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Checkpoint Kinase 1 (Chk1) Plays an Important Role in MVM Infection

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Previous work in our lab has demonstrated that Minute Virus of Mice (MVM) infection induces a significant DNA Damage Response (DDR), transduced by the ATM kinase, while the ATR kinase is inactivated. Atypically, during infection, the cell cycle regulator Chk1, a major target of ATR, is not phosphorylated at position S345, which activates its checkpoint function, despite an ongoing DDR and the presence of RPA-coated viral single stranded DNA. Non-phosphorylated Chk1 is known to be associated with genomic DNA. When bound, non-phosphorylated Chk1 increases expression of some genes through its kinase activity on histone H3 resulting in epigenetic modifications of H3 which facilitate transcription. This process occurs even as the phosphorylated Chk1 elsewhere phosphorylates numerous targets participating in the DDR, cell cycle control and DNA repair. Our Chromatin Immunoprecipitation Assays (ChIP) confirmed previously reported association of histone H3 on parvovirus DNA. In addition, we identified Chk1, ATR, ATRIP, TopBP1, and additional factors required for ATR activation associated with MVM DNA. Importantly, overexpression of the TopBP1 ATR activation domain, known to be necessary and sufficient for activation of ATR, restored Chk1 S345 phosphorylation during infection, indicating that mechanism/s involved in ATR regulation are disabled upon MVM infection. Additional ChIP assays revealed Chk1-associated epigenetic modifications of MVM DNA-linked H3. Treatment with Chk1-specific inhibitor, but not an ATR inhibitor, reduced these H3 modifications and caused a significant decrease in the accumulation of viral transcripts, while Chk1 overexpression upregulated expression from the viral promoters, demonstrating the significance of the observed chromatin modifications. Thus, while MVM inactivation of ATR prevents use of the checkpoint activity of Chk1, non-activated Chk1 plays an important role in MVM infection. Our current work will investigate mechanism/s used by MVM to prevent the Chk1 phosphorylation and accurately determine the extent of Chk1 influence on MVM gene expression.