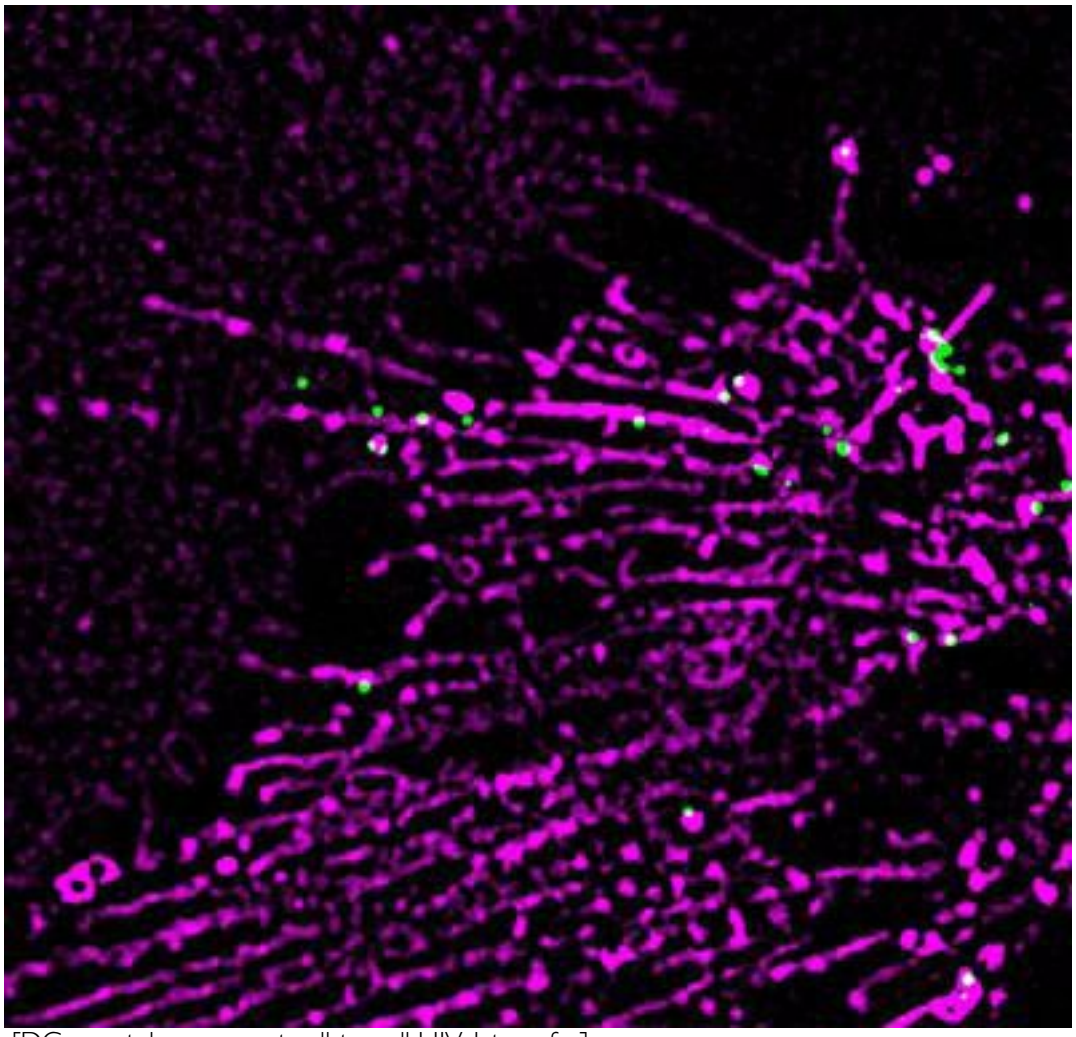
PE23

CD40L-induced tunneling nanotube networks facilitate proinflammatory dendritic cell-mediated HIV-1 trans-infection of CD4+ T-cells

Zaccard C.[1], Mailliard R.[1], Rappocciolo G.[1], Watkins S.[2], Rinaldo C.[1]
[1]University of Pittsburgh, Infectious Diseases and Microbiology, Pittsburgh, United States, [2]University of Pittsburgh, Cell Biology and Physiology, United States

Background: We have found that, in addition to their high IL-12p70 producing capacity, dendritic cells (DC) matured in the presence of acute inflammatory mediators are uniquely programmed to form intercellular networks of tunneling nanotubes, or 'reticulate', in response to T helper cell-associated CD40L. We also recently revealed a relationship between HIV-1 disease progression and trans-infection when we demonstrated that DC from HIV-1-infected non-progressors (NP) lack the ability to transmit virus to CD4+ T cells due to a paucity of cellular cholesterol. Here we investigate a relationship between inducible nanotube formation, which also requires the presence of cholesterol-rich lipid rafts, DC-mediated trans-infection, and HIV-1 disease progression.



[DC nanotubes support cell-to-cell HIV-1 transfer]

Methods: DC were generated using monocytes isolated from HIV-1 seronegative donors or NP from the Multicenter AIDS Cohort Study. NP displayed stable CD4+ T cell counts in the absence of antiretroviral drug therapy over many years of HIV-1 infection. Differential polarization of DC was achieved by exposure to an IFN-g- or PGE2-containing cocktail to mimic a setting of acute or chronic inflammation, respectively. We treated DC types with CD40L or media, and quantitatively assessed morphological alterations using live-cell confocal microscopy and 3D imaging analysis software. The ability of DC types to transmit virus to CD4+ T cells was determined using our trans-infection model, followed by intracellular HIV-1 core antigen staining and flow cytometry.

Results: We determined that CD40L-induced reticulation increases the surface area and spatial reach of proinflammatory DC, facilitating intercellular trafficking of antigens as well as HIV-1 for amplification of virus transmission. Moreover, IFN-g-programmed DC display a superior capacity to mediate HIV-1 trans-infection of CD4+ T cells compared to PGE2-programmed DC, which is further enhanced by the addition of soluble CD40L. Importantly, IFN-g-programmed DC generated from NP display a dramatically reduced ability to reticulate in response to CD40L, which coincides with their failure to effectively mediate HIV-1 trans-infection of CD4+ T cells.

Conclusions: The link between inhibited disease progression in HIV-1-infected NP and the inability of their proinflammatory DC to reticulate and trans-infect CD4+ T cells provides a rationale for further exploration of therapeutic strategies to target this immune process and potentially control HIV-1 disease progression.