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CHARACTERIZATION OF THE ACETYLATED-INHIBITOR BINDING SITE IN HIV-1 INTEGRASE

Jacques Kessl¹, Jocelyn Norris¹, Nick Shkriabai¹, Zhuojun Zhao¹, Sonja Hess³, Terrence R. Burke, Jr.², Mamuka Kvaratskhelia¹

¹College of Pharmacy, Center for Retrovirus Research and Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43210; ²Laboratory of Medicinal Chemistry, National Cancer Institute-Frederick, Frederick, MD 21702; ³Proteome Exploration Laboratory, Beckman Institute, California Institute of Technology, Pasadena, CA 91125

HIV-1 integrase (IN) is an important therapeutic target. The functional enzyme is a multimer and dynamic interplay between the individual protein subunits is essential for the IN catalytic activities. Using affinity acetylation and mass spectrometry we previously found that a small molecule acetylated-inhibitor methyl N,O-bis(3,4-diacetoxycinnamoyl)serinate (MDACS) selectively acetylated K173 near the IN dimer interface. We herein extend our efforts to characterize the MDACS binding pocket and mechanism of action. Comparison of MDACS with structurally related acetylated chicoric acid revealed a striking difference between these compounds in their interactions with the IN dimer interface. Furthermore, MDACS in dose dependent manner interfered with IN subunit-subunit interactions, while acetylated chicoric acid did not affect the dynamic structure of the multimeric IN. The only structural difference between MDACS and acetylated-chicoric acid is that the former contains a methyl ester group within its linker region, while the latter possesses two carboxylic acids in its linker segment. Molecular modeling studies indicated two distinct potential MDACS binding pockets flanking K173: one overlapping the cellular cofactor LEDGF binding site and another cavity located on the C₂ symmetry axis at the dimer interface. Of these, the docking studies indicated a marked preference for the latter pocket and revealed additional amino acids interacting with MDACS. These findings shed light on structural features essential for productive binding of small molecule inhibitors to the IN dimer and extend our previous findings that the IN dimer interface is potentially a valuable selective target for a new class of inhibitors.