

Temporal host transcription during spontaneous HTLV-1 proviral reactivation

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Background:

HTLV-1 viral transactivator Tax has pleiotropic functions affecting cell-cycle regulation and apoptosis. It has remained a long-standing question how the contrasting observations of Tax promoting proliferation and protecting infected cells from apoptosis, or inducing apoptosis or senescence, relate to naturally-infected T-cells. It is now known that Tax expression occurs in self-limiting transcriptional bursts. We studied the temporal changes in host transcription of naturally-infected T-cell clones accompanying the early, mid and late phases of spontaneous HTLV-1 proviral plus-strand expression, to understand how proviral reactivation affects cell cycle regulation and apoptosis.

Methods:

Two naturally-infected T-cell clones were transduced with a Tax-responsive Timer Protein reporter, which expresses a protein that undergoes a time-dependent shift from blue to red fluorescence. These cells were flow-sorted into silent, early, mid and late phases of HTLV-1 plus-strand expression and submitted to RNA-sequencing. The sequencing data were analyzed to obtain temporal trajectories of differentially expressed host genes during the plus-strand burst.

Results:

Activation of NF- κ B by HTLV-1 was immediate, but was confined to the duration of the plus-strand burst. Expression of genes regulating the cell cycle differed strongly between the two T-cell clones. There was transient, clone-independent up-regulation of DNA damage response genes, followed by up-regulation of senescence markers. The plus-strand burst was accompanied by anti-apoptotic gene expression; however, sustained expression of apoptosis-promoting genes outlasted the burst.

Conclusion:

NF- κ B activation is associated with the burst of plus-strand expression; constitutive NF- κ B activation may not be required for the persistence of infected cells. Naturally infected T-cells can vary in their expression of genes regulating cell-cycle progression, emphasizing the heterogeneity between cells naturally infected with HTLV-1. Clone-independent up-regulation of anti-apoptotic genes may protect the cells from the toxic effects of plus-strand expression. However, uncontrolled and sustained plus-strand expression may result in cell apoptosis or senescence.

Disclosure of Interest Statement:

Authors declare that they have no competing interests.