IFI16 PARTNERS WITH KAP1/TRIM28 TO MAINTAIN EBV LATENCY

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Upon entry into a new cell, herpesviruses are rapidly silenced by the host, thereby limiting the destructive lytic phase while allowing the virus to hide from the immune system. As illustrated by EBV, establishment of latency requires expression of viral latency genes and host mechanisms, but latency can be maintained with negligible expression of viral genes. Several herpesviruses including EBV point toward the DNA sensor IFI16 as an important facilitator of latency via the heterochromatin mark H3K9me3; this silencing mark is typically imposed by the constitutive heterochromatin machinery (HCM). This machinery, in an antiviral role, is also known to silence the lytic phase of EBV and other herpesviruses. We therefore investigated if IFI16 restricts EBV lytic activation by partnering with the HCM. We find that IFI16 indeed interacts with core components of the HCM including TRIM28/KRAB-associated protein (KAP1) and the site-specific DNA binding KRAB-ZFP SZF1; this partnership silences the EBV lytic switch protein ZEBRA, encoded by the *BZLF1* gene, thereby favoring viral latency. In defining topology, we find that IFI16 co-enriches with KAP1 at the *BZLF1* promoter, and while IFI16 and SZF1 are each adjacent to KAP1 in latent cells, IFI16 and SZF1 are not. Importantly, we also find that disruption of latency involves rapid downregulation of IFI16 transcription. These findings reveal a previously unknown partnership between IFI16 and the core HCM that supports EBV latency via antiviral heterochromatic silencing.