

**POSTER 25****INOSITOL PHOSPHATE-MEDIATED SWITCH IN THE NUCLEIC ACID CHAPERONE ACTIVITY OF HIV-1 Gag**

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Reverse transcription of the human immunodeficiency virus type-1 (HIV-1) single-stranded RNA genome into double-stranded cDNA requires a complex series of extensions, jumps, and template switches. Reverse transcriptase uses a host cell tRNA<sup>Lys,3</sup> primer, which must be unwound and annealed onto the viral RNA at a complementary primer binding site. *In vitro*, the restructuring of these RNAs is greatly enhanced by the presence of the potent nucleic acid chaperone, HIV-1 nucleocapsid protein (NC). However, *in vivo* evidence suggests that the Gag poly-protein precursor is responsible for facilitating tRNA annealing. Before proteolysis, Gag consists of matrix (MA), capsid (CA), spacer 1 (p2), NC, spacer 2 (p1), and p6 domains. Previous studies demonstrated that Gag can facilitate tRNA annealing *in vitro*; however, the contribution of each domain to its nucleic acid chaperone activity is unknown. In this work, we show that Gag mediates tRNA annealing at a reduced rate relative to HIV-1 NC. The NC domain is essential for Gag-mediated annealing, while the MA domain appears to inhibit Gag's chaperone activity. Whereas WM-Gag, a monomeric variant harboring mutations at the dimerization interface within CA, displays similar annealing rates as wild-type Gag, Gag variants containing NC but lacking MA (i.e., CANC) show elevated rates of tRNA annealing. Interestingly, inositol phosphates (IPs), which are known to bind to basic residues K30 and K32 within MA and modulate Gag particle assembly *in vitro*, stimulate the chaperone activity of Gag. Stimulation by IPs was shown to depend on the presence of MA residues K30 and K32, and the maximum effect was achieved at a 1:1 Gag:IP ratio. Taken together with previous data, these results suggest that IP or membrane binding by the MA domain results in a conformational switch that stimulates Gag's ability to facilitate annealing of the tRNA primer via the NC domain. This work was supported in part by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.