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Structure of the Antiviral Assembly Inhibitor CAP-1 Complex with the HIV-1 CA Protein

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The CA domain of the human immunodeficiency virus type 1 (HIV-1) Gag polyprotein plays critical roles in both the early and late phases of viral replication and is therefore an attractive antiviral target. Compounds with antiviral activity were recently identified that bind to the N-terminal domain of CA (CA^N) and inhibit capsid assembly during viral maturation. We have determined the structure of the complex between CA^N and the antiviral assembly inhibitor *N*-(3-chloro-4-methylphenyl)-*N′*-{2-[({5-[(dimethylamino)-methyl]-2-furyl}-methyl)-sulfanyl]ethyl}-urea) (CAP-1) using a combination of NMR spectroscopy and X-ray crystallography. The protein undergoes a remarkable conformational change upon CAP-1 binding, in which Phe32 is displaced from its buried position in the protein core to open a deep hydrophobic cavity that serves as the ligand binding site. The aromatic ring of CAP-1 inserts into the cavity, with the urea NH groups forming hydrogen bonds with the backbone oxygen of Val59 and the dimethylamonium group interacting with the side-chains of Glu28 and Glu29. Elements that could be exploited to improve binding affinity are apparent in the structure. The displacement of Phe32 by CAP-1 appears to be facilitated by a strained main-chain conformation, which suggests a potential role for a Phe32 conformational switch during normal capsid assembly.

Keywords: HIV capsid; inhibitor; structure; assembly; CAP-1

Introduction

The AIDS epidemic continues to be a significant international health problem, with approximately 40 million people living with human immunodeficiency virus (HIV) infection world-wide.[1] In 2006 alone, 4.3 million individuals became infected with HIV, and approximately 3 million deaths were attributed to AIDS. Therapeutic agents currently used to treat HIV infection target the viral reverse transcriptase, protease, and envelope proteins, and drugs that target the integrase enzyme are undergoing clinical trials‡. Although sustained reductions in viral load can be achieved for many years with combination drug therapies,[2–4] inadequate suppression due to poor compliance, resistance, and interactions with other drugs or diet can be a significant problem for some patients and can lead to the spread of drug-resistant strains.[2,3,5–8] Inhibition of other viral components may provide the best approach for attacking viral resistance.[2]

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Abbreviations used: CA^N and CA^C, N and C-terminal domains of the CA protein, respectively; CAP-1, *N*-(3-chloro-4-methylphenyl)-*N′*-{2-[({5-[(dimethylamino)-methyl]-2-furyl}-methyl)-sulfanyl]ethyl}-urea); Gag, Gag polyprotein; HS/MQC, heteronuclear single/multiple quantum coherence; NOE, nuclear Overhauser effect; NOESY, NOE spectroscopy; HIV-1, human immunodeficiency virus type 1; EM, electron microscopy; NNRTI, non-nucleoside reverse transcriptase inhibitor; DMSO, dimethyl sulfoxide; MLV, murine leukemia virus.

‡ http://www.aidsinfo.nih.gov