O-17

Adeno-Associated Virus Rep Proteins Antagonize Phosphatase PP1 to Counteract KAP1 Repression of the Latent Viral Genome

Sarah Smith-Moore[a], Stuart J.D. Neil[a], Cornel Fraefel[b], R. Michael Linden[a], Mathieu Bollen[c], Helen M. Rowe[d], and Els Henckaerts[a]

[a]Department of Infectious Diseases, School of Immunology and Microbial Sciences, King's College London, London, UK; [b]Institute of Virology, University of Zurich, Zurich, Switzerland; [c]KU Leuven Department of Cellular and Molecular Medicine, University of Leuven, Leuven, Belgium; [d]Centre for Medical Molecular Virology, Division of Infection and Immunity, University College London, London, UK

Despite great recent successes in AAV-based gene therapy, further improvements in vector technology may be hindered by an inadequate understanding of various aspects of basic AAV biology. In the absence of helper virus coinfection, wild-type AAV establishes latency through mechanisms that are not yet fully understood. Given that AAV vectors likely mimic the latent phase of the viral life cycle, defining the mechanisms involved in the regulation of AAV latency is of particular importance. We have previously shown that AAV latency is partly regulated by epigenetic modification of the viral genome. Specifically, we were able to demonstrate that the corepressor Krüppel-associated box domain-associated protein 1 (KAP1) binds the latent AAV2 genome at the rep ORF, leading to trimethylation of AAV2-associated histone 3 lysine 9 and that the inactivation of KAP1 repressive function through phosphorylation of KAP1-S824 is necessary for AAV2 reactivation and replication. Here we describe a viral mechanism for the counteraction of KAP1 in which interference with the KAP1 phosphatase protein phosphatase 1 (PP1) by the AAV2 Rep proteins mediates enhanced phosphorylation of KAP1-S824 and thus relief from KAP1 repression. Furthermore, we show that this phenomenon involves recruitment of the NIPP1 (nuclear inhibitor of PP1)–PP1α holoenzyme to KAP1 in a manner dependent upon the NIPP1 FHA domain, identifying NIPP1 as an interaction partner for KAP1 and shedding light on the mechanism through which PP1 regulates cellular KAP1 activity.