

Analysis in the mechanism of co-operative and mutual regulation among viral proteins in HTLV-1 infection

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Background: After infecting T cells, the human retrovirus HTLV-1 is maintained in the carrier for life as a provirus integrated into the human genome. During the early stage of infection, it expresses viral proteins and actively replicates, after which infected cells are immortalized and rapidly enter a latent state. Approximately 5% of carriers develop adult T-cell leukemia/lymphoma (ATL), and 0.3% develop HTLV-1 associated myelopathy (HAM) or uveitis (HU) due to alterations in the phenotype of the latently infected cells. On the other hand, in most cases, infected cells remain in a stable latent state, and 95% of carriers remain asymptomatic for life. We believe that HTLV-1 has evolved mechanisms to regulate the time course of active replication, followed by a stable latent-infection state. We also speculate that the orchestrated function of viral proteins, such as Tax, Rex, and HBZ in the early stage of infection is deeply related to the fate of infected cells, i.e., maintaining a silent latent infection or transforming to disease-causing cells. It has been well known that Tax regulates LTR activation and gene expression, Rex regulates viral mRNA stabilization and extranuclear trafficking, and HBZ, expressed from the antisense strand, regulates infected cell proliferation. However, most of these reports are based on experiments of individual proteins, and the realistic interaction of these proteins at the site of HTLV-1 infection remains unclear.

Methods: In this study, we aimed to elucidate the co-operatively and mutually regulated function of Tax, Rex, and HBZ in HTLV-1 infection. We performed gene expression analysis in CEM cells (TALL-derived human T cell line) that express Tax, Rex, and HBZ individually or together. We also performed gene expression profiling in CEM cells infected with cell-free HTLV-1 viral particles. Then integrated and comparative analysis among those data sets was conducted to elucidate the interaction of those viral proteins.

Results: We demonstrated that Tax/Rex, Rex/HBZ, or Tax/HBZ co-expressing cells exhibit more extensive changes in gene expression profiles compared with individually expressing cells. Interestingly, those co-expressing cells show changes in expression not only in genes observed in individually expressing cells but also in many new genes, indicating synergistic activity of those viral proteins. Principal Component Analysis (PCA) and clustering analysis show that the gene expression profile of Tax/Rex, Rex/HBZ, or Tax/HBZ co-expressing cells are closer to that of HTLV-1 infected cells than those of individually expressing cells, and Tax/Rex/HBZ co-expressing cells are the closest to the HTLV-1-infected cells.

Conclusion: Our results suggest that Tax, Rex, and HBZ work together to exhibit a new synergistic function, which cannot be performed individually. Such co-operative and mutual regulation among those viral proteins may be essential to fine-tune the chronological events after HTLV-1 infection in T cells, such as setting the cellular environment beneficial to viral replication and maintaining a stable latent state afterward.

Disclosure of Interest Statement: The authors declare no conflict of interest.