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"A Cytoplasmic Histone Deacetylase Positively and Negatively Regulates Reactivation of a Nuclear Herpesvirus"

by
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Molecular Biology, Genetics, and Cancer Program

BSc, 2014, Federal University of Rio Grande do Sul, Brazil

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Associate Professor
Department of Microbiology, Biochemistry, and Molecular Genetics

Friday, April 8th, 2022
1:00 PM
ICPH Auditorium

Join Zoom Presentation:
https://rutgers.zoom.us/j/95482876998?pwd=MHZRSHpCRzc2MXE5NkhrZTRGa0N6UT09

Meeting ID: 954 8287 6998
Password: 619775

ABSTRACT

Kaposi's Sarcoma-associated herpesvirus (KSHV) is the etiologic agent of Kaposi's Sarcoma and other AIDS-related cancers. Reactivation of KSHV from latency requires expression of the viral protein Rta and is a necessary step for progression of these diseases. Host cell histones maintain the latent KSHV genome as a nuclear DNA episome largely through the repressive activity of histone deacetylases (HDACs). We previously published the first evidence of a positive role for an HDAC, HDAC6, in KSHV reactivation. HDAC6 is a key regulator of protein degradation and cytoskeletal dynamics that functions primarily in the cytoplasm of eukaryotic cells. In this thesis, we sought to determine the mechanism by which HDAC6 regulates KSHV reactivation.

Specific inhibition of HDAC6 by Tubacin revealed an unexpected negative role of HDAC6 in KSHV reactivation that was time-dependent. We found that addition of Tubacin as early as 1h post-Valproic Acid (VPA, reactivation inducer) greatly increases Rta expression and production of infectious virus. Interestingly, Tubacin does not affect reactivation when added simultaneously with VPA. The major cellular target of HDAC6's deacetylase activity is the cytoplasmic alpha-tubulin subunit of microtubules, and we show that ectopic hyperacetylated microtubules significantly increase VPA-induced reactivation, recapitulating Tubacin's effect. Overall, our data indicate that HDAC6's effect on microtubule acetylation regulates successful KSHV reactivation from latency.

Using cell imaging and fractionation experiments we confirm that the majority of HDAC6 is found in the cytoplasm, and VPA-induced reactivation leads to expulsion of HDAC6 from the nucleus. Ectopic WT HDAC6 represses KSHV reactivation, but expression of an HDAC6 mutant lacking its cytoplasmic anchoring domain does not. Our data indicate that HDAC6 subcellular localization to the cytoplasm is critical for repressing viral reactivation.

Finally, complementation of HDAC6 expression in HDAC6 knockdown cells reveal dual anti and pro-viral roles for HDAC6 in viral reactivation. Knockdown of HDAC6 significantly reduces viral reactivation, and ectopic expression of a catalytically dead HDAC6 mutant, but not WT HDAC6, rescues KSHV reactivation. Taken together, our new data reinforce our published conclusion that HDAC6 activity is pro-viral, but also reveal an additional negative role for HDAC6 in reactivation via its deacetylase domain that operates from the cell cytoplasm.