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HIV-1 Nef Mediates Host Invasion by Differential Expression of Alpha-Enolase

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Abstract : HIV-1 transmission and spread involves significant host-virus interaction. Potential targets for prevention of HIV-1 lies at the site of mucosal barriers. Thus a better understanding of how HIV-1 infects target cells at such sites and lead their invasion is required, with prime focus on the host determinants regulating HIV-1 spread. HIV-1 Nef is important for viral infectivity and pathogenicity. It promotes HIV-1 replication, facilitating immune evasion by interacting with various host factors and altering cellular pathways via multiple protein-protein interactions. In this study nef was sequenced from HIV-1 patients, and showed specific mutations revealing sequence variability in nef. To explore the difference in Nef functionality based on sequence variability we have studied the effects of HIV-1 Nef in human SupT1 T cell line and (THP-1) monocyte-macrophage cell lines through proteomics approach. 2D-Gel Electrophoresis in control and Nef-transfected SupT1 cells demonstrated several differentially expressed proteins with significant modulation of alpha-enolase. Through further studies, effects of Nef on alpha-enolase regulation were found to be cell lineage-specific, being stimulatory in macrophages/monocytes, inhibitory in T cells and without effect in HEK-293 cells. Cell migration and invasion studies were employed to determine biological function affected by Nef mediated regulation of alpha-enolase. Cell invasion was enhanced in THP-1 cells but was inhibited in SupT1 cells by wildtype nef. In addition, the modulation of enolase and cell invasion remained unaffected by a unique nef variant. These results indicated that regulation of alpha-enolase expression and invasive property of host cells by Nef is sequence specific, suggesting involvement of a particular motif of Nef. To precisely determine this site, we designed a heptapeptide including the suggested alpha-enolase regulating sequence of nef and a nef mutant with deletion of this site. Macrophages/monocytes being the major cells affected by HIV-1 at mucosal barriers, were particularly investigated by the nef mutant and peptide. Both the nef mutant and heptapeptide led to inhibition of enhanced enolase expression and increased invasiveness in THP-1 cells. Together, these findings suggest a possible mechanism of host invasion by HIV-1 through Nef mediated regulation of alpha-enolase and identifies a potential therapeutic target for HIV-1 entry at mucosal barriers.

Keywords : HIV-1 Nef, nef variants, host-virus interaction, tissue invasion
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