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SMR-DERIVED PEPTIDE DISRUPTS HIV-1 NEF'S INTERACTION WITH MORTALIN AND BLOCKS VIRUS AND NEF EXOSOME RELEASE

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Abstract: Nef is secreted from infected cells in exosomes and is found in abundance in the sera of HIV-infected individuals. Secreted exosomal Nef (exNef) induces apoptosis in uninfected CD4 T cells and may be a key component of HIV pathogenesis. The exosomal pathway has been implicated in HIV-1 virus release, suggesting a possible link between these two processes. We have previously described a Nef motif, the secretion modification region (SMR; amino acids 66-70), that is required for exNef secretion. We hypothesized that the Nef SMR binds a cellular protein involved in protein trafficking and that inhibition of this interaction would abrogate exNef secretion. By using tandem mass spectrometry and coimmunoprecipitation with a novel SMR-based peptide (SMR*wt*) that blocks exNef secretion and HIV-1 virus release, we identified mortalin as an SMR-specific cellular protein. A second set of coimmunoprecipitation experiments with full-length Nef confirmed that mortalin interacts with Nef via the SMR motif and that this interaction is disrupted by the SMR*wt* peptide. Overexpression and microRNA knockdown of mortalin revealed a positive correlation between exNef secretion levels and mortalin protein expression. Using antibody inhibition we demonstrated that the Nef/mortalin interaction is necessary for exNef secretion. This work constitutes a significant step in understanding the mechanisms underlying exNef secretion, identifies a novel host-pathogen interaction, and introduces an HIV-derived peptide with antiviral properties.

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