

POSTER 43

CRYSTAL STRUCTURE OF THE TSG101 UEV DOMAIN IN COMPLEX WITH THE PTAP MOTIF OF THE HIV-1 GAG PROTEIN

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HIV-1 viral budding requires a direct interaction between the PTAP motif within the viral Gag protein and the cellular endosomal sorting factor Tsg101. Tsg101 is a subunit of human ESCRT1 complex which plays a key role in HIV budding and in multivesicular body biogenesis. The N-terminal domain of Tsg101 (UEV) binds both ubiquitin and the PTAP motif. In an effort to develop competitive inhibitors of this interaction, we determined the high resolution crystal structures of Tsg101 UEV with a HIV Gag peptide PTAPPEE or with its modified peptides. The PTAP peptide binds in a groove formed by two β -hairpin structures. Each PTAP residue makes important contact and the backbone atoms of upstream and downstream residues make additional interaction with the UEV domain. Two peptide inhibitors, Fa258 and Fa459 contain a 3, 4-dimethoxybenzyl oxime group at the Pro7 position in the PTAP peptide. The oxime group makes additional interaction with the β -sheet surface of UEV domain, which explains the enhanced binding affinity of the modified PTAP peptides. The high resolution structures reveal a molecular basis of HIV PTAP motif recognition by the UEV domain and provide a starting point for the design of novel inhibitors of viral budding.