Roles of cellular DNA replication proteins in papillomavirus DNA replication

Thomas Melendy
University at Buffalo, USA

Other than E1, the papillomavirus (PV) DNA helicase, and E2, the PV transcriptional regulator (that also assists E1 in recognizing the HPV origin of replication and assembling into E1's hexameric helicase configuration), PVs rely entirely on host proteins to replicate their viral DNA. Much of what we know about the enzymes involved in the synthetic stages of eukaryotic DNA replication were initiated in studies using a similar small DNA tumour virus, the polyomavirus, SV40. Studies on SV40 helped identify and/or confirm a role in DNA replication for: DNA polymerase alpha-primase (PolPrim), Topoisomerase I (TopoI), the major cellular ssDNA binding complex (RPA), Replication Factor C, Proliferating Cell Nuclear Antigen, DNA polymerase delta (PolD), and others. Another cellular replication complexes such as DNA polymerase epsilon (PolE), and origin recognition and licensing factors such as: The Origin Recognition Complex, The Mini-Chromosome, Maintenance proteins, Cdc45p, and others, were not required. SV40 hijacks the cellular machinery by its helicase binding to just RPA, TopoI and PolPrim, and the remaining factors are recruited by secondary interactions. A major focus of my laboratory has been on elucidating how the PV DNA replication proteins, E1 and E2, interact with and recruit the cellular replication proteins. We found that as with SV40, the PV helicase, E1 binds to: RPA, TopoI and PolPrim; and we have elucidated some of the mechanisms behind why these interactions are so vital for viral DNA replication. Moreover, we have recently discovered additional interactions unlike those seen in the SV40 system, including interactions between E1 and PolD and PolE and the PV E2 transcription protein with TopoI and PolE. These are highly novel as no other virus has ever been shown to evolve to utilize PolE to replicate their viral genomes, and E1 in particular confers a novel and highly unusual stimulation to synthesis by the cellular PolE enzyme. These findings show that PV DNA replication is actually quite different than polyomavirus DNA replication, from a functional and viral recruitment perspective; and show that PV DNA replication is apparently more similar to cellular DNA replication than polyomavirus (SV40) DNA replication. Further, our results provide novel biochemical targets for development of new anti-PV therapeutics.

Speaker Biography

Thomas Melendy has completed his PhD at UCLA, was a Post-doctoral Fellow with Bruce Stillman (NAS and FRS) at Cold Spring Harbor Laboratory where he wrote and published the seminal Nature article on DNA polymerase switching. He is currently an Associate Professor at the University at Buffalo, where he continues his ground-breaking work on the mechanisms of viral DNA replication. He is an AAAS Fellow, Presidential Scholar, Damon Runyon Fellow, Roche Award winner, served on ACS and NIH Review Panels, has held numerous NIH/ACS grants and career development awards, and has published over 40 papers in highly reputed journals.

e: tmelendy@buffalo.edu

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