

HIV-1 BUDDING AND THE ESCRT COMPLEXES

James H. Hurley, Young Jun Im, Hyung Ho Lee, Dong Yang, Xuefeng Ren, Thomas Wollert, Michael S. Kostelansky, Sangho Lee, Jaewon Kim, and Rodolfo Ghirlando

Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, U. S. Department of Health and Human Services, Bethesda, MD 20892

The scission of nascent HIV-1 virions from the plasma membrane of human cells requires the human host encoded ESCRT (Endosomal Sorting Complexes Required for Transport) machinery. The ESCRT machinery consists of five complexes conserved from yeast through humans, ESCRT 0-III and VPS4-VTA1, together with the monomeric ALIX protein and associated ubiquitin ligases. These complexes are thought to carry out a conserved membrane scission reaction both in HIV-1 budding and in normal cell pathways that include the biogenesis of multivesicular bodies (MVBs; an intermediate in lysosome biogenesis), the membrane abscission step in cytokinesis, and autophagy. ESCRT 0-II are soluble complexes that are constitutively assembled, and cycle between a cytosolic and peripherally membrane-bound state. ESCRT-III consists of a pool of cytosolic monomers that, upon activation, assemble into a detergent-insoluble spiral array on membranes. ESCRT-I and ALIX are targeted to the site of HIV-1 budding by direct interactions with PTAP and YPXL motifs, respectively, in HIV-1 Gag p6. ESCRT-I and ALIX then, either directly or indirectly, recruit ESCRT-III. ESCRT-III is thought to be responsible for the membrane scission. Structural studies in our lab and others have led to a model for the recruitment of the ESCRTs and ALIX to their sites of action in HIV-1 budding and in normal physiology.