Potential Helpful Sources

Summary info on MUP1:
https://www.yeastgenome.org/locus/S000003287

Menant A, Barbey R, Thomas D. Substrate-mediated remodeling of methionine transport by multiple ubiquitin-dependent mechanisms in yeast cells. EMBO J. 2006 Oct 4;25(19):4436-47. doi: 10.1038/sj.emboj.7601330. Epub 2006 Sep 14. PMID: 16977312; PMCID: PMC1589980.

https://pmc.ncbi.nlm.nih.gov/articles/PMC1589980/

"Therefore, high methionine exposure results into a rapid elimination of the high-affinity methionine permease Mup1 through two additive ubiquitin-based mechanisms: repression of transcription and protein destabilization."

Jaroslav Horák, The role of ubiquitin in down-regulation and intracellular sorting of membrane proteins: insights from yeast, Biochimica et Biophysica Acta (BBA) - Biomembranes, Volume 1614, Issue 2, 2003, Pages 139-155, ISSN 0005-2736, https://doi.org/10.1016/S0005-2736(03)00195-0. (https://www.sciencedirect.com/science/article/pii/S0005273603001950)

Abstract: Ubiquitination is a versatile tool used by all eukaryotic organisms for controlling the stability, function, and intracellular localization of a wide variety of proteins. Two of the best characterized functions of protein ubiquitination are to mark proteins for degradation by cytosolic proteasome and to promote the internalization of certain plasma membrane proteins via the endocytotic pathway, followed by their degradation in the vacuole. Recent studies of membrane proteins both in yeast and mammalian cells suggest that the role of ubiquitin may extend beyond its function as an internalization signal in that it also may be required for modification of some component(s) of the endocytotic machinery, and for cargo protein sorting at the late endosome and the Golgi apparatus level. In this review, I will attempt to bring together what is currently known about the role of ubiquitination in controlling protein trafficking between the yeast plasma membrane, the trans-Golgi network, and the vacuole/lysosome.

Keywords: Ubiquitin; Proteolysis; Vacuole; Membrane protein; Sorting; Yeast

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Lee S, Ho HC, Tumolo JM, Hsu PC, MacGurn JA. Methionine triggers Ppz-mediated dephosphorylation of Art1 to promote cargo-specific endocytosis. J Cell Biol. 2019 Mar 4;218(3):977-992. doi: 10.1083/jcb.201712144. Epub 2019 Jan 4. PMID: 30610170; PMCID: PMC6400557.

https://pmc.ncbi.nlm.nih.gov/articles/PMC6400557/

Abstract: Regulation of plasma membrane (PM) protein abundance by selective endocytosis is critical for cellular adaptation to stress or changing nutrient availability. One example involves rapid endocytic turnover of Mup1, a yeast methionine transporter, in response to increased methionine availability. Here, we report that methionine triggers rapid translocation of the ubiquitin ligase adaptor Art1 to the PM and dephosphorylation of Art1 at specific threonine residues. This methionine-induced dephosphorylation of Art1 is mediated by Ppz phosphatases, and analysis of phosphomimetic and phosphorylation-defective variants of Art1 indicates that these events toggle Art1 recognition of Mup1 at the PM. Importantly, we find that Ppz phosphatases are dispensable for Art1 PM translocation, but are required for Art1 interaction with Mup1. Based on our findings, we propose that methionine influx triggers Art1 translocation to the PM, followed by Ppz-mediated dephosphorylation which promotes cargo recognition at the PM.

Lin, C. H., MacGurn, J. A., Chu, T., Stefan, C. J., & Emr, S. D. (2008). Arrestin-related ubiquitin-ligase adaptors regulate endocytosis and protein turnover at the cell surface. *Journal of Cell Biology*, *135*(4), 714-725. https://doi.org/10.1083/jcb.200805151

https://www.cell.com/cell/fulltext/S0092-8674(08)01182-3?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867408011823%3Fshowall%3Dtrue

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Isnard AD, Thomas D, Surdin-Kerjan Y. The study of methionine uptake in Saccharomyces cerevisiae reveals a new family of amino acid permeases. J Mol Biol. 1996 Oct 4;262(4):473-84. doi: 10.1006/jmbi.1996.0529. PMID: 8893857.

https://pubmed.ncbi.nlm.nih.gov/8893857/

Abstract: The screening of mutants resistant to the oxidized analogues of methionine (methionine sulphoxide and ethionine sulphoxide) allowed the characterisation of a yeast mutant strain lacking the high affinity methionine permease and defining a new locus that was called MUP1. The study of MUP1 mutants showed that methionine is transported into yeast cells by three

different permeases, a high affinity and two low affinity permeases. The MUP1 gene was cloned and was shown to encode an integral membrane protein with 13 putative membrane-spanning regions. Database comparisons revealed that the yeast genome contains an ORF whose product is highly similar to the MUP1 protein. This protein is shown here to encode very low affinity methionine permease and the corresponding gene was thus called MUP3. It has previously been suggested that the amino acid permeases from yeast all belong to a single family of highly similar proteins. The two methionine permeases encoded by genes MUP1 and MUP3 are only distantly related to this family and thus define a new family of amino acid transporters.

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Kasey J. Day, Jason C. Casler, Benjamin S. Glick, Budding Yeast Has a Minimal Endomembrane System, Developmental Cell, Volume 44, Issue 1, 2018, Pages 56-72.e4, ISSN 1534-5807, https://doi.org/10.1016/j.devcel.2017.12.014.(https://www.sciencedirect.com/science/article/pii/S1534580717310304)

Abstract: Summary

The endomembrane system consists of the secretory and endocytic pathways, which communicate by transport to and from the trans-Golgi network (TGN). In mammalian cells, the endocytic pathway includes early, late, and recycling endosomes. In budding yeast, different types of endosomes have been described, but the organization of the endocytic pathway has remained unclear. We performed a spatial and temporal analysis of yeast endosomal markers and endocytic cargoes. Our results indicate that the yeast TGN also serves as an early and recycling endosome. In addition, as previously described, yeast contains a late or prevacuolar endosome (PVE). Endocytic cargoes localize to the TGN shortly after internalization, and manipulations that perturb export from the TGN can slow the passage of endocytic cargoes to the PVE. Yeast apparently lacks a distinct early endosome. Thus, yeast has a simple endocytic pathway that may reflect the ancestral organization of the endomembrane system.

Keywords: membrane traffic; endosomes; Golgi; trans-Golgi network; endocytic pathway; yeast

This paper shares that MUP1 is bidirectional.

Garneau MG, Lu MZ, Grant J, Tegeder M. Role of source-to-sink transport of methionine in establishing seed protein quantity and quality in legumes. Plant Physiol. 2021 Dec 4;187(4):2134-2155. doi: 10.1093/plphys/kiab238. PMID: 34618032; PMCID: PMC8644406.

Abstract: Grain legumes such as pea (*Pisum sativum* L.) are highly valued as a staple source of protein for human and animal nutrition. However, their seeds often contain limited amounts of high-quality, sulfur (S) rich proteins, caused by a shortage of the S-amino acids cysteine and methionine. It was hypothesized that legume seed quality is directly linked to the amount of organic S transported from leaves to seeds, and imported into the growing embryo. We expressed

a high-affinity yeast (*Saccharomyces cerevisiae*) methionine/cysteine transporter (*Methionine UPtake 1*) in both the pea leaf phloem and seed cotyledons and found source-to-sink transport of methionine but not cysteine increased. Changes in methionine phloem loading triggered improvements in S uptake and assimilation and long-distance transport of the S compounds, S-methylmethionine and glutathione. In addition, nitrogen and carbon assimilation and source-to-sink allocation were upregulated, together resulting in increased plant biomass and seed yield. Further, methionine and amino acid delivery to individual seeds and uptake by the cotyledons improved, leading to increased accumulation of storage proteins by up to 23%, due to both higher levels of S-poor and, most importantly, S-rich proteins. Sulfate delivery to the embryo and S assimilation in the cotyledons were also upregulated, further contributing to the improved S-rich storage protein pools and seed quality. Overall, this work demonstrates that methionine transporter function in source and sink tissues presents a bottleneck in S allocation to seeds and that its targeted manipulation is essential for overcoming limitations in the accumulation of high-quality seed storage proteins.