Involvement of Human Topoisomerase II isoforms in the Strand transfer events of HIV-1 Reverse Transcription

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Background: HIV-1 reverse transcription (RTn) involves synthesis of double strand DNA (ds DNA) from viral genomic RNA. RTn is promoted by a coordinated activity of viral and host proteins through unknown mechanism. Topoisomerase II (Topo II) alpha and beta maintains topological reorganization of dsDNA regions and catalytic inhibition of these isoforms inhibited viral replicative cycle. The aim of this study is to understand the role of Topo II isoforms in HIV-1 early replication.

Principal findings: Topo IIα and β showed differential expression during early hours of HIV-1 infection where Topo IIα expression decreased during the first hour and then increases after 4 h, while Topo IIβ showed relatively higher expression at 1 and 4 h. Thus both α and β isoforms promote early events of viral replication. In Topo IIα and/or β down regulated cells, transcription of viral genes *gag, pol* and *env* as well as proviral DNA synthesis was abolished, affecting HIV-1 replication. Molecular analysis of RTn events showed that strong stop DNA synthesis was unaffected in Topo IIα and/or β down regulated cells, while other downstream events of RTn such as first strand transfer, full length minus strand synthesis, and second strand transfer were completely inhibited. Further, these results were confirmed by strong association of Topo IIα and β with HIV-1 reverse transcriptase in cellular localization studies.

Conclusion: These results suggest a potential role of Topo II isoforms in HIV-1 RTn through regulating the downstream events of strong stop DNA synthesis during RTn possibly by promoting strand transfer events and alignment of RNA-DNA hybrids.