ERK-SIGNALING REGULATES HUMAN T CELL LEUKEMIA VIRUS TYPE 1 RNA STABILITY AND GENE EXPRESSION IN LATENTLY INFECTED CD4 T CELLS

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Background:
Regulated expression of HTLV-1 genes from integrated proviruses plays an important role in HTLV-1-associated disease pathogenesis. Previous studies have shown that T cell receptor and phorbol ester (PMA) stimulation of latently infected CD4 T cells increases the expression of integrated HTLV-1 proviruses through increased *tax/rex* mRNA stability. We are interested in identifying signaling pathways and RNA-binding proteins that regulate HTLV-1 RNA stability in chronically infected cells, that may contribute to pathogenesis.

Methods:
HTLV-1 latently infected, FS cells were used for these studies. Specific inhibitors of MAPKs (PD184352 and SB203580) were used to dissect pathways important for PMA-stimulated, HTLV-1 RNA expression and mRNA stability. Phosphorylation status of ERK and p38 proteins was assayed by Western blot analysis. Expression of HTLV-1 RNAs was measured by quantitative RT-PCR. Measurements of RNA levels following actinomycin D treatment were used to determine RNA stability. An oligonucleotide-hybridization based method (HyPR) was used to purify HTLV-1 RNA-protein complexes. Enriched mRNA was detected by qRT-PCR, and precipitated RNA-binding proteins were detected by Western blot analysis.

Results:
PMA treatment resulted in increased ERK1/2 phosphorylation, but not p38 phosphorylation in FS cells. Inhibition of ERK by PD184352 blocked PMA-induced HTLV-1 RNA expression and blocked increased *tax/rex* mRNA stability, but had no effect on *gag/*pol RNA stability. Hybridization-Purification of RNA-Protein Complexes using a *tax/rex* mRNA-based oligonucleotide probe specifically enriched *tax/rex* mRNA. The AU-rich RNA binding protein HuR was detected as associated with *tax/rex* mRNA in untreated FS cells but was not detected using a scrambled oligonucleotide probe.

Conclusion:
Our data suggest that PMA-induced, increased *tax/rex* mRNA stability and HTLV1 RNA expression in latently infected FS cells is dependent on ERK signaling. The AU-rich RNA binding protein HuR is associated with this mRNA in these HTLV-1 infected cells and may play a role in regulating its stability.

Disclosure of Interest Statement:

The Child Health Institute of New Jersey is funded by grants from the National Institutes of Health and from the Robert Wood Johnson Foundation, and by Rutgers RWJMS. No pharmaceutical grants were received in the development of this study.