

Dynamic assembly and disassembly of Endosomal Sorting Complex Required for Transport-III (ESCRT-III) drives membrane scission reactions at endosomes and the plasma membrane, but regulation of this activity is poorly understood. A major objective is to identify ESCRT-III interactions that influence both the polymerization state of the complex and membrane scission activity by the complex. I will present data showing that ESCRT-III in yeast is regulated by Doa4, the ubiquitin hydrolase that deubiquitinates transmembrane proteins that are sorted by ESCRT-III into intraluminal vesicles (ILVs) at endosomes. Deletion of Doa4 destabilizes the ESCRT-III complex and results in smaller ILVs. Conversely, Doa4 overexpression increases ESCRT-III stability, and this activity is inhibited through its interaction with Vps20, the subunit of ESCRT-III that initiates complex assembly. These results suggest that the timing of ILV membrane scission by ESCRT-III is coordinated with the removal of ubiquitin from transmembrane protein cargoes sorted into nascent ILVs.