

THE HIGHLY DYNAMIC STRUCTURE OF MULTIMERIC HIV-1 INTEGRASE AS A NOVEL THERAPEUTIC TARGET

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The mandatory integration of the reverse-transcribed HIV-1 genome into host chromatin is catalyzed by the viral protein integrase (IN). Numerous viral and cellular proteins could modulate IN activity. Among these, LEDGF is a principal binding partner of HIV-1 IN. The x-ray crystal structure of the catalytic core domain (CCD) of IN in complex with the IN binding domain (IBD) of LEDGF has furthermore revealed essential protein-protein contacts. However, mutagenic studies indicated that interactions between the full length proteins were more extensive than the contacts observed in the co-crystal structure of the isolated domains. To characterize interactions between full length IN and LEDGF we employed a number of innovative biophysical approaches. Our studies revealed a highly dynamic nature of IN subunit-subunit interactions. LEDGF strongly stabilized these interactions and promoted IN tetramerization. Mass spectrometric protein footprinting and molecular modeling experiments uncovered novel intra- and inter-protein-protein contacts in the full length IN-LEDGF complex that lay outside of the observable IBD-CCD structure. In particular, our studies defined the IN tetramer interface important for high affinity LEDGF binding and IN enzymatic activities. These findings provide new insight into how LEDGF modulates HIV-1 IN structure and function, and highlight the potential for exploiting the highly dynamic structure of multimeric IN as a novel therapeutic target. In a related study, we found that a small molecule acetylated inhibitor selectively binds to a novel cavity located at the IN dimer interface and interferes with IN subunit-subunit interactions. Further studies in this direction may lead to development of novel types of HIV-1 IN inhibitors.