

ROLE OF CTCF IN HTLV-1 DNA METHYLATION, GENE EXPRESSION AND PATHOGENESIS

Authors:

Joseph A¹, Cheng X¹, Harding J¹, Rauch DA¹, Challen GA¹, Green P⁵, Griffith M¹, Payton JE³, Edwards J^{1,4}, Ratner L^{1,2}

¹Departments of Medicine, and ²Molecular Microbiology, ³Pathology and Immunology, and ⁴Center for Pharmacogenomics, Washington University School of Medicine, St Louis, MO, USA, ⁵Center for Retrovirus Research and the Department of Veterinary Biosciences, The Ohio State University, Columbus, OH, USA

Background:

HTLV-1 integrates into the host cell DNA and includes a single CCCTC-binding protein (CTCF) binding site (BS) in its proviral genome. CTCF is a 11-zinc finger DNA binding protein that plays a role in higher-order chromatin structure, gene expression, genomic imprinting and a barrier to epigenetic modification. This protein is important in the regulation of many DNA viruses, as well as many properties of normal and malignant cells. We studied the role of CTCF-BS in HTLV-1's replication and pathogenesis using cell culture and humanized mouse models.

Methods:

In this study, we established infected cell lines using HTLV-1 lacking the CTCF BS and assessed the impact through analysis of viral integration, epigenetic modifications, transcription, latency establishment and reactivation, in cell cultures and in humanized mice.

Results:

We found that disruption of CTCF binding to the viral DNA caused a significant alteration of DNA methylation on both sense and antisense strands in the 3' portion of the genome of the provirus. Blocking CTCF binding by shRNA knockdown of CTCF in multiple HTLV-1 infected cell clones differentially affected proviral gene expression and the overall effect was integration site dependent. Loss of the CTCF binding site resulted in increased histone methylation 5' and 3' of the CTCF BS, suggesting that CTCF binding may act as a boundary element to epigenetic modification. In a CD34+ hematopoietic stem cell humanized mouse model, infection with WT HTLV-1 resulted in CD4+ lymphoma whereas infection of mice with HTLV-1 lacking CTCF BS had a significantly lower proviral load and significant delay in progression to lymphoma.

Conclusion:

Overall, these findings indicate that CTCF binding regulates HTLV-1 gene expression, DNA and histone methylation in an integration site dependent fashion and deletion of CTCF BS causes a delay in pathogenicity in humanized mice.

Disclosure of Interest Statement:

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