Most proteins targeted for degradation in the multivesicular bodypathway are monoubiquitinated, then passed through the ESCRT complexes, a series of highly-conserved multisubunit complexes. ESCRT I, II, and III are sequentially mobilized to endosomal membranes, where they direct protein sorting and MVB biogenesis, and play a crucial role in retrovirus budding. ESCRT IIis a 155-kDa trilobal cytoplasmic complex that transiently associates with endosomes and appears to regulate the formation of ESCRT III. The ESCRT II core, which contains two copies of Vps25p, one copy of Snf8p, and the C-terminal region of Vps36p, consists of eight repeats of a common building block, a \"winged helix\" domain. Two PPXY-motifs from Vps25p are involved in contacts with Snf8p and Vps36p, and their mutation leads to disruption of the complex. Each ESCRT II subunit binds the other two subunits of ESCRT II, as well as Vps28p of ESCRT I and Vps20p of ESCRT III, with Vps25p being the main subunit responsible for the interaction with Vps20p. Vps36p also binds ubiquitinated target proteins. Null mutants in SNF8, VPS25, or VPS36 are extremely sensitive to calcium, lithium or manganese ions, and to high temperatures. These mutants also display mislocalization of Rim20p to a few large perivacuolar foci, suggesting that ESCRT II is involved in regulating Rim20p localization. snf8, vps20 or vps36 nulls also accumulate Fur4p at the plasma membrane, which increases uptake of 5-fluorouracil, a toxic analog of uracil. The human homologs of the ESCRT II proteins interact with one another, with human Vps20pand with their yeast homologs. siRNA depletion of mammalian ESCRT II does not affect degradation of epidermal growth factor, a known cargo of the multivesicular body protein sorting pathway, suggesting that mammalian ESCRT II may be redundant, cargo-specific, or not required for protein sorting at the multivesicular body.In addition to vacuolar protein sorting defects, vps25 null mutants display increased sensitivity to the antifungal agent caspofungin, which interferes with glucan synthesis and cell wall formation. vps25 nulls also display a reduced frequency of Rim20p-GFP foci under alkaline conditions as compared to wild type. VPS25 has homologs in mouse, human, and fission yeast, and is similar to Drosophila melanogaster l44Db and Caenorhabditis elegans W02A11.2.