Retrovirology

Oral presentation

Nef and HIV/SIV Replication

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Nef is an accessory protein of primate lentiviruses that is required for high levels of viremia and progression to AIDS in infected individuals. Our studies on Nef have centered around its effects on budding and release of optimally infectious virions from cells. To these ends, we have characterized interactions between Nef and the transframe portion of the GagPol polyprotein, AIP1 and cholesterol. Specific sequences in Nef were identified that mediate these interactions. For example, the flexible loop in Nef binds p6* that connects Gag and PR. It is via this interaction that Nef helps to aggregate viral structural proteins in lipid rafts and is itself incorporated into progeny virions. A sequence in the core of the protein binds AIP1 that helps HIV-1 form multivesicular bodies and be released from cells. Indeed, fusing Nef with a mutant Gag that lacks the late domain allows for the release of VLPs into the supernatant. Finally, at its very C-terminus, Nef binds newly synthesized cholesterol, which is incorporated into viral particles that are more infectious. To detemine which one of these interactions was more important for high levels of viremia and progression to AIDS in the rhesus macaque, multiple mutations were engineered into the *nef* gene in SIVmac239. Of interest, before high levels of viral replication could be observed in monkeys infected with the mutant SIVmac239, both the binding to GagPol and AIP1 had to be restored in the mutant Nef protein. From these studies, it appears that Nef also plays a critical role in the later phases of the viral replicative cycle and ensures that optimally infectious virions are released from infected cells.