

**POSTER 22****A COMMON TETRAMER INTERFACE IMPORTANT FOR IN INTERACTIONS WITH DNA SUBSTRATES AND LEDGF**

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The integration of the reverse-transcribed HIV-1 genome into the host chromosome is catalyzed by the viral protein integrase (IN) and is mandatory for productive infection. The activity of integrase is regulated by numerous viral and cellular proteins. Among these, LEDGF has been identified as a cellular cofactor that is critical for integration of the viral genome. Structural studies indicate that LEDGF binding stabilizes the HIV-1 integrase tetramer. Here, our mass spectrometric protein foot-printing approach has been employed to examine protein-protein interactions in the LEDGF-stabilized integrase tetramer using full length proteins. In parallel experiments, surface accessible maps for the IN-LEDGF complex were compared with that of free IN. For this, Lysine and Arginine specific small molecule modifiers were employed and affected residues were identified following tryptic digestion and MALDI-TOF analysis. The footprinting method revealed positions K14, K186, R187, and K188 near the IN dimer-dimer interface that were specifically shielded from modification in the presence of LEDGF. The importance of these residues in tetramer formation was confirmed by site-directed mutagenesis of the identified residues and size-exclusion chromatography of the mutant proteins. Further studies indicated a strong correlation between the IN tetramer formation and high affinity binding to LEDGF. Moreover, the mutations at the IN tetramer interface compromised both 3' processing and strand transfer activities. These findings provide new insight into the structure of the IN tetramer and its role in HIV-1 integration.