blocks late stages of both cytokinesis[7; 8] and enveloped virus budding (reviewed in [13; 14; 15]). At a minimum, Vps4 ATPase activity appears to be required to release and recycle the assembled ESCRT machinery, because the other ESCRT factors assemble but are not released in the absence of Vps4 activity[16]. Vps4 activity may also be mechanistically coupled to membrane deformation and/or fission, though such coupling has not been demonstrated experimentally.

Vps4 proteins belong to the large and diverse family of AAA ATPases (ATPases Associated with diverse cellular Activities) (reviewed in [17; 18; 19; 20; 21; 22; 23]). AAA ATPases can contain either one (class I) or two (class II) ATPase cassettes, and Vps4 is a class I ATPase. Yeasts express a single Vps4 protein, whereas humans and other mammals express two closely related Vps4 proteins, termed VPS4A and VPS4B/SKD1[24]. As summarized in Fig. 1a, Vps4 proteins contain an N-terminal MIT domain that binds ESCRT-III protein substrates, a central ATPase cassette composed of large and small domains, and a three-stranded antiparallel sheet (the β domain) inserted within the small ATPase domain [25; 26; 27; 28]. On its own, the linker between the MIT and ATPase regions lacks a persistent structure[26], and can be hyper-susceptible to proteolysis in the context of the full length protein. This linker undergoes nucleotide-dependent changes in proteolytic susceptibility[28], however, suggesting that it serves as a semi-flexible tether that can adopt different conformations.

Most AAA ATPases function as closed hexameric rings, although other arrangements are known[29]. Ring formation is mediated by the AAA ATPase cassette, and ATP binding typically promotes ring assembly because nucleotides