Dynamic interplay between HIV-1 integrase and host cofactors

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Invited speaker presentation

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Due to its limited genomic capacity, HIV-1 must interact with several cellular partners to replicate. Integration of a cDNA copy of its RNA genome into a chromosome of the host cell is a key step of retroviral replication that is under the control of Integrase. Although, the recombinant integrase is necessary and sufficient to catalyze the integration reaction *in vitro*, numerous studies have showed that cellular cofactors of integrase are involved in viral replication. Large-scale yeast two-hybrid screening (y2HS) has been proven to be a powerful approach to identify new protein-protein interactions. Using this method, we were able to isolate several new host cofactors interacting with integrase.

Together, our studies have identified the human lens epithelium-derived growth factor (LEDGF/p75), Transportin-SR2 (TNPO3), and von Hippel-Lindau binding protein 1 (VBP1) as cellular binding partners of HIV-1 integrase. For these cell factors, we have generated and characterized loss of affinity mutants of integrase, which, when combined with viral functional assays, validated their involvement in early step of the HIV-1 replication cycle. Using a biochemical approach to follow PIC components in different cellular compartments, the dynamic interaction between integrase and cellular cofactors was further explored within infected cells. Cellular cofactors are required for the completion of the HIV replication cycle and it is critical to elucidate on their mechanism of action. Novel therapeutic strategies aim to develop antiviral compounds targeting interactions between integrase and host-cell partners. Such novel targets are continuously needed to overcome the problem linked to the somewhat frequent occurrence of multi-drug-resistance, that in turn leads to complete therapeutic failure for patients infected with drug resistant viral strains.