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HIV-1 capsid binds host cofactors to mediate nuclear import

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The capsid (CA) protein of HIV-1, which forms the core of the virus, has been shown to have an increasingly important role in the early stages of the virus lifecycle, in particular during reverse transcription and nuclear import. We recently solved the structure of a fragment of the human cofactor CPSF6 in complex with the N-terminal domain of HIV-1 CA, revealing a previously unknown interface used by the virus to recruit CPSF6, which is required for the virus to successfully complete the early stages of its lifecycle. Using a recently developed hexameric unit of CA, we have solved the structure of the CPSF6 peptide with CA in a context that more closely resembles an intact CA lattice. This has revealed that CPSF6 contacts HIV-1 CA using an additional second site only present in the hexameric form of CA. Furthermore, we have now solved the structure of a fragment of NUP153 (an HIV-1 cofactor that is integral to the nuclear pore) in complex with hexameric CA and discovered that this also forms contacts specific to hexameric CA. Moreover, the binding sites for CPSF6 and NUP153 on CA overlap at one crucial residue, which is remarkably mimicked by two drugs independently discovered to bind at this same site. Together, these data provide evidence for an essential role for CA in HIV-1 infection, and highlights CA as an important target for antiretroviral drugs.

[1] *A. Price, A. Fletcher, T. Schaller et al., PLoS Pathogens, 2012, 8, e1002896*

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