Public Abstract
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Title:The Parvovirus Minute Virus of Mice modulates the DNA damage response to facilitate viral replication and a pre-mitotic cell cycle block

The DNA damage response (DDR) is a critical cellular network that affords cells the ability to repair DNA damage, thus preventing the development of cancer and ensuring passage of intact genomic information to offspring. It has become appreciated in the last 15 years that viruses activate, interact with, utilize, and modulate this vital cellular response, which has been hypothesized to be an ancient anti-viral system in addition to its role in maintaining genomic integrity. Viruses of many types and families interact with the DDR, and understanding this interaction can deepen our knowledge of how these viruses survive and continue to infect humans. Importantly, this information can also inform us of novel methods to treat and prevent infection, as this interface is central to many viral lifecycles.

Our research probes the interaction of the DDR with the parvovirus Minute virus of mice (MVM), which provides a simple, tractable system to investigate at the molecular level how and why viruses negotiate this cellular response. Parvoviruses are incredibly small viruses capable of infecting species ranging from moths to humans, which rely on hijacking cellular components to replicate and complete their viral lifecycle. Previous work from our lab has shown that MVM utilizes and modulates the DDR to halt the cell cycle, which provides an environment conducive for viral replication. Unexpectedly, we found that MVM induces this cell cycle block in a novel manner, dissimilar to typical cellular methods, by specifically depleting a key CDK-inhibitor, p21, and a key mitotic cyclin, Cyclin B1.The loss of p21 during viral infection was confounding, as a cell will typically utilize p21 to induce this type of cell cycle block, suggesting to us that MVM depletes p21 for a specific reason. Careful investigation into the virally-induced loss of p21 revealed that MVM hijacks a key cellular protein that targets p21 for degradation. Introduction of mutant p21 proteins into MVM infected cells allowed up to determine that p21 must be depleted during infection to allow the activity of a key cellular cofactor, PCNA, which is utilized for viral replication.

As the virally-induced cell cycle block did not utilize the CDK-inhibitor p21 as predicted, we next focused on the key mitotic cyclin, Cyclin B1, which would also be expected to halt the cell cycle. Previous work from our lab demonstrated that MVM programmed the depletion of Cyclin B1 in a novel manner by targeting its encoding RNA, which no other virus is known to do. Our research demonstrated that MVM prevents key cellular factors from binding to the Cyclin B1 gene, thus preventing the generation of Cyclin B1 RNA. Importantly, reconstituting some of these factors onto the Cyclin B1 gene during viral infection could overcome this virally-induced RNA depletion.

Taken together, our findings suggest that MVM can target key cellular processes utilizing a multitude of methods, demonstrating that this “simple” virus is a master of regulating and modulating its host cell. This research has made significant contributions to our understanding of how parvoviruses interact with and modulate their cellular hosts. European clinical trials are currently investigating certain parvoviruses that preferentially infect, and kill, cancerous cells. The DDR is as the crux of understanding why parvoviruses target these cells and how they are destroyed. In addition to making significant contributions to the advancement of our field, our insights may inform these studies and aid in our understanding of oncolytic therapy.