The Chromatin Modification by SUMO-2/3 Prevents the Epigenetic Activation of Immune-related Genes during Kaposi's Sarcoma Associated Herpesvirus Reactivation

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Background/Objective

Kaposi's sarcoma associated herpesvirus (KSHV) is an etiologic agent of KS in AIDS patient. Similar to all herpesviruses, it evolves mechanisms that directly or indirectly modulate the SUMO machinery in order to evade host immune surveillance, thus advancing their survival. SUMOylation, as part of the epigenetic regulation of transcription, has been intensively studied in lower eukaryotes that contain only a single SUMO protein; however, the functions of SUMOylation during mammalian epigenetic transcriptional regulation are largely uncharacterized. Mammals express three major SUMO paralogues: SUMO-1, SUMO-2, and SUMO-3 (normally referred to as SUMO-1 and SUMO-2/3). We have previously reported that KSHV K-bZIP is a SUMO-2/3 specific E3 ligase and suggests that KSHV may exploit SUMO modification to globally regulate host transcriptional programs.

Method

Genome-wide mapping of chromatin modification by SUMO paralogues was performed in a KSHV infected B lymphoma cell line during herpesvirus reactivation using chromatin immunoprecipitation sequencing (ChIP-seq). Expression profiling during KSHV reactivation was analyzed by RNA-seq.

Result

Interestingly, ChIP-seq experiments showed that KSHV reactivation is accompanied by a significant increase in SUMO-2/3 modification around promoter regions, but SUMO-1 enrichment was absent. Large scale comparative analysis of ChIP-seq and transcriptome results of RNA-seq indicates that both SUMO-2/3 label the promoters of highly active genes that show no expression changes during viral reactivation. Gene ontology (GO) analysis further showed that these genes are involved in cellular immune responses and cytokine signaling. High-throughput annotation of SUMO occupancy of transcription factor binding sites (TFBS) pinpointed the presence of three master regulators of immune responses, IRF-1, IRF-2, and IRF-7, as potential SUMO-2/3 targeted transcriptional factors after KSHV reactivation.

Conclusion

Our study identify differential genome-wide modifications between SUMO paralogues during herpesvirus reactivation. Our findings indicate that SUMO-2/3 modification near protein-coding gene promoters occurs in order to maintain host immune-related gene unaltered during viral reactivation.