Bul1pis a ubiquitin-binding protein that is a nonessential component of the Rsp5p E3-ubiquitin ligase complex, and has been implicated in controlling aspects of post-Golgi endosomal-vacuolar protein sorting. BUL2 is a functional homolog of BUL1, and each Bul protein has a putative PY-motif that has been predicted to interact with one of three WW-domains of the Rsp5p ubiquitin ligase. Bul1p and Bul2p, together with Rsp5p, generate a polyubiquitin signal on Gap1p, the general amino acid permease, that specifies its intracellular targeting to the vacuole. In addition, Bul1p and Bul2p are required for GLN3 activation under poor nitrogen conditions, and antagonistically control GLN3-dependent transcription in concert with Npr1p, a protein kinase that controls post-Golgi sorting of amino acid permeases, suggesting a role for regulated ubiquitination in the control of nutrient-responsive transcription. Mutations in BUL1 render cells resistant to isoflurane and other volatile anesthetics, and disruption of BUL1 causes temperature-sensitive growth which can be partially suppressed by high dosage of ubiquitin-encoding UBI1. A bul1 bul2 double disruptant is sensitive to temperature, salt, and carbon stress, and the temperature sensitivity can be suppressed by multiple copies of kinase-encoding MCK1, and also by mutations in genes encoding the Rog1p lipase and Nat5p acetyltransferase. Overexpression of Bul1p or Bul2p causes Gap1p to be sorted to the vacuole, whereas the double mutant bul1 bul2 has the inverse phenotype, causing Gap1p to be delivered to the plasma membrane more efficiently than in wild-type cells. Further, bul1 bul2 can reverse the effect of mutations in the Lst4p protein transporter that normally prevent Gap1p from reaching the plasma membrane.