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Abstract

Central role of HIV Nef in pathogenesis of HIV-associated co-morbidities

Michael Bukrinsky
The George Washington University School of Medicine and Health Sciences

Abstract:
Combination antiretroviral therapy (cART) transformed HIV infection from a death sentence to a manageable chronic disease. However, several serious co-morbidities, such as cardio-vascular disease (atherosclerosis) and HIV-associated neurocognitive disorders (HAND), affect large proportion of HIV infected individuals even when successfully treated with cART. The pathogenic mechanisms behind this phenomenon and its link to HIV infection remain unknown. We propose that the driver for these co-morbidities is the HIV protein Nef released within the extracecellular vesicles (EVs) from infected cells persisting in the viral reservoirs. Nef-containing EVs are detected in the blood of up to 50% of cART-treated individuals with undetectable viral load. Our studies demonstrated that Nef EVs impair the cholesterol metabolism in cells by inhibiting the activity of the main cellular cholesterol transporter, ABCA1, responsible for cholesterol efflux. Inhibition of ABCA1 leads to increased abundance of cholesterol-rich regions of the plasma membrane, lipid rafts. Nef also impairs functionality of the lipid rafts. Lipid rafts are the key regulators of inflammatory responses and brain cell interactions, suggesting that via this mechanism the Nef EVs may contribute to atherosclerosis and HAND. We have demonstrated that injection of Nef EVs into mice induces inflammatory response and promotes atherogenic changes consistent with findings in HIV-infected subjects. Analysis of brain samples from individuals who died with HAND diagnosis demonstarted increased lipid rafts which correlated with Nef concentartion. These results suggest that treatments aimed at normalization of abundance and function of the lipid rafts may be effective against HIV co-morbidities.

Biography:

Michael Bukrinsky has completed his MD at the 2nd Moscow State Medical School, and obtained PhD degree from the Engelhardt Institute of Molecular Biology in Moscow, Russia. He did his postdoctoral studies in Moscow at the Institute of Virology, and then in Omaha, NE, at the University of Nebraska Medical Center. He is now Professor of Microbiology, Immunology and Tropical Medicine at the GWU SMHS, Director of the Developmental Core at teh DC CFAR, and Editor-in-Chief of The Open AIDS Journal. He has published more than 170 papers in reputed journals and has been serving on several editorial boards.

Recent Publications:

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