Transient expression of HTLV-1 Tax induces epigenetic alterations and mimics early T-cell activation

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Background:
We previously reported that HTLV-1 Tax is transiently expressed in a small subpopulation of ATL cells, which induces drastic changes of host transcriptome. In this study, we investigated epigenetic alterations induced by transient Tax expression to elucidate transcriptional regulation of host genes in ATL cells.

Methods:
Tax-expressing and -non-expressing cells were sorted from two ATL cell lines (MT-1 and KK-1), and analyzed the differences in the epigenetic status between Tax (+) and Tax (-) cells with ATAC-seq and histone H3K27ac ChIP-seq.

Results:
ATAC-seq results showed that motifs related to early T-cell activation, such as AP-1, NF-κB, and early growth response (EGR) genes, were significantly enriched in Tax (+) cells compared to Tax (-) cells. These results coincide with data of RNA-seq. Interestingly, the expression of those early response genes was upregulated by Tax expression, but proapoptotic genes, which are upregulated in normal T cells, were not significantly increased by Tax, whereas anti-apoptotic genes were upregulated by Tax. These results suggest that transient Tax expression mimics early T-cell activation without pro-apoptotic effects. Furthermore, multiple super-enhancer (SE) regions were identified accompanied with transient Tax expression by H3K27ac-seq. In the Tax-related-SE regions, the expression of NR4A2 was significantly increased in Tax (+) cells, and knockdown analysis of NR4A2 demonstrated significant suppression of cell growth of MT1 and KK-1. Suppression of NR4A2 also inhibited the expression of genes related to early T-cell activation (JUN, FOSL2, EGR2, CD28), and dysregulated the apoptotic signaling pathways. Furthermore, CRISPR-interference analysis targeting SE region of NR4A2 demonstrated marked reduction of NR4A2 gene expression and suppression of cell growth of MT1 and KK-1.

Conclusion:
These findings indicate that transient Tax expression induces structural changes of host chromatin and activates SEs to mimic early T-cell activation, which is likely a strategy of this virus to hijack T cells.

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