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"NOVEL INSIGHTS INTO THE INTERPLAY BETWEEN VIRAL RTA AND HOST NOTCH TO REGULATE LYTIC REACTIVATION IN KAPOSI'S SARCOMA-ASSOCIATED HERPESVIRUS"

By

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Tuesday, July 22nd, 2025
ICPH Auditorium
1:00 P.M.

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ABSTRACT

Kaposi's **s**arcoma (**KS**) is the most common cancer in HIV-infected individuals, and its progression is dependent on the reactivation of its etiologic agent, **K**aposi's **s**arcoma-**a**ssociated **h**erpesvirus (**KSHV**), from latency. In addition to KS, KSHV is also the etiologic agent of **P**rimary **E**ffusion **L**ymphoma (**PEL**), **M**ulticentric **C**astleman's **D**isease (**MCD**), and **K**SHV **I**nflammatory **C**ytokine **S**yndrome (**KICS**). Lytic reactivation of KSHV requires the viral protein, ***R****eplication and* ***t****ranscriptional* ***a****ctivator (****Rta****)*, to form a complex with the host cell protein ***R****ecombination signal-****B****inding* ***P****rotein for* ***Jκ (RBPJκ)***, the DNA binding component and primary effector of the host oncogenic Notch signal transduction pathway. During reactivation, Rta-RBPJκ complexes bind and transactivate viral promoters to initiate a cascade of viral gene expression that leads to viral replication and production of progeny viruses. While viral gene expression is highly restricted during latency, most KSHV oncogenes are expressed during reactivation. We previously demonstrated that Rta is the sole viral component necessary and sufficient to drive this lytic switch – and though Notch is required for optimal latent escape, it is not sufficient alone to induce reactivation. Despite the central roles of Rta and Notch in facilitating reactivation – and their convergence on RBPJκ as a shared effector – the underlying mechanisms of how Rta and Notch specify transcriptional targets remain unclear.

In this study, we extend our recent findings implicating Notch1 as a proviral factor of KSHV reactivation and are the first to demonstrate via ChIP-qPCR that activated Notch (NICD1) forms promoter-specific complexes with viral DNA to transactivate viral genes. We have additionally characterized a set of host cellular proteins, or **M**otif **B**inding **P**roteins (**MBP**s), identified by bioinformatic analyses of ChIP-seq of the KSHV genome, that are candidates to associate preferentially with RBPJκ binding during latency or reactivation. We hypothesized that MBPs are induced by Rta and bind to viral DNA to stimulate RBPJκ binding to reactivation-specific genes to allow transactivation by Rta or NICD1. We identified MAF bZIP transcription factor B (MafB) as an MBP whose expression is induced by Rta and stimulates viral reactivation. Our data suggest that other candidate MBPs also contribute to this regulatory mechanism. These findings, together with the pipelines developed, establish a novel axis for the discovery and characterization of viral and host factors that mediate the coordinated regulation of productive viral gene transactivation and reactivation through integrated host–viral mechanisms.