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HIV-1 hijacks tunneling nanotubes and secretory microvesicles for intercellular spread in monocyte-derived macrophages

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Background

Tunneling nanotubes (TNT) are cytoskeletal bridges that support intercellular exchanges of receptors, lysosomes and mitochondria. HIV-1 transmission by intercellular connections such as TNT and immunological synapses may facilitate cellular transmission when compared to classical receptor-mediated mechanisms. This permits for acactive viral spread despite neutralizing antibodies. Mechanisms of TNT formation and pathogen immune escape through TNT transport have generated intense interest after failure of vaccination strategies.

Methods

To determine the mechanisms underlying the formation of TNT and intra- and intercellular viral trafficking we used still and time lapse confocal imaging, transmission and scanning electron microscopy, antibodies to and chemical inhibitors of motor and cytoskeletal proteins. Proteomics techniques were sued to assist in determining the biochemical composition of TNT as well as the type of vesicular cargoes adopted for viral transport along these structures.

Results

We now demonstrate that HIV-1-infected human monocyte-derived macrophages (MDM) can establish direct cell-cell contacts via the TNT networks. In parallel to structural organization HIV-1 induces an increase in vesicle sorting and turnover. Co-cultivation of uninfected and infected cells resulted in formation of intercellular contacts extending over 700 μm in length. Electron and confocal microscopy revealed the tubular nature of TNT tethered at the perinuclear/Golgi regions of the connected cells, and rich in vesicular compartments confined by the TNT limiting membranes. Accumulation of adherence junction components along the TNT at the contact sites was observed. Use of cytoskeleton-disrupting drugs such as cytochalsin D, nocodasole indicated a critical role for actin in driving TNT formation. Proteomic analysis of TNT collected from infected cells showed substantial presence of early, late and recycling endosomes together with vesicle trafficking components including Rab GTP-ase family proteins (Rab2a/5a/7, 11) and myosins along the TNT. Proteomic analysis identified HIV-1 proteins including HIV-1 Tat, Rev, Gag and gp120 along TNT. Confocal imaging showed TNT support active and bi-directional vesicle exchange at an average velocity of 1.5 μm/s. These events are accompanied with significant co-localisation of Env and Gag proteins with vesicle-cargo motor proteins and actively transported from the infected to uninfected target cells. Inhibition of myosin II by blebbistatin and butandiene monoxime together with use of cytochalasin D/nocodasole completely abrogated movement of HIV+ vesicles along the TNT.

Conclusion

These data provide new evidence that HIV-1 may escape immune surveillance and neutralizing antibodies by inducing both structural rearrangements (TNT formation) and membrane turnover (increased vesicle sorting) in human macrophages and uses such processes for direct transport from infected to the target uninfected cells.