

JOINT EVENT

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Effects of HIV-1 Nef on bystander uninfected cells

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Statement of the Problem: Recent studies demonstrated that Nef is incorporated into extracellular vesicles (exosomes) produced by HIV-infected cells and that exosomal Nef has pathogenic activity against uninfected by-stander cells. However, mechanisms of this activity have not been determined, limiting the search for therapeutic agents. The purpose of this study is to determine whether the effects of exosomal Nef mimic the effects of endogenously produced Nef.

Methodology: Exosomes were purified by differential centrifugation from supernatants of Nef-transfected HEK293T cells. Monocyte-derived macrophages were differentiated for 6 days in the presence of GM-CSF (M1 polarization) or M-CSF (M2 polarization) and treated with Nef exosomes for 48 h. ABCA1 expression was assayed by Western blot, cholesterol efflux – by release of radiolabeled cholesterol, and lipid rafts – using fluorescently labeled cholera toxin B subunit. HIV infection was analyzed by fusion assay.

Findings: Exosomal Nef down-regulated ABCA1, inhibited cholesterol efflux, and increased abundance of lipid rafts. It also shifted macrophage polarization to the M1 phenotype. Nef-treated macrophages became more susceptible to HIV infection and exhibited pro-inflammatory features.

Conclusion & Significance: Nef exosomes released from HIV-infected cells suppress cholesterol efflux in macrophages and likely in other cells. They increase susceptibility of by-stander macrophages to HIV infection. Nef also promoted M1 polarization of macrophages and may be responsible for the sustained pro-inflammatory phenotype of these cells. Given that Nef is produced from infected cells even when virus production is fully blocked by anti-retroviral treatment, these findings may explain persistent inflammation observed in successfully treated HIV patients with undetectable HIV load.

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