HIV-1 Nef upregulates CCL2/MCP-1 expression in astrocytes in a myristoylation- and calmodulin-dependent manner.

Abstract:

HIV-associated dementia (HAD) correlates with infiltration of monocytes into the brain. The accessory HIV-1 negative factor (Nef) protein, which modulates several signaling pathways, is constitutively present in persistently infected astrocytes. We demonstrated that monocytes responded with chemotaxis when subjected to cell culture supernatants of nef-expressing astrocytic U251MG cells. Using a protein array, we identified CC chemokine ligand 2/monocyte chemotactic protein-1 (CCL2/MCP-1) as a potential chemotactic factor mediating this phenomenon. CCL2/MCP-1 upregulation by Nef was further confirmed by ribonuclease protection assay, RT-PCR and ELISA. By applying neutralizing antibodies against CCL2/MCP-1 and using CCR2-deficient monocytes, we confirmed CCL2/MCP-1 as the exclusive factor secreted by nef-expressing astrocytes capable of attracting monocytes. Additionally, we showed that Nef-induced CCL2/MCP-1 expression depends on the myristoylation moiety of Nef and requires functional calmodulin. In summary, we suggest that Nef-induced CCL2/MCP-1 expression in astrocytes contributes to infiltration of monocytes into the brain, and thereby to progression of HAD.