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Perturbation of SWI/SNF Chromatin Remodeling Suppresses Tumorigenesis and Induces Metabolic Dysregulation in KSHV-Mediated Cellular Transformation

Kaposi's sarcoma-associated herpesvirus (KSHV) is one of seven known human oncogenic viruses and is etiologically linked to several malignancies, including Kaposi sarcoma (KS), the most common cancer in patients with acquired immunodeficiency syndrome (AIDS). Despite its established oncogenic role, the epigenetic mechanisms underlying KSHV-driven oncogenesis remain incompletely defined. The SWI/SNF chromatin remodeling complexes, including canonical BAF (cBAF), polybromo-associated BAF (pBAF), and non-canonical BAF (ncBAF), are critical regulators of transcriptional programs and are frequently altered in cancer.

To delineate the role of SWI/SNF complexes in KSHV-mediated oncogenesis, we pharmacologically inhibited or degraded key components of cBAF, pBAF, and ncBAF in KSHV-transformed primary metanephric mesenchymal precursor (KMM) cells and their uninfected counterparts (MM). Selective perturbation of cBAF, but not pBAF or ncBAF, significantly suppressed KMM cell proliferation and induced G0/G1 cell-cycle arrest, and exhibited minimal effects on MM cells. Targeting cBAF with the selective degrader ACBi1 reduced anchorage-independent growth in a dose-dependent manner and markedly impaired KSHV-driven tumorigenesis in nude mice, establishing a predominant role for cBAF in viral transformation.

Transcriptomic profiling revealed that KSHV transformation is associated with dysregulation of lipid and nucleoside metabolic pathways. ChIP-seq analysis demonstrated altered H3K4me3 enrichment at a subset of these genes, correlating with transcriptional reprogramming. Importantly, cBAF inhibition disrupted both lipid and nucleoside biosynthesis in KMM cells, whereas MM cells exhibited primarily lipid pathway alterations, indicating that KSHV-transformed cells acquire distinct metabolic dependencies.

Mechanistically, we demonstrate that the KSHV latency-associated nuclear antigen (LANA) interacts with SWI/SNF components, particularly cBAF, suggest that KSHV hijacks this chromatin remodeling complex to reprogram host metabolic pathways and promote tumorigenesis.

Collectively, our findings identify cBAF as a critical epigenetic driver of KSHV-mediated transformation and highlight SWI/SNF chromatin remodeling as a promising vulnerability in KSHV-associated malignancies.

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