Introduction

The processes of vesicle budding into multivesicular bodies (MVBs), retrovirus release, and cytokinesis share a common requirement for an overlapping subset of cellular machinery, termed the Endosomal Sorting Complexes Required for Transport (ESCRT)[1; 2; 3]. The ESCRT machinery may perform analogous functions at the final stages of all three processes, where a membrane fission event is required to resolve a thin, cytosol-containing membrane tubule. At steady state, ESCRT factors bind weakly to membranes throughout the cell[4], but they can be recruited to function at specific sites of membrane remodeling including the late endosome, the plasma membrane, and the midbody. Most ESCRT factors function as subunits of one of four different complexes, termed ESCRT-0, -I, -II, and -III. Although their functions are not yet fully defined, ESCRT-0, -I, and -II appear to act as adaptors, binding directly to both membranes and protein cargoes as they are sorted into vesicles or virions. ESCRT-III subunits, in contrast, appear to co-assemble into membrane-associated filaments that play a more direct role in membrane remodeling, possibly mediating membrane extrusion and/or fission[5].

Once assembled on membranes, the ESCRT machinery is released by the action of the Vps4 ATPases, the only known enzymes in the ESCRT pathway. A direct role for Vps4 function in the ESCRT pathway is indicated by a number of observations, including: 1) Vps4 localizes to endosomal membranes[6] and to the midbody during cytokinesis[7; 8], 2) MVB protein sorting and intralumenal vesicle formation are inhibited in the absence of Vps4 or upon expression of dominant negative Vps4 that cannot bind or hydrolyze ATP[6; 9; 10; 11; 12], and 3) Depletion or dominant inhibition of Vps4