a catalytic subunit of human telomerase enzyme is essential for maintaining telomere length (TL) and cellular replicative capacity. Although predominantly inactive in most somatic cells, hTERT appears to be partially reactivated during chronic malaria, contributing to limited restoration of telomere loss. Mechanisms that drive this unprecedented response is yet to be elucidated. Interferon-gamma (IFN- $\gamma$ ) is a key mediator of malaria immunity, driving immune activation, lymphocyte proliferation, and parasite clearance. Evidence from other disease contexts, like cancer, where IFN- $\gamma$  signaling has been linked to hTERT regulation, it is plausible to hypothesize that sustained IFN- $\gamma$  activity may influence hTERT expression during malaria infection; however, this remains hypothetical. While cytokines such as interleukin-6 (IL-6) have been suggested to modulate hTERT, the involvement of IFN- $\gamma$  in regulating hTERT in its regulation during malaria has not been experimentally validated. Herein, we review emerging evidence on IFN- $\gamma$ -association to immune activation and explores its potential implications for hTERT regulation and telomere dynamics in malaria, a key knowledge gap that is relevant to immune senescence and susceptibility to reinfection.

## KEYWORDS

chronic inflammation, human telomerase, immune senescence, interferon-gamma (IFN- $\gamma$ ), malaria, telomere length



## 1 Introduction

Malaria is one of the deadliest diseases, caused by the *Plasmodium* parasite and transmitted by the female *Anopheles* mosquito, considered one of the deadliest animals. This parasitic infection, continues to be a major global health challenge contributing to an estimated 282 million cases and over 610,000 deaths in 2024 alone (1). The parasite-causing malaria has a complex life cycle in two hosts: human and mosquito. The pathophysiology of malaria is directly linked to effects from the host-parasite interactions and the ensuing immune responses (2, 3). Several challenges have hampered the successful elimination of this diseases. Drug resistance and recurrent infections due to immune evasion require more efforts to deeper understanding of malarial immunity (4–6).

The pressure of malaria on the host is largely determined by responses orchestrated by immune response cytokines, which are central to controlling the disease pathogenesis. IFN- $\gamma$  stands out as a critical cytokine, playing an indispensable role in activating antigen presenting cells (APCs) and orchestrating parasite elimination (7, 8). However, an imbalanced or excessive IFN- $\gamma$  response has been linked to immunopathologies and chronic inflammatory conditions (9, 10).

We recently showed that global research output has been overwhelmingly focused on viral infections like HIV and COVID-19, leaving a significant gap in research on other infections, with malaria research being notably limited and almost neglected, particularly in African contexts (11). Chronic infections, such as malaria, can accelerate telomere shortening in immune cells, leading to cellular senescence and potentially weakening immune responses over time (12). This phenomenon has been observed in human cohorts, where acute *P. falciparum* infection results in significant telomere shortening in peripheral blood cells (13).

In this review, we examine the intersection of IFN- $\gamma$  signaling and hTERT regulation in malaria and propose potential avenues for

further investigation of their prognostic and therapeutic relevance in combating an infection that disproportionately affects vulnerable communities. A deeper understanding of existing evidence may provide a framework for elucidating how sustained immune activation, particularly mediated by IFN- $\gamma$ , influences telomere length dynamics and cellular senescence. These processes may contribute to disease chronicity and increased susceptibility to reinfection, with important implications for the development of novel therapeutic and prognostic strategies.

### 1.1 Overview of malaria pathophysiology and immune activation

The *Plasmodium* parasite undergoes a complex life cycle, involving asexual reproduction in humans and sexual reproduction in mosquitoes. Upon infection, sporozoites rapidly infect hepatocytes, developing into merozoites that subsequently infect red blood cells (RBCs), leading to the symptomatic blood stage of malaria (2). The host's immune response to malaria involves both innate and adaptive arms. Innate immune responses are rapidly activated upon parasite recognition, often through pathogen-associated molecular patterns (PAMPs) and Toll-like receptors (TLRs). This leads to the release of various cytokines, including IFN- $\gamma$ , and the recruitment of immune cells such as Natural Killer (NK) cells and macrophages (14, 15). NK cells are a significant early source of IFN- $\gamma$  in response to *P. falciparum*-infected erythrocytes (8).

Adaptive immune responses develop after repeated exposure and involve CD4+ T helper 1 (Th1) cells, B cells, and antibody production (16, 17). IFN- $\gamma$  production by  $\alpha\beta$ T cells,  $\gamma\delta$ T cells, and NK cells is robustly induced and long-lived after *P. falciparum* infection, persisting for at least 14 months (18, 19). Prior exposure influences the immune response: while rapid IFN- $\gamma$  production can lead to efficient parasite control, individuals with histories of prior

malaria show an inverse relationship between neopterin and IFN- $\gamma$  levels and the number of previous infections, suggesting a dampened IFN- $\gamma$ -mediated T cell-macrophage interaction with repeated exposure (20).

### 1.2 IFN- $\gamma$ plays a dual role in malaria

Interferon-gamma (IFN- $\gamma$ ) cytokine plays a central role in host defense against *Plasmodium* parasites, and its activity has been linked to immune cell activation and parasite clearance (7, 21, 22). It is well known for activating macrophages and promoting parasite phagocytosis (23). For instance, increased IFN- $\gamma$  production is associated with a reduced incidence of clinical malaria episodes (24). However, excessive or dysregulated IFN- $\gamma$  can contribute to immunopathology, inflammation, and tissue damage (8). The magnitude and timing of the IFN- $\gamma$  response are critical, as observed in murine models where early IFN- $\gamma$  production distinguishes nonlethal from lethal infections (25). Figure 1 illustrates the proposed relationship between IFN- $\gamma$  signaling and hTERT regulation in the context of malaria infection.

As shown in Figure 1, IFN- $\gamma$ -mediated immune activation is linked to alterations in hTERT regulation, potentially influencing telomere dynamics and cellular senescence during malaria.

### 1.3 Telomere dynamics, hTERT expression, and malaria-driven inflammation

Telomeres are repetitive DNA sequences (TTAGGG) at chromosome ends that protect genomic integrity (26; 27). Their length dictates cellular replicative capacity; critical shortening triggers cellular senescence or apoptosis (28–30). Telomere shortening occurs through both replicative processes (the end-replication problem) and non-replicative factors like oxidative stress and inflammation as shown in Figure 1 (31, 32).

### 1.4 Regulation of hTERT

The expression of hTERT, the rate-limiting component of telomerase, is tightly regulated at multiple levels, primarily transcriptionally(27). Key transcription factors involved include activators like c-Myc, Sp1, NF- $\kappa$ B, STAT3, STAT5, and NFAT1, and repressors such as Mad1, E2F1, NFX1-91, WT1, p53, p27KIP1, and p16 (33, 34). Alternative splicing and post-translational modifications also modulate hTERT activity (35, 36). Telomere length itself provides a feedback mechanism on gene expression through “telomere position effects over long distances” (TPE-OLD), where long telomeres can repress genes like hTERT, and short telomeres can lead to their activation by altering chromatin structure (37).

### 1.5 Malaria’s impact on telomere dynamics

Malaria-driven inflammation, characterized by oxidative stress and cytokine production, directly causes telomere attrition (12, 38). Human studies provide compelling evidence: a single acute *P. falciparum* infection leads to significant telomere shortening and decreased telomerase activity in peripheral blood cells within three months, alongside elevated CDKN2A expression (a senescence marker) (39). Longitudinal data from travelers show that, following successful treatment, telomerase activity can increase, and telomere length can be gradually restored over a year, suggesting a capacity for telomere repair and reversal of cellular aging in single acute episodes (13). However, this is contrasted by observations in birds where chronic malaria leads to accelerated and systemic telomere shortening across multiple organs (liver, lungs, spleen, heart, kidney, brain) (40).

The impact of malaria on TL is different in acute and chronic exposure conditions. Acute malaria infection induces rapid telomere degradation and suppression of telomerase expression, with partial recovery as parasites are cleared (12).

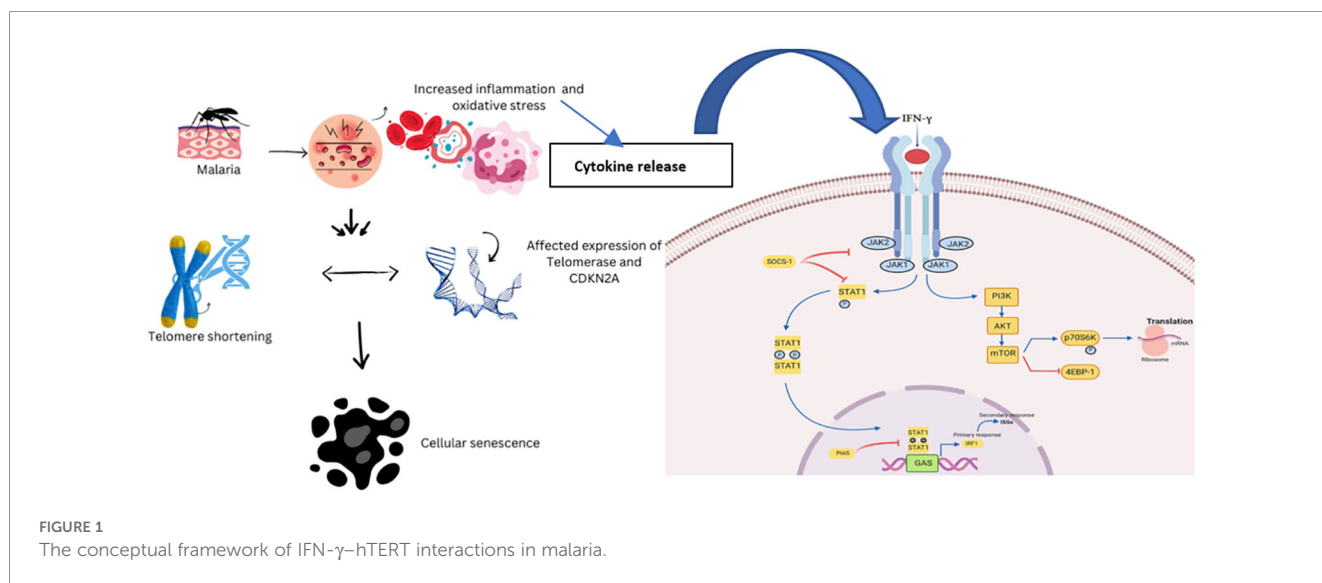


FIGURE 1 The conceptual framework of IFN- $\gamma$ -hTERT interactions in malaria.

In contrast, prolonged exposure to *Plasmodium* infection, prevalent in endemic regions, can lead to cumulative senescence from repeated infections, exacerbating malaria pathogenesis and accelerating telomere shortening (41). This chronic state can be marked by a progressive decrease or suppression of IFN- $\gamma$ -mediated T cell-macrophage interactions observed with increasing numbers of prior infections (9).

Malaria impact specific immune cells. In human lymphocytes, telomerase activity is expressed during development, differentiation, and activation (42). However, malaria-induced telomere shortening could limit the clonal expansion of T cells, NK cells, and  $\gamma\delta$  T cells, ultimately impairing anti-*Plasmodium* responses and contributing to immune senescence (43, 44). This senescence may heighten reinfection risk by diminishing the capacity for effective and sustained adaptive immunity (45).

Cellular senescence is often accompanied by the Senescence-Associated Secretory Phenotype (SASP), where senescent cells secrete pro-inflammatory cytokines such as IL-6 and TNF- $\alpha$  (45, 46). This perpetuates a vicious cycle where chronic inflammation further drives telomere erosion and accelerates immune aging in malaria (47).

## 1.6 Interplay of IFN- $\gamma$ and hTERT expression

The molecular interplay between IFN- $\gamma$  and hTERT expression is multifaceted, primarily mediated through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway (48, 49).

### 1.6.1 IFN- $\gamma$ signaling pathway

IFN- $\gamma$  binding to its receptor triggers the activation of JAKs, leading to the phosphorylation of STAT1. Phosphorylated STAT1 dimerizes, translocates to the nucleus, and binds to Gamma-activated Sequences (GAS) elements in the promoters of Interferon-Stimulated Genes (ISGs), thereby inducing their transcription (50).

### 1.6.2 IFN- $\gamma$ 's effects on hTERT

IFN- $\gamma$  plays an essential protective immunity against blood-stage malaria (18). Human data consistently demonstrate a repressive effect of IFN- $\gamma$  on hTERT. IFN- $\gamma$  signaling represses telomerase activity and hTERT transcription, a process mediated by Interferon Regulatory Factor-1 (IRF-1) (51, 52). Ectopic expression of IRF-1 significantly attenuates hTERT promoter activity, and conversely, IRF-1-deficient murine fibroblasts exhibit over 15-fold higher hTERT promoter activity (53). This effect is further propagated by IRF-1's induction of the cell cycle inhibitor p27Kip1, which subsequently downregulates hTERT mRNA and telomerase activity in human cervical cancer (54). Interferon-inducible IFI16 also negatively regulates hTERT by inhibiting the transcription factor c-Myc, a potent activator of hTERT (51). In

glioblastoma cell lines, IFN- $\gamma$  treatment alone significantly downregulates hTERT mRNA and protein levels and upregulates p21Waf1 and p27Kip1, further supporting its repressive role (55).

### 1.6.3 Epigenetic mechanisms

While direct studies linking STAT1-mediated recruitment of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs) to hTERT promoter silencing specifically in human malaria are not explicitly detailed in the provided literature, the broader understanding of hTERT regulation highlights the importance of epigenetic control. hTERT promoter activity is influenced by DNA methylation and histone modifications, such as histone acetylation and methylation patterns. For example, telomerase expression correlates with histone H3 and H4 hyperacetylation and H3K4 methylation. Conversely, repressive epigenetic marks like H3K27me3 are associated with silenced hTERT alleles<sup>13</sup>. STAT proteins are known transcriptional regulators, and their interaction with epigenetic machinery represents a plausible, though not yet fully elucidated in malaria, mechanism for hTERT modulation. Recent studies on chronic inflammation and cell cycle regulation continue to explore these intricate connections, suggesting that IFN- $\gamma$ -induced signaling could indirectly influence hTERT through modulation of epigenetic modifiers (56, 57).

### 1.6.4 Context-dependent hTERT regulation by IFN- $\gamma$

The seemingly dual roles of IFN- $\gamma$ —repressing hTERT under certain conditions while being integral to immune responses that necessitate cell proliferation (and thus potentially hTERT activity)—can be reconciled through context-dependent mechanisms, particularly distinguishing acute versus chronic inflammation (23, 49). In acute immune activation, such as during the initial phase of malaria infection, the rapid proliferation of immune cells (T cells, NK cells) requires telomerase activity to maintain telomere length during intense clonal expansion (44, 58). Here, factors like Nuclear Factor of Activated T cells (NFAT1), which directly activates hTERT transcription upon lymphocyte activation, might transiently override direct repressive signals (59). This is supported by the observation that hTERT is expressed soon after lymphocyte activation (60, 61).

However, sustained, chronic exposure to IFN- $\gamma$ , as observed in prolonged malaria infections, can lead to the repression of hTERT and contribute to immune senescence (62). This is evident in studies showing that IFN- $\gamma$  downregulates hTERT via IRF-1/IFI16 pathways (54) and that chronic malaria accelerates telomere degradation (12). The inverse correlation between neopterin/IFN- $\gamma$  levels and previous malaria infections further supports a dampened IFN- $\gamma$  response in chronic settings (63). The distinction between avian and human contexts is important; studies on IRF-4 and IRF-8 in avian systems are not directly applicable to human immune senescence in malaria (49). The primary focus here remains on human-relevant mechanisms and data.

### 1.6.5 Relevance of IFN- $\gamma$ in immune defense and telomere attrition during malaria to malaria

Elevated IFN- $\gamma$  during malaria infection plays a critical role in host defense. However, the regulatory effects on hTERT expression can exacerbate telomere attrition in immune cells. This creates a delicate balance: while IFN- $\gamma$  is vital for immediate protection and parasite clearance, its sustained presence and the resulting hTERT regulation might drive immune exhaustion and accelerate cellular aging, impacting long-term immunity against *Plasmodium* parasites (39). Interventions that selectively temper chronic IFN- $\gamma$ -mediated hTERT repression, or enhance repair mechanisms for telomeres, could potentially restore durable immunity and reduce reinfection risk.

## 2 Clinical relevance and future considerations

The interplay between IFN- $\gamma$  and hTERT in malaria is complex. While IFN- $\gamma$  generally suppresses hTERT expression *in vitro*, its role in the context of malaria-induced immune activation and telomere shortening needs further elucidation. Malaria infection leads to robust immune cell activation, including T cells, which are known to express telomerase transiently upon activation (38). However, the progressive telomeric loss seen in immune cells during malaria could be exacerbated by high levels of IFN- $\gamma$ , which promotes telomere attrition. CD4+ T cell-derived IFN- $\gamma$  is essential for controlling blood-stage malaria, highlighting the critical, yet potentially double-edged, nature of this cytokine in infection (18, 19).

Conversely, the overall immune response during malaria, including IFN- $\gamma$  production, might also influence the longevity and function of immune cells by affecting their telomere dynamics. Asymptomatic *Plasmodium vivax malaria*, for example, is associated with an IFN- $\gamma$ -program on adaptive immunity, suggesting a role for IFN- $\gamma$  in maintaining a controlled immune state that limits parasite growth (64, 65). However, the rapid establishment of parasite-specific immune regulatory networks after malaria exposure can hinder vaccine efforts (66, 67). Understanding how IFN- $\gamma$ -mediated immune activation intersects with hTERT regulation and telomere dynamics is critical for clarifying malaria pathogenesis, immune durability, and treatment outcomes. Elucidating this relationship may provide novel biomarkers of immune aging and identify therapeutic windows to balance effective parasite control with long-term immune competence, thereby informing vaccine design and host-directed interventions.

Future research should focus on elucidating the precise molecular mechanisms by which IFN- $\gamma$ -induced STAT1 activation influences epigenetic modifiers to regulate hTERT expression in human immune cells during malaria. Longitudinal studies in human malaria cohorts are necessary to track telomere dynamics and hTERT expression in specific immune cell subsets (T cells, NK cells,  $\gamma\delta$  T cells) across acute and chronic infection stages. Such studies would provide critical insights into the context-dependent effects of IFN- $\gamma$  and help identify optimal windows for

interventions targeting hTERT regulation to combat immune senescence and enhance long-term protective immunity against adverse effects of malaria.

## 3 Conclusion

Ultimately, malaria places the immune system in a difficult dilemma: it must fight hard to survive the present infection, even if that fight quietly erodes its future strength. IFN- $\gamma$  stands at the center of this trade-off—indispensable for parasite control, yet potentially costly to immune cell longevity through sustained hTERT repression and telomere erosion. Recognizing this tension reframes malaria not only as an infectious disease but also as a driver of immune aging. Addressing it will require strategies that do more than clear parasites; they must also protect the long-term vitality of the immune system. Only by striking this balance can we move toward durable immunity, more effective vaccines, and interventions that safeguard both survival today and immune resilience tomorrow.

## Author contributions

IA: Conceptualization, Writing – review & editing, Supervision, Validation. CF: Conceptualization, Writing – original draft, Writing – review & editing. EO: Writing – review & editing. TW: Conceptualization, Writing – original draft, Writing – review & editing.

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