

P007 The role of a novel p97/VCP-interacting motif (VIM) in ER-associated degradation

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Endoplasmic Reticulum (ER)-associated degradation (ERAD) plays a major role in protein quality control system, ensuring that misfolded proteins not to transit through the secretory pathway. ERAD requires misfolded protein ubiquitination and retrotranslocation to the cytosol for degradation by the proteasome. We have previously reported that direct interaction between gp78, an ER-resident ubiquitin ligase, and p97/VCP, an AAA ATPase, couples the ubiquitination with retrotranslocation. We found that gp78 interacts with and recruits p97/VCP to the ER membrane via a novel p97/VCP interacting motif (VIM). A highly conserved VIM is also found in the small p97/VCP interacting protein (SVIP). We hypothesized that SVIP is a regulator of gp78-mediated ERAD. Indeed, the VIM of gp78 is essential for degradation of ERAD substrates CD3 δ and the Z variant of α -1-antitrypsin (ATZ), whereas SVIP via its VIM inhibits the degradation of these proteins. We demonstrated that, by sharing the VIM, gp78 and SVIP compete to interact with p97/VCP and Derlin1. ER stress inversely regulates the abundances of SVIP and gp78 proteins. We further showed that SVIP serves as an endogenous inhibitor of ERAD through regulating the assembly of the gp78-p97/VCP-Derlin1 complex.