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MASS SPECTROMETRY-BASED FOOTPRINTING OF LEDGF INTERACTIONS WITH CHROMATINIZED TEMPLATES

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HIV-1 replication requires integration of the viral cDNA made by reverse transcription into the host chromosome for effective infection and maintaining the infected state in the host. The integration step is catalyzed by the retroviral enzyme integrase (IN). *In vivo* this process is regulated by multiple viral and cellular cofactors. Among these, lens epithelium derived growth factor (LEDGF) has been identified as the principal cellular cofactor critical for effective HIV-1 integration. LEDGF has been shown to tether the viral protein to chromosomal DNA. The N-terminal region of LEDGF contains a PWWP domain, nuclear localization signal, and a dual copy of the AT-hook DNA binding elements, while the C-terminal end contains the integrase binding domain. The N-terminal region of LEDGF has the ability to interact with the chromatin, but the molecular mechanism of its binding to the chromatin is not well understood. We have utilized our mass spectrometry-based protein footprinting approach to identify LEDGF residues interacting with naked DNA and mononucleosomes (MN). LEDGF surface residues readily modified in the free protein but protected from modification in both LEDGF-DNA and LEDGF-MN complexes will be interpreted as the direct contacts with DNA. Whereas the additional protections detected only in the LEDGF-MN complex will reveal potential protein-protein contacts established between LEDGF and chromatinized template. This research will help us to better define the nature of LEDGF interactions with chromatin and their role in targeting HIV integration.