Localization and sub-cellular shuttling of HTLV-1 Tax with the microRNA machinery

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From 16th International Conference on Human Retroviruses: HTLV and Related Viruses Montreal, Canada. 26-30 June 2013

The innate ability of the human cell to silence endogenous retroviruses through RNA sequences encoding micro-RNAs suggests that the cellular RNAi machinery is a major means by which the host mounts a defense response against retroviruses. Indeed, cellular miRNAs target and hybridize to specific sequences of both HTLV-1 and HIV-1 viral transcripts. However, the virus itself contains various mechanisms that assist in the evasion of viral inhibition through control of the cellular RNAi pathway. Retroviruses can hijack components of the RNAi pathway, in some cases to produce novel viral miRNAs that can either assist in active infection or promote a latent state. Here, we show that HTLV-1 Tax contributes to the dysregulation of the RNAi pathway by altering the expression of key components. A survey of uninfected and HTLV-1 infected cells revealed that Drosha is present at lower levels in all HTLV-1 infected cell lines and infected primary cells, while other components such as DGCR8 were not dramatically altered. We show co-localization of Tax and Drosha in the nucleus in vitro as well as co-immunoprecipitation in the presence of proteasome inhibitors, indicating that Tax interacts with Drosha and may target it to specific areas of the cell, namely, the proteasome. In the presence of Tax we observed a prevention of primary miRNA cleavage by Drosha. Finally, the changes in cellular miRNA expression in HTLV-1 infected cells can be mimicked by the add back of Drosha or the addition of antagonomiRs against the cellular miRNAs which are down-regulated by the virus.

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Published: 7 January 2014

doi:10.1186/1742-4690-11-S1-O73

Cite this article as: Van Duyne et al.: Localization and sub-cellular shuttling of HTLV-1 Tax with the microRNA machinery. Retrovirology 2014 11(Suppl 1):O73.

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