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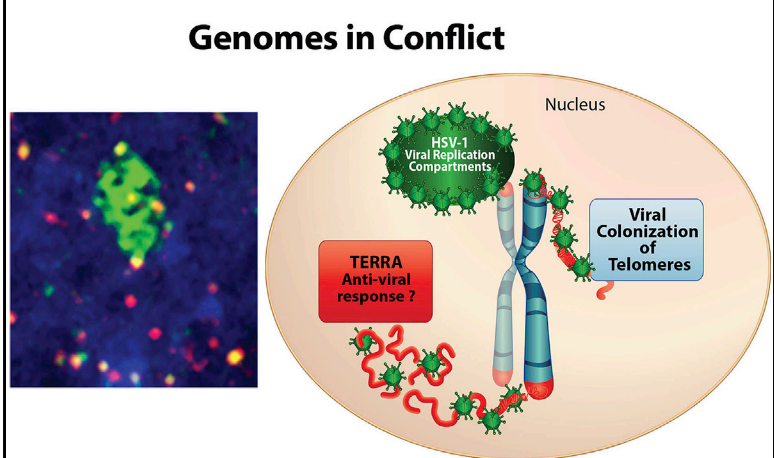
HSV-1 Remodels Host Telomeres to Facilitate Viral Replication

Graphical Abstract



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In Brief

Telomeres are extensively remodeled by viral infection. HSV-1 induces telomeric transcription, single-strand formation, and DNA degradation. Telomeric factors resist viral genome replication, while viral replication factors bind and form foci at telomeres. Deng et al. propose that telomeres are sites of conflict between virus and host genomes.

Highlights

- HSV-1 induces telomere dysfunction
- ICP0 ubiquitin ligase is required for TERRA induction and telomere remodeling
- ICP0 promotes ICP8 binding and colocalization with telomeric DNA
- Telomeric factors restrict HSV-1 replication

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HSV-1 Remodels Host Telomeres to Facilitate Viral Replication

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SUMMARY

Telomeres protect the ends of cellular chromosomes. We show here that infection with herpes simplex virus 1 (HSV-1) results in chromosomal structural aberrations at telomeres and the accumulation of telomere dysfunction-induced DNA damage foci (TIFs). At the molecular level, HSV-1 induces transcription of telomere repeat-containing RNA (TERRA), followed by the proteolytic degradation of the telomere protein TPP1 and loss of the telomere repeat DNA signal. The HSV-1-encoded E3 ubiquitin ligase ICP0 is required for TERRA transcription and facilitates TPP1 degradation. Small hairpin RNA (shRNA) depletion of TPP1 increases viral replication, indicating that TPP1 inhibits viral replication. Viral replication protein ICP8 forms foci that coincide with telomeric proteins, and ICP8-null virus failed to degrade telomere DNA signal. These findings suggest that HSV-1 reorganizes telomeres to form ICP8-associated prereplication foci and to promote viral genomic replication.

INTRODUCTION

Telomeres are the functional genetic elements that protect and monitor the ends of linear chromosomes. The terminal TTAGGG repeats of mammalian telomeres assemble into a nucleoprotein complex that is collectively referred to as shelterin (de Lange, 2005). The core shelterin components include the telomere repeat DNA-binding factors TRF1 and TRF2, the single-stranded DNA binding protein Pot1, and their interacting proteins hRap1, TIN2, and TPP1. Shelterin components have essential and distinct roles in telomere length homeostasis and control of DNA damage response (DDR) signaling at the chromosome termini (de Lange, 2010). Loss or damage of the telomere repeat DNA can initiate a DDR and trigger cellular replicative senescence (Deng et al., 2008). Similarly, mutation, deletion, or post-translational modification of shelterin proteins can activate DDR signaling and cause cell-cycle arrest (Sfeir and de Lange, 2012). Telomeres also form higher-order chromosomal structures that undergo conformational changes that are important for telomere homeostasis and chromosome integrity (Taddei et al., 2004). The extent to which viruses modify or utilize telomeric factors and structure is not well understood.

Herpesviruses are large double-stranded DNA viruses that yield either a productive lytic infection or establish a long-term latent infection (Roizman and Whitley, 2013). Herpes simplex virus 1 (HSV-1) can productively infect many different types of epithelial cells and establish latent infections in neuronal ganglia in vivo (Knipe and Cliffe, 2008). Productive infection requires the activation of viral transcription and DNA replication as well as the inactivation of host-intrinsic defenses. The HSV-1 ICP0 protein is an immediate early protein that inactivates host-intrinsic defense proteins and stimulates viral transcription (Boutell and Everett, 2013). ICP0 has intrinsic E3 ubiquitin-ligase activity mediated by an N-terminal RING finger that targets several cellular proteins, directly or indirectly, for proteasome-mediated degradation. ICP0 causes the degradation of the promyelocytic leukemia (PML) protein and its associated nuclear body (PML-NB) that are implicated in the host-intrinsic defense to viral infection (Everett and Chelbi-Alix, 2007). ICP0 can also target other cellular factors, including centromeric proteins (Lomonte et al., 2001) and DNA damage repair proteins RNF8 and RNF168 (Chaurushiya et al., 2012; Lilley et al., 2010). ICP0 can interact with the chromatin regulatory factors, like BMAL (Kawaguchi et al., 2001), and reverse chromatin-mediated silencing (Ferenczy et al., 2011) to promote viral gene expression. How ICP0 transcription activation functions are coordinated with destruction of intrinsic resistance factors is not completely understood.

HSV-1 DNA replication requires the assembly of a viral replisome involving viral-encoded DNA polymerase and accessory factors (Weller and Coen, 2012). Viral replication occurs in large subnuclear structures referred to as replication compartments (Quinlan et al., 1984). Replication compartments form at a subset