Overturning the epigenetic silencing of Epstein-Barr virus genome in cancer cells

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Epstein-Barr virus is associated with several human cancers including Hodgkin’s disease, Burkitt’s lymphoma and nasopharyngeal carcinoma. Within cancer cells, EBV establishes latency, which allows the majority of its genes to be silenced, and so it evades destruction by the immune response. The current model to account for EBV latency, is that the viral genome is epigenetically silenced; it is heavily methylated at CpG residues during latency. The virus can be awoken from latency and triggered to replicate following exposure to a variety of drugs, making the cells susceptible to immune attack. Manipulating this process has been proposed as a route to achieve oncolytic therapy for EBV tumours, however reactivation only occurs the minority of cells. It is clearly important to understand the precise mechanisms by which the genome is silenced and how the epigenetic landscape changes during viral reactivation in order to be able to manipulate it in favour of reactivation within a therapeutic context. Using genome wide chromatin precipitation coupled to next-generation sequencing (ChIP-Seq), and sequential rounds of ChIP and ChIP followed by Me-DIP, we explored the interaction of the key EBV lytic cycle switch protein Zta (BZLF1, ZEBRA), post-translationally modified histones and their effectors with EBV genome. This revealed details of the repressive epigenetic environment associated with viral promoters during latency and revealed the dynamic changes that occur to the viral epignome during the reactivation from latency.