REGULATION OF HIV-1 NUCLEAR IMPORT

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We have previously shown that C-terminally truncated forms of cleavage and polyadenylation factor 6 (CPSF6), an SR family protein, interfere with infection by HIV-1 and SIV, but not MLV. HIV-1 entry and reverse transcription are not impaired in the presence of antiviral CPSF6, but nuclear forms of the vDNA are diminished. Strikingly, growth arrest of cells expressing antiviral CPSF6 intensifies the restriction of HIV-1 to over two orders of magnitude. A single amino acid change in HIV-1 CA, N74D, overcomes the restriction by antiviral CPSF6. While N74D HIV-1 can efficiently infect transformed cell lines and primary T cells in the presence or absence of antiviral CPSF6, this mutant virus is blocked at an early stage in the infection of macrophages. These data suggested that antiviral CPSF6 interfered with a nuclear entry pathway relevant to HIV-1 infection of primary target cells. To better understand how antiviral CPSF6 prevents HIV-1 nuclear entry, we examined whether a recently described HIV-1 dependency factor, TNPO3, was relevant to infection by wild-type (WT) but not N74D HIV-1. Whereas siRNA knockdown of endogenous CPSF6 or its binding factor CPSF5 did not impair HIV-1 infection, knockdown of the transportin-SR2 spliced isoform of TNPO3 specifically restricted WT but not N74D HIV-1. In contrast to the restriction mediated by truncated CPSF6, growth-arrest of cells knocked down for transportin-SR2 did not intensify the block to WT HIV-1 infection, indicating interaction with transportin-SR2 equally enhances infection in both dividing and nondividing cells. These data reinforce a role for transportin-SR2, a non-NLS karyopherin, in the early replication of HIV-1 and suggest migration through the nuclear pore to be an essential step in infection even in mitotic cells. Our findings provide the first genetic evidence that HIV-1 CA regulates interaction with a nuclear transport factor.