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The Parvovirus Minute Virus of Mice Localizes to Sites of Cellular DNA Damage that form Distinct Chromatin Domains to Establish and Amplify its Lytic Infection

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Nuclear DNA viruses must navigate the nuclear milieu to access the cellular machinery required to initiate and sustain their replication. Parvoviruses establish sub-nuclear compartments, termed APAR bodies, that contain replication factors, transcriptional apparatus and DNA-damage response machinery, which together provide a mise en scéne for viral gene expression and genome amplification. Using a high-throughput chromosome conformation capture assay we developed for use in trans (termed V3C-seq), we have mapped the cellular interaction sites for Minute Virus of Mice (MVM). Upon infection, MVM associates with chromatin domains that preferentially accrue DNA damage in uninfected cells and form distinct cis-interacting sub-chromosomal structures referred to as Topological Associating Domains (TADs). These TAD sites package “Type A” chromatin that is transcriptionally active, are gene dense, and whose DNA replicates during S-phase, consistent with a model in which MVM replicates at nuclear sites that contain all requisite cellular factors. Upon associating with these cellular sites, MVM induces further DNA damage that primarily overlaps with TADs and then additionally associates with these sites to amplify its genomes within the TAD interactome. Indeed, induction of additional Type A chromatin in cells using the DNA damaging agent hydroxyurea amplified MVM replication in multiple cell types. In addition to chemical induction, generation of DNA breaks using endonucleases and micro-irradiation led to the localization of MVM to these novel cellular sites. Taken together, our findings suggest a key role for cellular chromatin in supporting MVM association and replication at distinct nuclear sites.