Extracellular Vesicles activation of latent HIV-1 is driven by EV-associated c-Src and cellular SRC-1 via the PI3K/AKT/mTOR pathway

Robert Barclay, Gifty Mensah, Maria Cowen, Catherine DeMarino, and Fatah Kashanchi

Laboratory of Molecular Virology, George Mason University

Abstract

HIV-1 is the causative agent of AIDS, infecting nearly 37 million people worldwide. Currently, no cure exists, mainly due to HIV’s ability to evade latency. Our previous work has shown that exosome-like extracellular vesicles (EVs), from uninfected cells can activate HIV-1 in latently-infected cells, leading to increased production of HIV-1 RNA. However, the mechanism behind the activation of latent HIV-1 by EVs remains unknown. This study was conducted to elucidate how EVs activate latent HIV-1 and to identify the signaling pathways that are responsible for the activation of HIV-1 by EVs.

Methods

EVs were isolated from uninfected THP-1 cells and used to infect PBMCs. The activation of latent HIV-1 was assessed by measuring the production of HIV-1 RNA and p24Ag. The effects of EVs on the activation of latent HIV-1 were studied using a series of inhibitors targeted at different signaling pathways.

Results

EVs were found to activate latent HIV-1 in PBMCs, leading to increased production of HIV-1 RNA and p24Ag. The activation of latent HIV-1 by EVs was found to be dependent on c-Src and cellular SRC-1. The activation of latent HIV-1 by EVs was found to be mediated by the PI3K/AKT/mTOR pathway, which was activated by EVs.

Discussion

The results of this study suggest that EVs activate latent HIV-1 by activating c-Src and cellular SRC-1, leading to the activation of the PI3K/AKT/mTOR pathway. This activation results in the production of HIV-1 RNA and p24Ag, leading to the activation of latent HIV-1.

Conclusion

EVs from uninfected cells contain activated c-Src (phosphorylated at tyrosine-417) that can activate the signaling cascade involving EGFR, the PI3K/AKT/mTOR pathway, and SRC-1.

EV-associated c-Src is important in driving EV activation of latent HIV-1. Dasatinib (c-Src inhibitor) and WP1166 (stat3 inhibitor) can specifically block infected cells and could help mitigate this process.

References


Acknowledgements

This work was supported by National Institutes of Health Grants R01 AI065429, R01 AI095815, and R01 AI065429. We thank all members of the Kashanchi lab, especially Dr. Lijuan Su, for their assistance in preparing the manuscript. This work was supported by National Institutes of Health Grants R01 AI065429, R01 AI095815, and R01 AI065429.