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The Parvovirus Minute Virus of Mice Localizes to Sites of Cellular DNA Damage to Establish and Amplify its Lytic Infection

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Nuclear DNA viruses must be able to both access required cellular factors and evade others to initiate and sustain their replication. Establishment of the sites within the nucleus where particular DNA viruses initiate replication has likely evolved over time to optimize these needs. Parvoviruses, the simplest of the nuclear-replicating mammalian viruses, require host factors for every aspect of their life cycle. Parvovirus replication centers, called APAR bodies, are associated with multiple proteins involved in DNA replication, transcription, and DNA-damage signaling. We have developed a generally adaptable, novel, high-throughput chromosome conformation capture assay for use in trans (which we term V3C-seq), that allows genome-wide identification of the direct associations of a lytic virus genome with discreet regions of the cellular chromosome. Upon infection, the parvovirus Minute Virus of Mice genome associated directly with sites of cellular DNA damage. These sites also exhibited damage in uninfected cells when cycling through S-phase. As infection proceeded, new sites of DNA damage were induced, and virus subsequently associated with these sites during its amplification stage. MVM-associated sites overlap substantially with previously identified Topologically Associating Domains (TADs), which compartmentalize the mammalian genome into megabase-sized chromatin domains. Sites of association identified using V3C-seq were confirmed microscopically and by NS1 ChIP-seq. MVM could also be targeted specifically to sites of double-strand breaks or DNA damage induced artificially. Our data supports a model in which MVM initially establishes replication at cellular damage sites rich in replication and expression machinery; subsequently, as cellular DNA damage accrues, virus spreads additionally to these sites of damage to amplify infection.