The HIV-1 full length capsid protein (CA-FL) is increasingly viewed as an attractive therapeutic target since proper capsid formation is required for viral infection. CA-FL is synthesized as a central domain of a structural Gag polyprotein that is involved in both early and late stages of the viral life cycle. During the HIV-1 maturation process, Gag is cleaved by a viral protease to produce several discrete new proteins that include matrix, capsid (CA-FL), and nucleocapsid. After proteolytic cleavage, CA-FL forms hexamers and pentamers that rearrange into a fullerene cone-shaped structure, which surrounds the viral genome at the center of the mature virus. Crystal structures of the native unassembled hexameric CA-FL (without cross-linked residues that might prevent changes in the inter- or intra-subunit interactions) are of great interest, as they may provide insights relevant to the development of drugs that prevent or impede the transition from the preassembled to the assembled capsid states. Recently, we crystallized and solved the crystal structure of the first hexameric HIV-1 CA-FL in its native form (without engineered cross-linking cysteines). There is one molecule per asymmetric unit, and the P6 space group generates the native hexameric assembly. We have also identified a small molecule, 18E8, which exhibits broad anti-HIV activity in cell-based assays, and targets CA-FL. This was demonstrated by experiments that selected for viruses with drug resistance and revealed that an A105T mutation in CA-FL confers resistance to the compound. Time-of-inhibitor addition experiments showed that 18E8 targets an early step in the HIV replication cycle, after reverse transcription and before integration. Electron microscopy experiments suggest that 18E8 does not impart significant morphological changes in CA-FL tubular assemblies. Our structure of CA-FL and our ongoing work with the CA-FL/18E8 complex will provide a system for the investigation of molecular interactions between CA-FL and small molecule antivirals that work with a novel mechanism of action.

Keywords: HIV, Capsid, Antivirals

Acta Cryst. (2014), A70, C696