Intragenic viral enhancer of HTLV-1 is dispensable for in vitro immortalization and in vivo persistence

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Background:
Human T-cell leukemia virus type 1 (HTLV-1) is the causative infectious agent of adult T-cell leukemia/lymphoma (ATL) and chronic neurological disease. The disparity between silenced sense transcription versus constitutively active antisense (Hbz) transcription from the integrated provirus is not fully understood. The presence of an internal viral enhancer has recently been discovered in the Tax gene near the 3' long terminal repeat (LTR) of HTLV-1. In vitro, this enhancer has been shown to bind host transcription factors, maintain chromatin openness and viral gene transcription, and induce aberrant host gene transcription near viral integration sites. However, the function of the viral enhancer in the context of early HTLV-1 infection events remains unknown. In this study, we evaluated the effects of the internal viral enhancer on HTLV-1-mediated in vitro immortalization and establishment of persistent infection in an in vivo rabbit model.

Methods:
A mutant enhancer (mEnhancer) proviral clone was generated using an infectious HTLV-1 molecular clone and virus producer cells were made by stable transfection. The mEnhancer was characterized in vitro and in vivo by co-culture immortalization assays and inoculation into rabbits, respectively.

Results:
The wild-type (wt) and mEnhancer viruses demonstrated similar capacities in 5' LTR transactivation, virus production, and immortalization in vitro. Over a 25-week study, the mEnhancer virus was able to establish persistent infection in rabbits, and there were no significant differences in proviral load or HTLV-1-specific antibody responses in animals infected with the mutant compared to wtHTLV-1.

Conclusion:
Mutation of the internal viral enhancer has no significant effect on T-cell immortalization induced by HTLV-1 in vitro, and the mEnhancer virus demonstrates early in vivo persistence. Future studies may elucidate whether the viral enhancer cooperates with other transcriptional regulatory elements to induce viral gene expression and contribute to HTLV-1 persistence and pathogenesis.
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None.

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