EPSTEIN-BARR VIRUS MANIPULATES CELLULAR CHROMATIN STRUCTURE DURING ITS LYTIC PHASE

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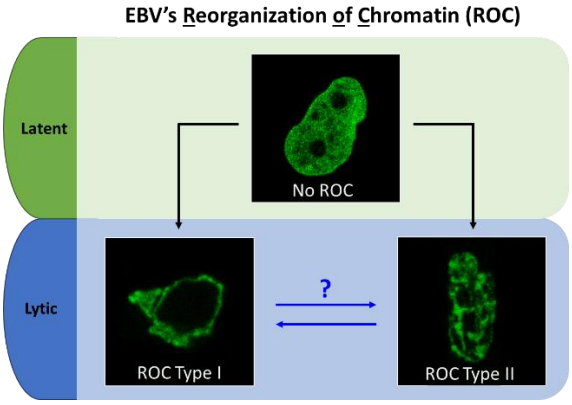

Epstein-Barr virus (EBV) alters many cellular processes to support its lytic phase. Among these changes, EBV manipulates the host nuclear structure by reorganizing cellular chromatin[1]. This reorganization of chromatin (ROC) involves the spatial compaction and margination of host chromatin towards the periphery of the nucleus, and away from EBV's DNA replication factories. ROC is also observed in other herpesviruses as well as other families of viruses, and is likely to be important in viral life cycles. In EBV, we found that EBV's core lytic DNA synthesis proteins (BALF5, BALF2, BBLF2/3, BBLF4, BSLF1, BMLF1, and BMRF1)[2] and its origin of lytic replication (*oriLyt*) are each required for ROC. In contrast, the early protein BGLF4 encoding the Thr/Ser kinase, which has been previously reported to induce premature chromosome condensation[3], is not required for ROC. We also found that ROC can occur in the absence of EBV's Late genes; thus Late genes are dispensable for ROC. To further elucidate the mechanism underlying ROC, we treated lytic cells with the viral DNA synthesis inhibitor ganciclovir (GCV) or phosphonoacetic acid (PAA). Either treatment successfully inhibited viral DNA synthesis, but does not abrogate ROC. However, they did affect the ROC phenotype. We have observed two types of ROC: Type I involves chromatin compaction and margination to the periphery of the nucleus, while Type II involves chromatin compaction without margination. In a typical lytic cell population, ≥78% of lytic cells display ROC Type I. In contrast, GCV or PAA treatment resulted in a significant increase of ROC Type II. Thus, EBV lytic DNA synthesis is dispensable for chromatin compaction, but necessary for its margination. Our study with a catalytic-dead mutant of the viral DNA polymerase, BALF5, further elucidates the requirement of lytic DNA synthesis for ROC. These findings define requirements for ROC and provide insights into its mechanism: only limited viral DNA synthesis is needed for EBV's dramatic manipulation of chromatin during its lytic phase.

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