Inhibition of DNA virus replication in histone methyltransferase.

Mariela Monti*

Department of Molecular Neuroscience, University of Science and Technology, China

Introduction

Several diseases, such as cancer and neurodegenerative diseases are associated with latent infection with DNA viruses. However eliminating latent DNA viruses remains a challenge, and new antiviral strategies are essential for treating the disease. Here we screen a pool of small chemical molecules and identify a histone ethyltransferase inhibitor as a potent inhibitor of several DNA viruses not only enhances antiviral gene expression in THP-1 cells, but also suppresses viral DNA replication in several cGAS pathway-deficient cell lines. We show that SETD8 promotes DNA virus replication dependent on its enzymatic activity. Our results further showed that SETD8 is required for PCNA stability, a key factor in viral DNA replication. Viral infection stimulates the interaction between SETD8 and PCNA, improving PCNA stability and viral DNA replication. Taken together, our study reveals a novel mechanism regulating viral DNA replication and provides potential strategies for treating DNA virus-associated diseases [1].

Initiates mismatch repair by detecting mismatches in newly replicated DNA. Specific interactions between and mismatches within the double-stranded DNA promote ADP-ATP exchange and conformational change to the sliding clamp. Here, we showed that Pseudomonas aeruginosa MutS associates with primed DNA replication intermediates. The predicted structure of this MutS-DNA complex revealed a novel DNA-binding site in which and appear to interact directly with her 3′-OH end of primed DNA. Mutation of these residues resulted in marked defects in interaction of MutS with primed DNA substrates. Strikingly, interaction of MutS with mismatches within primed DNA induced a tightening of protein structure and prevented the formation of ATP-bound slide clamps. Our results demonstrate novel DNA binding modes, conformational changes, and intermolecular signalling for MutS mismatch detection within primed DNA structures [2].

Viral infections are the cause of many diseases and are one of the greatest threats to human health worldwide. Compared to RNA viruses, DNA viruses infect large numbers of people worldwide and are much more difficult to purify due to their potential for infection. Innate immunity mediated by the cGAS pathway is believed to be the primary pathway for human cells to fight DNA viruses. Viral double-stranded DNA is recognized by cGAS, which synthesizes the second messenger cGAMP that activates signalling pathways. cGAMP then activates a key adapter protein it recruits and promotes phosphorylation of TANK-binding kinase 1 (TBK1) and subsequent phosphorylation of interferon regulatory factor 3. Phosphorylated IRF3 enters the nucleus and turns on the expression of type I interferon's. Interferon then further activates the JAK/STAT pathway to express multiple antiviral genes and eliminate viruses interestingly, many cell types, especially cultured cancer cell lines, lack the cGAS pathway upon viral infection. It will be interesting to investigate whether other antiviral signalling pathways exist in these cells [3].

DNA viruses are typically much larger than RNA viruses and encode more proteins, which can lead to more complex cellular responses. Transcriptomic studies have shown that DNA virus infections often cause alterations in numerous host genes, suggesting that virus-host-cell interactions are highly complex. After infection, the DNA virus genome quickly enters the host cell nucleus, transcribes the viral genes, and undergoes rapid DNA replication. Viruses use a combination of viral and host protein machinery to navigate their life cycle. For example, several viral proteins such as ICP4 and ICP8 are enriched in the viral genome during HSV-1 DNA replication, along with cellular PCNA and topoisomerases [4].

Recent studies have shown that many epigenetic factors, such as histones, bind to the viral genome and play important roles in viral gene transcription and DNA replication. Various forms of histone modifications have also been detected in the viral genome They appear in the viral genome rapidly after infection and change dynamically during the viral life cycle. The formation of heterochromatin marks on the HSV-1 genome has been reported to be important for ordered genes Inhibition of the histone H3K4 demethylase LSD1 results in heterochromatin repression of the HSV-1 genome, which subsequently affects viral infection epigenome studies used high-throughput sequencing to map the location of nucleosomes on the HSV-1 An epigenetic study of the HSV-1 genome showed that histone H3K9me3 decreased and H3K27ac increased during the viral life cycle and that C646, an inhibitor of H3K27ac, could suppress his HSV-1 in cultured cells. Several histone modification landscapes on the KHSV genome have also been described *in vitro* and *in vivo.* It will be interesting to know whether other modified histones are also present in the viral genome and regulate viral activity.

In the current study, we performed a screen using a pool of epigenetic factor inhibitors to identify potential epigenetic-

***Correspondence to:** Mariela Monti, Department of Molecular Neuroscience, University of Science and Technology, China, E-mail: mariela.monti@unc.edu.ar

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associated small-molecule chemicals that suppress DNA viruses. We then found that UNC0379, an inhibitor of the H4K20 methyltransferase SETD8, could suppress several DNA viruses. Further studies then show that SETD8 promotes DNA virus replication by stabilizing the host factor PCNA and promoting viral genome replication [5].

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