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Comparative interactome of HIV-1 Tat and HTLV-1 Tax and the cellular transcriptional machinery

Pathogenic human retroviruses include the human immunodeficiency virus type 1 and 2 (HIV-1 and 2) and the Human T lymphotropic virus type-1 (HTLV-1). HIV and HTLV have elaborate pathogenicity, involving transcriptional activation of specific cellular genes, and modulation of cell death and proliferation pathways. Both types of retroviruses target T lymphocytes but induce distinctly different disease outcomes. HIV invades CD4+ T-helper lymphocytes, giving rise to the severe defect in cell-mediated immune response of acquired immunodeficiency syndrome (AIDS). Unlike HIV-1 and 2, HTLV-1 does not destroy the immune system through destruction of T-cells, but instead, induces Adult T-cell Leukemia/Lymphoma (ATLL), an aggressive lymphoproliferative disease. HTLV-1 is also associated with tropical spastic paraparesis (TSP), a neurological degenerative syndrome. These alterations of cellular function rely on crosstalk between the few viral encoded proteins with specific human proteins.

One approach to understand how these two retroviruses exploit distinct or common strategies to subvert cellular pathways towards disease progression is to investigate protein-protein interactions (PPi) between the viral and the host proteins. Viral transactivators HIV-1 Tat and HTLV-1 Tax have been extensively studied and numerous interacting factors have been identified. The results are collected in various databases including HIV-1 Human Interaction Database (ref), VirusMINT and VirHostNet. HIV-1 Tat and HTLV-1 Tax interact with several transcription regulators for their ability to modulate transcription of viral and cellular genes. To better visualize and compare HIV-1 Tat and HTLV-1 Tax interactomes with the transcription machinery, we collected from different databases (1, 2, 3), HIV-1 Tat and HTLV-1 Tax partners involved in the transcriptional regulation. We found 258 and 77 interactions involving HIV-1 Tat and HTLV-1 Tax, respectively. These interactions are visualised using cityscape (3).

The mechanistic models of HIV-1 Tat and HTLV-1 Tax transcriptional regulation of viral expression are different: HIV-1 Tat activity is dependent on its direct binding to the stem-loop structure viral RNA (called TAR), while HTLV-1 Tax acts through cellular proteins such as CREB/ATFs able to bind the Tax-responsive elements (TRE) of the HTLV-1 LTR promoter. Our comparative map also highlight distinct cellular cofactors recruited by both retroviral proteins to subvert cellular pathways.

Twenty-two common targets were identified and include members of the NF-kB pathway (REL, RELA, NFKB1, NFKBIA), the transcription factor (TF) Sp1, the SWI/SNF complex (SMARCA4, ACTL6A), elements of the serum-responsive factors (SRF) (SPI1, ETS, JUN), the

CREB/ATF factors (ATF4, CEBBP, KAT2B), chromatin modifying enzymes (HDAC1 and MBD2) and cyclin T1, a member of the positive transcription elongation factor pTEF-B.

Our visualisation map of HIV-1 Tat and HTLV-1 Tax interactomes could be used to raise new hypotheses regarding pathologies induced by HIV and HTLV viruses.

References

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