THE CONSTITUTIVE HETEROCHROMATIN MACHINERY DIFFERENTIALLY RECOGNIZES AND SILENCES SELF GENOMES VERSUS FOREIGN EBV GENOMES

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Latency of Epstein-Barr virus (EBV) depends on expression of viral latency proteins *and* silencing of lytic genes. Indeed, the constitutive heterochromatin machinery (HCM) composed of Krüppel-associated box-domain zinc finger protein (KRAB-ZFP) transcriptional repressors that recruit KAP1/TRIM28, epigenetically silences lytic genes of all kinetic classes of human herpesviruses (EBV, KSHV, HSV-1, and CMV). However, with the constitutive heterochromatin (H3K9me3) also shielding pericentromeric regions and endogenous retroviral elements from genomic instability, how does the HCM distinguish between self and foreign target genomes? To address this question, we performed *in situ* footprint mapping of SZF1, the relevant KRAB-ZFP, on both viral and host genomes in physically separated B-lymphocytes bearing latent or replicative/active EBV genomes. Remarkably, we find that SZF1 uses a repeat sequence-bearing motif to recognize self DNA but non-consensus binding sites to target EBV lytic genes, allowing the HCM to distinguish between friend and foe. EBV mutagenesis studies show that these distinct binding sites are not only key to maintaining the established latent phase but also silencing the lytic phase in newly-infected cells, thus enabling the incoming virus to establish latency and transform cells [1]. This differential approach towards target site recognition reflects a strategy by which the host silences and regulates genomes of persistent invaders without jeopardizing its own homeostasis.

[1] A heterochromatin inducing protein differentially recognizes self versus foreign genomes. Eric M Burton, Ibukun A. Akinyemi, Tiffany R. Frey, Huanzhou Xu, Xiaofan Li, Lai Jing Su, Jizu Zhi, Michael T. McIntosh, Sumita Bhaduri-McIntosh, 2021, PLoS Pathogens, 17(3):e1009447. doi: 10.1371/journal.ppat.1009447