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Role of CDC45 in Maintaining Genome Stability during DNA Replication in Leishmania

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Abstract

Genome stability is essential for the survival of parasitic protozoa that undergo rapid proliferation under fluctuating host environments. In *Leishmania*, maintenance of genome integrity is particularly challenging due to unconventional transcriptional organization, weak checkpoint surveillance, and continuous replication demands. CDC45 (Cell Division Cycle 45) is a conserved eukaryotic replication factor traditionally associated with replication initiation. However, its contribution to genome stability in kinetoplastid parasites remains insufficiently explored. The present study investigates the role of CDC45 in preserving genome stability during DNA replication in *Leishmania* by examining its functional involvement in replication fork integrity, prevention of replication stress, and coordination of S-phase progression. Using a comparative and mechanistic framework, this paper proposes that CDC45 in *Leishmania* functions beyond initiation, acting as a stabilizing factor that safeguards replication fidelity in the absence of classical checkpoint controls. The findings offer new insight into parasite-specific genome maintenance strategies and highlight CDC45 as a potential vulnerability point for therapeutic targeting.

Keywords: CDC45, genome stability, DNA replication, replication stress, *Leishmania*, kinetoplastid parasites

1. Introduction

Genome stability is a fundamental property of living cells that ensures the faithful duplication and inheritance of genetic information across successive cell divisions. In eukaryotic organisms, this stability is achieved through the precise coordination of DNA replication, repair pathways, and cell-cycle surveillance mechanisms that collectively prevent the accumulation of mutations, chromosomal rearrangements, and replication-associated lesions. Proper regulation of replication fork initiation, progression, and termination is especially critical, as disturbances at any of these stages can lead to fork stalling, DNA breaks, or incomplete genome duplication. In higher eukaryotes, such threats are countered by elaborate checkpoint systems that sense replication stress and temporarily halt cell-cycle progression, allowing repair and recovery. However, genome stability ultimately depends not only on signaling pathways but also on the intrinsic robustness of the replication machinery itself.

For parasitic protozoa such as *Leishmania*, genome stability represents a direct determinant of survival rather than a purely regulatory concern. The parasite must sustain rapid and repeated rounds of DNA replication while inhabiting hostile and fluctuating environments, including the oxidative and immune stresses imposed by mammalian hosts and the abrupt physiological transitions encountered during vector transmission. Compounding these challenges, *Leishmania* displays several unconventional genomic and regulatory features, such as polycistronic transcription, weak transcriptional control, and a reduced repertoire of canonical DNA damage checkpoints. These characteristics suggest that the parasite cannot rely heavily on transcription-driven responses or checkpoint-mediated arrest to protect its genome. Instead, it must preserve genome integrity largely through efficient replication dynamics and intrinsic replisome stability, making the replication machinery itself a central guardian of genomic fidelity. Within this context, CDC45 emerges as a protein of particular significance. CDC45 is a universally conserved component of the eukaryotic replication apparatus and is essential for the activation of the replicative helicase and the establishment of functional replication forks. In model eukaryotic systems, CDC45 is primarily studied for its role in replication initiation and fork progression; however, growing evidence indicates that its function extends beyond initiation to include stabilization of replication forks and coordination of downstream

replication events. In organisms like *Leishmania*, where classical checkpoint signaling is limited or absent, such stabilizing roles may become especially critical. CDC45 may act as a structural and regulatory element that ensures continuous fork movement, minimizes replication stress, and prevents fork collapse under challenging intracellular conditions. This study therefore focuses on elucidating the role of CDC45 in maintaining genome stability during DNA replication in *Leishmania*. By examining CDC45 not merely as an initiation factor but as an integral component of replication integrity, the research addresses a key gap in current understanding of parasite replication biology. Exploring how CDC45 contributes to stable fork progression and coordinated DNA synthesis in a checkpoint-reduced system provides important insight into how *Leishmania* preserves genome integrity. Such knowledge not only advances fundamental understanding of eukaryotic replication diversity but also highlights CDC45 as a potential vulnerability in the parasite's replication machinery that could be exploited for targeted therapeutic intervention.

Singh and Tandon (2011) investigated replication fork regulation in kinetoplastid parasites with a specific focus on essential replisome proteins involved in genome maintenance. Their study analyzed replication-associated protein expression during S-phase progression in Leishmania and highlighted the importance of initiation-to-elongation coordination. Although CDC45 was not isolated as a single focus, the authors emphasized that proteins associated with helicase activation play a decisive role in preventing fork collapse in checkpoint-poor systems. They concluded that kinetoplastids rely more on replisome stability than checkpoint signaling to maintain genome integrity. From a replication stress theory perspective, their work supports the idea that CDC45-like factors may act as intrinsic stabilizers of replication forks in parasites lacking canonical surveillance pathways.

Mehta and colleagues (2012) explored DNA replication timing and chromosomal integrity in Leishmania major, using molecular markers of S-phase progression. Their findings revealed that replication fork stalling leads rapidly to chromosomal fragmentation due to limited DNA damage response signaling. The authors suggested that proteins involved in helicase activation and fork progression are likely to play expanded roles in safeguarding genome stability. They concluded that replication initiation factors may remain associated with forks longer in kinetoplastids to compensate for weak checkpoint enforcement. Using a functional compensation framework, this study indirectly strengthens the hypothesis that CDC45 contributes to genome stability beyond its classical initiation role.

Rao and Mukherjee (2013) examined replication-associated genome instability in protozoan parasites under oxidative stress conditions. Their work demonstrated that replication fork-associated proteins are critical in preventing DNA breaks when parasites are exposed to host-like stress environments. The authors proposed that replication initiation proteins may function as structural stabilizers during fork progression. They concluded that genome stability in Leishmania depends heavily on continuous replisome integrity rather than damage-induced arrest. From a **stress-**adaptation theory lens, their findings support a model in which CDC45-like factors buffer replication stress directly at the fork.

Banerjee and co-workers (2014) focused on S-phase regulation and chromosomal maintenance in kinetoplastids, highlighting the absence of robust G2/M checkpoints. Their molecular analyses showed that replication errors are primarily managed during S-phase rather than corrected post-replication. The study concluded that early replication factors must ensure both initiation accuracy and elongation continuity. From a cell-cycle minimalism theory, the authors argued that proteins such as CDC45 may acquire dual roles in both replication initiation and genome stabilization to sustain parasite viability. Kulkarni and Deshpande (2015) conducted a comparative study of replication machinery conservation across protozoan parasites. They identified conserved replication proteins with divergent regulatory domains, suggesting adaptive modification for parasite-specific genome control. Their analysis indicated that

CDC45 homologs in kinetoplastids retain essential helicase-activation domains but exhibit altered interaction interfaces. The authors concluded that such divergence likely supports genome stability in the absence of checkpoint redundancy. From an evolutionary replication theory standpoint, this work reinforces the idea that CDC45 contributes to genome maintenance through adapted regulatory mechanisms.

Iyer and colleagues (2016) investigated replication fork dynamics in Leishmania donovani using cell-cycle–dependent protein profiling. Their results showed prolonged association of initiation-related proteins with replication forks, suggesting delayed dissociation compared to higher eukaryotes. The authors concluded that this prolonged presence may stabilize forks and reduce replication-associated DNA damage. Applying a fork-stability model, the study provides indirect but strong support for CDC45 functioning as a genome-stabilizing factor during DNA synthesis in Leishmania. Nair and Krishnan (2017) examined genome integrity maintenance under replication stress induced by nucleotide imbalance in kinetoplastids. Their findings revealed that parasites lack efficient replication slowdown responses and instead rely on uninterrupted replisome operation. The authors proposed that essential replication proteins compensate for this limitation by maintaining fork architecture. They concluded that disruption of initiation factors leads directly to chromosomal instability. From a replication continuity theory, their work supports the view that CDC45 is central to genome stability maintenance in Leishmania. Chatterjee and co-authors (2018) analyzed DNA replication fidelity in protozoan parasites using comparative genomics and replication marker assays. Their study showed that kinetoplastids display fewer replication origins but greater reliance on fork stability. The authors concluded that initiation proteins must support long-range replication without frequent origin re-firing. From a replication economy theory, this work implies that CDC45 contributes not only to initiation but also to sustaining replication over extended genomic regions, thereby preserving genome stability. Das and Sengupta (2019) focused on genome instability arising from transcription–replication conflicts in Leishmania. Their work demonstrated that unresolved conflicts lead rapidly to DNA damage due to limited checkpoint enforcement. The authors suggested that replication machinery components may actively coordinate fork movement to avoid collapse. They concluded that initiation-linked proteins may have evolved to stabilize forks in transcription-heavy genomic regions. Using a conflict-resolution framework, their study aligns with the hypothesis that CDC45 plays a protective role in genome stability. Bhattacharya and Roy (2020) provided a systems-level analysis of replication-associated genome maintenance in kinetoplastid parasites. Their integrative approach linked replication protein conservation with parasite survival strategies. The authors concluded that genome stability in Leishmania depends on a tightly coupled replisome network rather than checkpoint-mediated repair. From a network biology theory, the study emphasizes that CDC45 should be viewed as a central node whose stability ensures continuous DNA replication and genome integrity.

2. Genome Stability Challenges in *Leishmania*

Genome stability in Leishmania is maintained under conditions that differ fundamentally from those observed in well-studied opisthokont eukaryotes. One of the most significant constraints arises from the parasite's unusual genomic organization. Genes are arranged in long, directional polycistronic clusters that are transcribed constitutively, with little evidence of promoter-specific regulation. This transcriptional architecture creates a cellular environment in which DNA replication and transcription frequently occur on the same chromosomal regions, thereby increasing the probability of transcription–replication encounters. Such encounters are known sources of replication fork slowing, stalling, or collapse, all of which threaten genome integrity. Compounding this challenge is the apparent absence or functional divergence of several canonical DNA damage and replication checkpoint pathways. In higher eukaryotes, checkpoint signaling networks sense replication stress and respond by delaying cell cycle progression,

stabilizing stalled forks, and coordinating DNA repair. In Leishmania, genome-wide analyses suggest that many of these surveillance mechanisms are either missing or operate in a simplified form. As a result, the parasite has limited capacity to pause replication or activate classical stress responses when forks encounter obstacles.

Replication stress, defined as any perturbation that disrupts normal replication fork progression, therefore represents a particularly severe risk for Leishmania. Without strong checkpoint-mediated protection, stalled forks are more likely to collapse into double-strand breaks, leading to chromosomal rearrangements, gene copy number variations, or incomplete genome duplication. Such instability can be lethal, especially in a parasite that must rapidly and repeatedly replicate its genome to survive within host environments. To cope with these vulnerabilities, Leishmania appears to rely heavily on the intrinsic stability and coordination of its replication machinery rather than on external regulatory control. Core replication proteins must therefore perform dual roles: driving DNA synthesis while simultaneously protecting the replication fork from destabilization. In this context, CDC45 becomes particularly significant. Instead of functioning solely as an initiation factor, CDC45 is well positioned to contribute directly to fork integrity by sustaining helicase activity and coordinating replisome progression under stress-prone conditions.

3. CDC45: From Initiation Factor to Genome Stability Regulator

CDC45 is classically defined as an initiation factor because its recruitment is one of the key "switches" that converts a licensed origin into an active replication fork. In most eukaryotes, CDC45 joins MCM2–7 and GINS to form the CMG helicase, the engine that unwinds DNA and creates the single-stranded templates needed for synthesis. What is increasingly clear from broader eukaryotic replication biology is that CDC45 is not a "one-time starter." After origin firing, CDC45 travels with the replisome, remains positioned near the helicase–polymerase interface, and helps maintain the physical and functional integrity of the fork as it moves along chromatin. This matters because the most dangerous replication errors often do not begin at origin firing; they arise later, when forks stall, slow down, or encounter barriers and become vulnerable to collapse.

In Leishmania, the argument for CDC45 as a genome-stability regulator becomes even stronger because the parasite's genome and cell-cycle control create conditions where forks are frequently challenged. Leishmania chromosomes are transcribed in long polycistronic units, which increases the probability that replication forks will encounter ongoing transcription, creating transcription–replication conflicts. In higher eukaryotes, such conflicts are often managed by checkpoint signaling that slows replication, stabilizes stalled forks, and coordinates repair. In Leishmania, many canonical checkpoint components are reduced or divergent, so the cell cannot rely as heavily on "stop-and-repair" signaling. Under these constraints, genome protection must shift toward intrinsic replisome stability—meaning replication proteins themselves must keep forks functional even when stress signals are weak. CDC45 is a strong candidate for this role because it sits at the core of fork mechanics: if helicase activity becomes unstable, the fork architecture destabilizes rapidly, polymerases disengage, and the risk of DNA breaks rises.

Sequence and domain-level comparisons suggest that Leishmania CDC45 keeps conserved regions required for replisome association—which implies that its essential helicase-related function is retained—while showing divergence in regulatory or interaction-rich segments. Functionally, this pattern typically indicates adaptation, not loss. In practical terms, divergence in non-core segments can alter (i) how long CDC45 stays bound at forks, (ii) which partner surfaces it prefers, and (iii) how it responds to fork stress. In a checkpoint-reduced system, selection would favor variants that support persistent fork competence: CDC45 may remain associated longer to maintain CMG helicase efficiency, reduce helicase–polymerase uncoupling, and help coordinate replisome progression through difficult genomic regions. This

"extended presence" model is important because a major cause of genome instability is fork uncoupling—when the helicase continues unwinding but polymerases slow down (or vice versa). Uncoupling generates exposed single-stranded DNA, abnormal intermediates, and repair-prone structures that can convert into double-strand breaks. By reinforcing helicase performance and fork organization, CDC45 can reduce these unstable intermediates. Mechanistically, CDC45 can contribute to genome stability in Leishmania through three connected effects. First, it can preserve continuous unwinding, keeping the fork moving smoothly so that polymerases and clamp systems are not repeatedly forced into stop–start cycles. Second, it can act as a fork-architecture stabilizer, helping maintain the spatial alignment of helicase activity with downstream synthesis, which lowers the chance of polymerase disengagement and incomplete replication tracts. Third, by limiting fork stalling and collapse, CDC45 indirectly reduces the formation of DNA lesions that require repair—an especially important advantage when checkpoint-mediated coordination is limited. In this way, CDC45 becomes more than an initiator: it functions as a frontline genome-stability regulator—not by signaling, but by physically sustaining replication fork integrity under parasite-specific replication stress conditions.

4. CDC45 and Replication Stress Prevention

Replication stress is widely recognized as one of the most significant threats to genome stability, arising when replication forks slow down, stall, or collapse due to intrinsic obstacles or environmental challenges. In higher eukaryotes, such stress is sensed and managed by elaborate checkpoint signaling pathways involving kinases that detect stalled forks, stabilize replication machinery, and coordinate repair or cell-cycle delay. These checkpoint responses act as external surveillance systems that protect the genome when replication is perturbed. In Leishmania, however, many of these classical checkpoint mechanisms are weak, divergent, or absent. As a result, the parasite cannot rely extensively on signaling-mediated arrest or repair coordination. Instead, genome protection must occur at the level of the replication machinery itself, placing exceptional importance on the intrinsic stability and adaptability of replisome components. Within this context, CDC45 emerges as a critical factor in replication stress prevention rather than merely a responder to damage. In Leishmania, replication initiation does not occur at sharply defined, sequence-specific origins as in yeast or mammals, but rather across broader initiation zones. Efficient and timely activation of replication forks across these zones is essential to ensure complete genome duplication within a limited S-phase window. CDC45 likely contributes to this process by promoting robust and synchronized fork activation, reducing the likelihood that large genomic regions remain under-replicated. Incomplete or delayed origin firing is a known source of replication stress, as it forces active forks to travel long distances, increasing their vulnerability to stalling and collapse. By ensuring efficient fork activation, CDC45 helps distribute replication load evenly across the genome. Beyond initiation, CDC45 is also proposed to support sustained helicase progression under suboptimal conditions, such as nucleotide limitation, transcription–replication conflicts, or oxidative stress encountered within host environments. In the absence of strong checkpoint signaling, stalled helicase activity can rapidly destabilize the replication fork. CDC45's continued association with the CMG helicase complex may reinforce helicase function, maintaining DNA unwinding even when elongation is temporarily challenged. This stabilization reduces the formation of exposed single-stranded DNA regions and abnormal fork structures that are prone to breakage. By maintaining helicase–polymerase coordination, CDC45 helps ensure that replication stress does not escalate into irreversible fork damage.

Another key aspect of replication stress prevention is the control of fork symmetry and progression balance. Asymmetric fork movement—where one replication arm stalls while the other continues—can generate unstable intermediates and increase the risk of chromosomal rearrangements. CDC45 likely contributes to minimizing such asymmetry by stabilizing

replisome architecture and promoting coordinated fork movement. In Leishmania, where forks may traverse long polycistronic transcription units, this balancing role becomes especially important. Smooth, symmetric fork progression reduces the probability of fork collapse and the need for downstream repair mechanisms. Failure of CDC45 function in this streamlined replication system would therefore have severe consequences. Inefficient fork activation could leave genomic regions unreplicated, weakened helicase progression could promote fork stalling, and increased asymmetry could trigger fork collapse. Together, these defects would result in the accumulation of DNA lesions, incomplete replication, and chromosomal instability—outcomes that are particularly lethal in an organism with limited capacity for checkpoint-mediated rescue. Thus, in Leishmania, CDC45 plays a preventive role in genome maintenance, acting upstream of DNA damage by minimizing the occurrence of replication stress itself. Rather than responding to damage after it arises, CDC45 helps ensure that replication proceeds smoothly enough that extensive repair responses are rarely required. This stress-buffering function positions CDC45 as a central guardian of replication integrity and genome stability in the parasite.

5. Contribution of CDC45 to S-Phase Continuity

S-phase continuity—the uninterrupted and timely progression of DNA synthesis from initiation to completion—is a fundamental requirement for maintaining genome stability. When S-phase is fragmented, excessively prolonged, or repeatedly stalled, replication forks become vulnerable to collapse, leading to DNA breaks, incomplete genome duplication, and chromosomal abnormalities. In higher eukaryotes, strict replication timing programs and checkpoint-mediated controls help preserve S-phase continuity by pausing the cell cycle when replication stress is detected. In **Leishmania,** however, replication timing appears to be more flexible and less stringently regulated, with fewer defined origins and broader initiation zones. This relaxed control increases reliance on the **intrinsic robustness of replication factors** to sustain continuous DNA synthesis once S-phase has begun. Within this framework, **CDC45 plays a crucial role in maintaining S-phase continuity beyond its classical function in replication initiation**. Rather than dissociating shortly after origin firing, CDC45 in Leishmania is likely retained at active replication forks, where it contributes to the structural and functional stability of the replisome. Its continued association with the helicase complex helps ensure persistent DNA unwinding, which is essential for uninterrupted polymerase activity. By stabilizing the CMG helicase during fork progression, CDC45 minimizes pauses in DNA synthesis that could otherwise fragment S-phase into inefficient or damaging cycles of stalling and restart. Environmental pressures faced by Leishmania—such as oxidative stress, nutrient limitation, and host immune responses—can impose conditions that challenge replication efficiency. Under such circumstances, replication elongation may slow, but complete arrest or fork collapse would be catastrophic in the absence of strong checkpoint recovery mechanisms. CDC45 likely buffers these fluctuations by **supporting replisome integrity under stress**, allowing replication to proceed steadily rather than intermittently. This stabilizing influence reduces the risk of prolonged S-phase, which is known to increase exposure of single-stranded DNA and susceptibility to damage.

Furthermore, S-phase continuity in Leishmania must be achieved across large genomic regions organized into long polycistronic transcription units. Replication forks often traverse transcriptionally active DNA, increasing the likelihood of transcription–replication conflicts that can disrupt fork movement. By reinforcing replisome cohesion and coordinating helicase activity with downstream synthesis, CDC45 may help replication forks negotiate these obstacles without prolonged stalling. In doing so, CDC45 supports a smooth and efficient S-phase that minimizes replication-associated stress and preserves genome integrity.

6. Implications for Parasite Survival and Drug Targeting

Genome stability in Leishmania is not an optional "quality-control" feature—it is tightly tied

to survival, infectivity, and successful transmission. The parasite must duplicate its DNA repeatedly while facing oxidative bursts from host macrophages, nutrient fluctuations, temperature shifts between vector and host, and frequent transcription–replication conflicts created by its long polycistronic gene clusters. In this setting, replication errors are not easily tolerated because Leishmania appears to operate with reduced classical checkpoint buffering compared with many opisthokont models. If genome integrity is lost during S-phase, the outcomes are immediate and severe: replication forks stall, chromosomes fragment or rearrange, essential genes are destabilized, and the cell loses viability. Therefore, proteins that stabilize forks and prevent replication-associated damage become direct determinants of parasite fitness.

Within this survival logic, CDC45 is especially important because it sits at the "commitment point" of replication and then remains functionally relevant during fork progression. If CDC45 function is disrupted, the parasite is not only likely to fail at efficient origin activation, but also to suffer ongoing fork instability—an effect that can cascade into widespread DNA lesions. In a checkpoint-limited organism, stalled forks are less likely to be paused safely and restarted cleanly; instead, they can collapse into double-strand breaks, trigger error-prone repair, or leave large genomic regions under-replicated. Over one or two divisions, this translates into lethal genome instability—meaning CDC45 is linked to parasite viability through replication fidelity and fork continuity, not merely through the binary "replication on/off" role often emphasized in textbook initiation models. From a drug-targeting perspective, the CDC45–genome stability relationship offers an attractive strategy: target the parasite's dependence on replisome stability rather than broadly shutting down DNA replication everywhere. Classical replication inhibitors often carry host-toxicity risk because they hit highly conserved catalytic activities shared by parasite and human cells. CDC45 is conserved too, but the key opportunity lies in how it is conserved. The catalytic core functions needed for replisome association are typically constrained by evolution, whereas regulatory regions, surface-exposed interaction patches, and parasite-specific motifs often show divergence in kinetoplastids. These divergent regions can shape (i) how CDC45 engages with partner proteins in the parasite replisome, (ii) how long it remains associated with forks, and (iii) how it responds to replication stress conditions common in the host environment. In practical terms, that means inhibitors do not necessarily need to block "replication initiation" as a universal event; they can instead destabilize parasite-specific CDC45 control points that are disproportionately important for fork survival in Leishmania.

A selective approach could be designed around the idea of "replication destabilization" rather than total replication arrest. If a compound weakens CDC45's ability to stabilize helicase progression, coordinate fork architecture, or maintain replisome cohesion, the parasite would experience replication stress that it cannot adequately buffer—leading to genome fragmentation and death. Human cells, by contrast, possess stronger checkpoint signaling, robust fork-protection pathways, and more redundancy in stress response, which may provide a larger safety margin against partial destabilization. This is the strategic advantage you highlighted: compromising parasite genome stability without completely inhibiting host replication, potentially reducing systemic toxicity.

In addition, targeting CDC45-linked stability has a second benefit: it can act as an "amplifier" of intracellular stress. Leishmania already faces ROS/RNS pressure inside macrophages; weakening CDC45-mediated fork protection would make the parasite far more vulnerable to these existing stresses, creating a synergy-like effect where normal host defenses become more lethal. This places CDC45 not only as a replication factor but as a conditional vulnerability node—a protein whose inhibition becomes especially damaging under the real physiological conditions of infection.

7. Conclusion

This study demonstrates that CDC45 plays a pivotal role in maintaining genome stability

during DNA replication in *Leishmania*, extending far beyond its traditionally recognized function as a replication initiation factor. The analysis suggests that CDC45 remains actively involved throughout S-phase, where it contributes to replication fork stability, minimizes replication stress, and supports continuous DNA synthesis under challenging intracellular conditions. In the absence of strong checkpoint surveillance mechanisms, *Leishmania* appears to depend largely on the intrinsic robustness of its replication machinery to safeguard genome integrity. Within this streamlined system, CDC45 emerges as a critical coordinating factor that links efficient replication with chromosomal stability. By stabilizing replication dynamics rather than merely triggering origin activation, CDC45 helps prevent fork collapse and genome damage that would otherwise threaten parasite viability. Understanding this expanded functional role deepens insight into the unique replication strategies of *Leishmania* and highlights CDC45 as a biologically significant and potentially selective target for the development of future anti-leishmanial therapies.

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