HIV-1 Nef Chimeric Viruses Define Amino Acid Polymorphisms Involved in Antagonism of the SERINC5 Restriction Factor

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The host restriction factor Serine Incorporator 5 (SERINC5) restricts HIV-1 infectivity by incorporating into virions during egress. The HIV-1 Nef protein accordingly interacts with the membrane trafficking Adaptor Protein 2 (AP-2) to internalize cell surface SERINC5 and re-route to the lysosome for degradation. Nef utilizes equivalent motifs to downregulate both SERINC5 and the CD4 HIV-1 entry receptor. Importantly, both Nef functions require interactions with AP-2 via the conserved Nef [D/E]xxxLL_{166} dileucine motif.

Herein, we demonstrate that primary Nef isolates acquired from acutely HIV-1 infected individuals, termed 2410 and 2391, downregulated CD4 from the cell surface. Interestingly, isolate 2410, but not 2391, retained SERINC5 downregulation function. We therefore hypothesized 2391 Nef encodes specific polymorphisms enabling CD4 downregulation, but not SERINC5 downregulation, to uncouple both pathways. To discern potential functional polymorphism(s), Nef chimeras were generated by swapping regions of 2410 Nef with the corresponding regions of 2391 Nef and assessing CD4 and SERINC5 downregulation. We mapped the polymorphism responsible for functional uncoupling to ND_{164}, located within the Nef dileucine motif. We further demonstrated that the ND_{164} polymorphism resulted in a significant decrease in infectious virus yield in the presence of SERINC5 compared to Nef isolates lacking this polymorphism.

Future research will define the specific mechanisms Nef utilizes to commandeer various aspects of the endolysosomal network to direct cell surface SERINC5 for degradation. Characterizing the pathways Nef hijacks could reveal an ‘Achilles Heel’ that could be exploited using novel therapeutics designed to block such interactions.