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Probing Cell-to-cell Transfer of Human T-cell Leukaemia Virus Type-1 Using Novel Inhibitors of Viral Entry

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Infection of human cells by human T cell leukaemia virus (HTLV-1) is mediated by the viral envelope glycoproteins. The gp46 surface glycoprotein makes first contact with the target cell through binding to the cell surface receptor Glut-1, thereby allowing the transmembrane glycoprotein to initiate fusion of the viral and cellular membranes. We have now used a soluble recombinant form of gp46 fused to the Fc-region of human IgG (sRgp46-Fc), and a panel of antibodies and inhibitory peptides to probe envelope function during cell-to-cell viral transfer. We have been able to recapitulate the transfer of HTLV-1 between cells through sites of tight cell-to-cell contact that have been termed the virological synapse. We now demonstrate that upon contact with HTLV-1 infected T-cells, the HTLV-1 receptor glucose transporter-1, Glut-1, is redistributed within the membrane of target cells. On the non-infected target cell Glut-1 is re-localized to, and enriched within, the point of synaptic T-cell contact. Importantly, this re-localization of Glut-1 on target cells occurs rapidly, and is specific for Glut-1, as irrelevant cell surface markers do not show polarized redistribution. Significantly, we find that redistribution of Glut-1 reflects the pattern of envelope accumulation on the HTLV-1 infected cell. Moreover, we find that sRgp46-Fc is also able to effect re-localization of Glut-1 on T cells, suggesting that envelope-mediated recruitment of Glut-1 to the site of synaptic transfer may be a crucial event in the cell-to-cell transfer of HTLV-1. Our recent results will be presented, and the implications of our findings for HTLV-1 pathogenesis will be discussed.