EA-D DIRECTS TRAFFIC AT THE INTERSECTION OF EBV TRANSCRIPTION AND REPLICATION

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Episomal genomes of DNA viruses such as herpesviruses are used as templates for both transcription and replication. For this to work, collisions between the replication and transcription machineries must be minimized while maximizing DNA replication and synthesis of viral gene products needed to replicate the genome. To accomplish this goal, herpesviruses such as EBV tightly regulate the ordered transition from early lytic gene transcription to genome replication – but how does EBV successfully navigate this transition? Using mass spectrometry to examine the replisome at EBV replication forks during the lytic cycle, we find that the well-known heterochromatin-inducing SUMO2 ligase KAP1/TRIM28 is associated with the viral replication machinery and contributes to OriLyt-dependent replication. We also find that the RECQ5 helicase, known to travel with the RNA polymerase II complex, directs KAP1 to SUMOylate the EBV polymerase processivity factor EA-D. SUMOylation of EA-D averts transcription-replication collisions and prioritizes replication over early gene transcription. In this way, EA-D, KAP1, and RECQ5 orchestrate the handover from transcription to replication of circular EBV genomes, ensuring an ordered cascade of events that results in efficient virus production.