Yhc3p is a vacuolar protein required for the ATP-dependent transport of arginine into the yeast vacuole, a process that also requires a functional vacuolar H+-ATPasecomplex. Yhc3p is also involved in vacuolar pH maintenance as deletion strains display abnormally acidic vacuolar pH during the early phases of growth. As a result the activity of the V-ATPase is down-regulated in deletion strains to compensate for the vacuolar pH imbalance. The altered ability to maintain pH homeostasis in the deletion strain results in an elevated rate of medium acidification during early growth that correlates with increased plasma membrane H+-ATPase activity, encoded by the Pma1p and Pma2p isozymes. The elevated acidification results in increased resistance to D--threo-2-amino-1-[p-nitrophenyl]-1,3-propanediol, a product derived from chloramphenicol. Several phenotypes associated with deletion of YHC3 are altered by addition of chloroquine to the growth medium including elevation of vacuolar pH, reversal of ANP resistance, decreased acidification of the growth medium, and decreased activity of the plasma membrane H+-ATPase.Expression of HSP30 and BTN2 are specifically induced in the YHC3 deletion stain to compensate for the elevated vacuolar pH. Deletion of either HSP30 or BTN2 does not alter vacuolar pH, but does increase the activity of the V-ATPase in late growth phase. Hsp30p, a plasma membrane localized heat shock protein, may also act to down regulate the activity of the plasma membrane H+-ATPase. Btn2p is also known to be required for the correct localization of Rhb1p, a negative regulator of the Can1p plasma membrane arginine transporter, thereby modulating cellular arginine levels in the YHC3 deletion strain.YHC3 has a high degree of functional and sequence similarity with the human CLN3 gene, mutations in which cause the progressive neurodegenerative Batten disease, also known as juvenile neuronal ceroid-lipofuscinoses, characterized by a decline in mental abilities, loss of motor skills, blindness, epileptic seizures and premature death. Lysosomesisolated from cell lines established from individuals with Batten disease display defective arginine transport which can be reversed by expression of CLN3. In addition, cells derived from individuals with juvenile Batten disease are depleted for arginine and CLN3 antibodies block lysosomal arginine transport in normal lymphoblasts. Heterologous expression of human CLN3 in yeast complements the ANP resistance phenotype of YHC3 deletion strains, as well as the arginine transport defect further emphasizing the functional conservation associated with these orthologs.