Ssm4p and Hrd1p are ubiquitin ligasesinvolved in endoplasmic reticulum-associated degradation. Ssm4p and Hrd1p are central members of the ubiquitin ligase complexes that are responsible for recognizing and ubiquitinating misfolded proteins in the ER for degradation by the proteasome. Misfolded cytosolic proteins are ubiquitinated by Ssm4p whereas misfolded luminal and membrane proteins are ubiquitinated by Hrd1p. The Ssm4p and Hrd1p ubiquitin ligase complexes also localize to different regions along the ER-nuclear membrane system: Ssm4p localizes to the inner nuclear membrane while Hrd1p remains in the ER membrane. Despite these differences, Ssm4p and Hrd1p appear to have overlapping substrate specificities and redundant functionalities. Each ubiquitin ligase complex interacts with the Cdc48p-Npl4p-Ufd1p AAA ATPase complex via Ubx2p in order to extract ubiquitinated substrates from the ER.Hrd1p forms a complex with Hrd3p, which stabilizes Hrd1p. Hrd3p also interacts with Kar2p and Yos9p to specifically target misfolded cytosolic proteins. Ubc7p or Ubc1p can act as the ubiquitin-conjugating enzymefor Hrd1p. Ubc7p interacts with the RING-H2 domain of Hrd1p.S. cerevisiae Hrd1p is related to the H. sapiens HRD1 and gp78, which is also known as the 603243>autocrine motility factor receptor. S. cerevisiae Hrd1p has also been shown to degrade the cystic fibrosis transmembrane conductance regulatorwhen CFTR is expressed in yeast.