

Interactome and epigenetic functions of HTLV-1 Tax

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Background:

HTLV-1 Tax is expressed in the early phase of infection and acts as a transcriptional activator during immortalization. Tax-dependent transcriptomic changes persist during long-term latency even in tumor cells in which Tax expression is lost, suggesting that Tax may induce epigenetic remodeling in the early phase of infection. Thus, we deeply analyzed the transcriptome, open chromatin region, interactome of Tax with host factors, and chromatin binding of Tax in Tax-expressing cells.

Methods:

We performed RNA-seq and ATAC-seq on Tax-introduced cells to obtain the transcriptome and open chromatin status. We also performed LC-MS/MS of host factors co-immunoprecipitated with Tax. Furthermore, we analyzed chromatin binding pattern of Tax and histone modifications by ChIP-seq. Through the Integrative analysis of these omics data, we detected several novel functions of Tax in the pathogenesis of the infected cells.

Results:

Interactome analysis showed that Tax interacted with several host factors involved in signaling pathways and transcriptions, including several NF- κ B subunits. ChIP-seq demonstrated co-localization of Tax with NF- κ B factors in a

part of the open chromatin regions where H3K27ac are accumulated. These results indicate that Tax forms complexes with multiple host factors and alters the host epigenome and gene expression.

Through the integrated analysis, we identified a number of genes that are directly induced by Tax, including RASGRP3. In addition, RASGRP3 was shown to be functionally involved in cell proliferation through activation of the MAPK/ERK pathway. Tax binds to the RASGRP3 enhancer together with NF- κ B, and induces its expression. In ATL cells, Tax expression is lost in most cases, but the chromatin in the enhancer region of RASGRP3 is still open and its expression is maintained.

Conclusion:

Our study suggests that Tax expression is involved in the dysregulation of signaling pathways through reprogramming the host epigenome.

Disclosure of Interest Statement:

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