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Poster presentation

HIV hijacks cholesterol transporter ABCA1 to get access to cellular cholesterol

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Cholesterol plays an important role in the HIV life cycle, and cholesterol depletion impairs both production and infectivity of HIV virions. Such dependence on cholesterol suggests that HIV may have evolved mechanisms to ensure access to cellular cholesterol during viral assembly. Recently, we demonstrated that HIV-1, via its protein Nef, inhibits activity of the cellular cholesterol transporter ABCA1 and impairs reverse cholesterol transport (RCT) from infected cells. In this study, we examined interaction between Nef and ABCA1 and investigated the role of ABCA1 in cholesterol delivery to nascent HIV virions. ABCA1 is a 12-transmembrane domain protein, and co-immunoprecipitation analysis using Nef and various fragments of ABCA1 identified multiple sites of interaction. Importantly, Nef was found to interact with the 46-aminoacid carboxyl-terminal domain of ABCA1, which was previously implicated in RCT. Mutation of leucines to alanines in positions 2230, 2233 and 2235 impaired interaction of this C-terminal domain of ABCA1 with Nef. When these mutations were introduced in the full-length ABCA1, such mutant protein was able to support RCT but lost sensitivity to Nef. To further characterize the role of ABCA1 inhibition in HIV biology, we analyzed cholesterol content of lipid rafts and HIV virions produced in cells expressing or not ABCA1. This analysis demonstrated that ABCA1 expression significantly reduced lipid raft cholesterol content, resulting in a corresponding reduction of virus-associated cholesterol and viral infectivity. This result is consistent with ABCA1-mediated redirection of cholesterol from lipid rafts (sites of HIV assembly) to non-raft regions of the plasma membrane (physiological localization of ABCA1). Intriguingly, Nef expression induced re-localization of ABCA1 to lipid rafts, suggesting that HIV hijacks the ABCA1 pathway to deliver cholesterol to the sites of HIV assembly.

Conclusion

Our results describe a novel interaction between HIV-1 Nef and ABCA1, the key cholesterol transporter of peripheral cells. We demonstrate that interaction of Nef with the C-terminal domain of ABCA1 is critical for Nef-mediated impairment of RCT. Intriguingly, Nef seems to hijack ABCA1 to deliver cholesterol to HIV assembly sites. It appears that in an infected cell there is a dynamic interaction between Nef and ABCA1: overexpression of Nef (a situation occurring in most HIV-infected cells) leads to inactivation of ABCA1 physiological activity (RCT), its re-localization to lipid rafts, delivery of cholesterol to assembling virions and production of highly infectious viral particles. In contrast, overexpression of ABCA1 (e.g., by drugs stimulating ABCA1 expression such as LXR agonists) stimulates RCT, reduces cholesterol in lipid rafts and virions, and inhibits HIV production and infectivity.