A Family of Basic Amino Acid Transporters of the Vacuolar Membrane from *Saccharomyces cerevisiae*  

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Among the members of the major facilitator superfamily of *Saccharomyces cerevisiae*, we identified genes involved in the transport into vacuoles of the basic amino acids histidine, lysine, and arginine. ATP-dependent uptake of histidine and lysine by isolated vacuolar membrane vesicles was impaired in YMR088c, a vacuolar basic amino acid transporter 1 (VBA1)-deleted strain, whereas uptake of tyrosine or calcium was little affected. This defect in histidine and lysine uptake was complemented fully by introducing the VBA1 gene and partially by a gene encoding VhAlp fused with green fluorescent protein, which was determined to localize exclusively to the vacuolar membrane. A defect in the uptake of histidine, lysine, or arginine was also observed in the vacuolar membrane vesicles of mutants YBR293c (VBA2) and YCL069c (VBA3). These three VBA genes are closely related phylogenetically and constitute a new family of basic amino acid transporters in the yeast vacuole.

Vacuoles are the largest organelles in the yeast *Saccharomyces cerevisiae*, occupying ~25% of the cell volume. Like lysosomes, vacuoles function as a digestive compartment but also serve as a storage compartment in which the bulk of basic amino acids is localized (1, 2). The concentration of arginine in the vacuoles of *S. cerevisiae* grown with arginine as the primary nitrogen source is about 20 times higher than in the cytoplasm (1, 2). In contrast, vacuoles contain little glutamic acid, which is the most abundant amino acid in yeast (2). Knowledge about vacuolar compartmentalization of amino acids is prerequisite to understanding the regulation of nitrogen metabolism. The vacuolar membrane catalyzes the active transport of a variety of amino acids (3, 4), a process that is driven by a proton electrochemical gradient generated via the action of the proton pumping vacuolar ATPase (5, 6) and is likely mediated by a proton/amino acid antiporter.

About two decades ago, kinetic experiments of amino acid uptake by vacuolar membrane vesicles suggested seven independent transport systems for amino acids in the *S. cerevisiae* vacuole: arginine, lysine-arginine, histidine, phenylalanine-tryptophan, tyrosine, asparagine-glutamine, and isoleucine-leucine (4). However, for many years the genes for the proteins involved in transport of these amino acids into vacuoles remained unknown. However, a recent report identified some of the genes involved in this process (7), namely AVT1 for the uptake of glutamine, isoleucine, and tyrosine and into vacuoles and both AVT3 and AVT4 for efflux of them. Moreover, AVT6 is likely responsible for aspartate and glutamate efflux from vacuoles (7).

Here, we have reported identification of genes encoding proteins involved in the uptake of basic amino acids into vacuoles. These genes constitute a new vacuolar transporter family in the major facilitator superfamily (MFS) of *S. cerevisiae*.

**Experimental Procedures**

*Strains, Media, and Gene Manipulation—* *S. cerevisiae* strains used in this study were YPH499 (MATa ura3-52 lys2-801 ade2-101 trpl-Δ53 his3-Δ200 leu2-1Δ), its VMA1-deleted mutant RH104 (Δvma1::TRP1) (8), ATCC 201388 (BY4741) (MATa his3Δ1 leu2Δ0 met15Δ0 ura3Δ0), and its major facilitator gene-deleted strains such as ATCC 4006223 (ymr088c::KanMX4), ATCC 4015741 (ybr293c::KanMX4), or ATCC 4003476 (yc069w::KanMX4), all purchased from the American Type Culture Collection (ATCC, Manassas, VA). To make double (Δymr088c::KanMX4) strains, media, and gene manipulations, a new vacuolar transporter family in the yeast vacuole.

1 The abbreviations used are: MFS, major facilitator superfamily; GFP, green fluorescent protein; VBA, vacuolar basic amino acid transporter; MES, 4-morpholineethanesulfonic acid.

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was conducted by using primers for $\Delta ymr088c::KanMX4$, a primer pair to clone the pVBA1 as described below, and for $\Delta ybr293::KanMX4$, a 5' primer, 5'-TTTGGTACGGAATAAGCAATTACACAG-3', and a 3' primer, 5'-CTGGCGAGCTAGATTCCC-3'. Cells were grown aerobically at 30 °C in YPD medium; if necessary, medium was supplemented with 200 μg/ml geneticin and 100 μg/ml neurosethin. Deletion of the corresponding gene was confirmed by chromosomal polymerase chain reaction (PCR). The gene YMR088c (VBA1) was amplified by PCR using a 5' primer with a KpnI site, TGGGGTACCACGAGGCTGGTCATGC, and a primer with a SacII site, ATTACCGCGGGGGAAAGCCCTTTG. After digestion with KpnI and SacII, the PCR product was inserted into the same restriction sites of plasmid pRS316 (10), yielding the recombinant plasmid pVBA1. For construction of the Vba1p-green fluorescent protein (GFP) fusion protein, an XbaI site, FM 4–64 (Molecular Probes) was added to growing cultures. The amino acid uptake reaction (performed at room temperature) was initiated by the addition of a specific amino acid (2 mM final concentration in the medium). At specific time intervals, 0.5-ml aliquots of cell suspension were withdrawn and layered on cellulose acetate membrane filters (0.45 μm; ADVANTEC, Japan) were used, and the radioactivity was measured using a liquid scintillation counter with xylene scintillator. All amino acid uptake by intact cells carrying putative multidrug permease mutants was performed as described previously (13). To stain vacuolar membranes, FM 4–64 (Molecular Probes) was added to growing cultures to a final concentration of 5 μM. The cells were further cultured for 20 min and harvested. After washing, the cells were resuspended in fresh YPD media for 30 min to allow the dye to stain the vacuole via endocytosis.

**RESULTS**

**Amino Acid Uptake by S. cerevisiae Mutants.—**Based on the complete genome sequence of *S. cerevisiae* (16, 17), a computer-aided analysis suggested the presence of the MFS comprising permeases that typically contain 12 transmembrane-spanning domains. This MFS is distributed in both prokaryotes and eukaryotes and includes uniporters, symporters, and antiporters. All MFS proteins can be further clustered into many permease families; the multidrug permease homologues, which confer multidrug resistance, constitute such a family (16, 17). It is now accepted that the multidrug permease family is further divided into two subfamilies (17). The multidrug permeases most likely are drug/proton antiporters and are therefore expected to be dependent on a proton electrochemical gradient across the membrane for activity. Because amino acid transport by yeast vacuoles is dependent on the proton electrochemical gradient across the vacuolar membrane (3, 4) and thus is likely mediated by an amino acid/proton antiporter, we expected yeast vacuolar amino acid transporters to be members of this multidrug permease family consisting of 28 proteins with 12 or more membrane-spanning regions (16). We purchased most of these deletion strains from ATCC and investigated their features.

Fig. 1 shows histidine uptake by intact *S. cerevisiae* cells. Histidine uptake was abrogated in mutant YPH499 cells lacking vacuolar H'-ATPase (Δvma1 RH104 cells; Fig. 1A). The vma1 mutation also impaired the uptake of other amino acids such as arginine, lysine, isoleucine, tyrosine, and phenylalanine (data not shown), each a substrate of vacuolar transport systems depending on the proton electrochemical gradient (3, 4). These results suggest that amino acid uptake by intact cells involves active transport into vacuoles. We therefore examined amino acid uptake by intact cells carrying putative multidrug permease mutants to identify a candidate gene involved in...
amino acid transport into vacuoles. Of the mutants tested, two (\(\Delta ymr088c\) or \(\Delta ybr293w\)) showed minimal histidine uptake compared with the parent BY4741 cells, and the \(\Delta ycl069w\) mutant showed transient uptake (Fig. 1B). The tyrosine and isoleucine uptake activities in these three mutants was equivalent to that in BY4741 (data not shown), excluding the possibly that these mutations promoted nonspecific defects in amino acid uptake. Thus, histidine uptake into vacuoles may be mediated by one or more of these genes.

**Uptake by Vacuolar Membrane Vesicles of Mutant VBA1 (\(\Delta ymr088c\))**—Fig. 2 shows amino acid and calcium uptake by vacuolar membrane vesicles of strains BY4741 (parent) and \(\Delta ymr088c\). Active transport of calcium by *S. cerevisiae* vacuoles is primarily mediated by a calcium/proton antiporter (18). ATP-dependent uptake of histidine, arginine, lysine, tyrosine, and \(^{45}\text{Ca}\) was clearly observed in BY4741 cells (Fig. 2, open circles). All these activities were completely inhibited by the protonophore carbonylcyanide \(m\)-chlorophenylhydrazone (data not shown). Consistent with the result for intact \(\Delta ymr088c\) mutant cells (Fig. 1B), ATP-dependent histidine uptake was nominal in vacuolar membrane vesicles (Fig. 2A, closed circles). The effect of this mutation on arginine uptake by vesicles was insignificant (Fig. 2B), but lysine uptake was severely impaired (Fig. 2C, closed circles). Tyrosine uptake (Fig. 2D), as described above for intact cells, was normal as was calcium uptake (Fig. 2E). Defects in both histidine and lysine uptake by the vesicles of the \(\Delta ymr088c\) mutant were clearly recovered by introducing the YMR088c gene on pRS316 (Fig. 2, A and C, open triangles), but not by the vector alone (open squares). These results suggest that the product of the YMR088c gene (VBA1, vacuolar basic amino acid transporter) is required for vacuolar uptake of at least histidine and lysine.

Fig. 2. ATP-dependent uptake of amino acids and calcium by vacuolar membrane vesicles of the VBA1 mutant. Yeast strains BY4741 (open circles) and \(\Delta yba1\) (\(\Delta ymr088c\)) (closed circles) and the transformants \(\Delta yba1\)/pVBA1 (open triangles), \(\Delta yba1\)/pVBA1GFP (closed triangles), and \(\Delta yba1\)/pRS316 (vector; open squares) were cultured inYPD medium and harvested at log phase. The preparation of the vacuolar membrane vesicles and the assay for the uptake of amino acids and calcium are described under “Experimental Procedures.” A, histidine; B, arginine; C, lysine; D, tyrosine; E, calcium (\(^{45}\text{Ca}\)).

Fig. 3. Fluorescence microscopy of the transformant \(\Delta yba1\)/pVBA1GFP. A, GFP fluorescence; B, FM 4–64 fluorescence; C, Nomarski; D, merged image.
Localization of Vba1p-GFP on the Vacuolar Membrane—

Complementation for a defect in histidine or lysine uptake by \(vba1\) mutant vesicles was also attempted with plasmid pVBA1GFP, encoding GFP fused to the carboxyl terminus of Vba1p (see “Experimental Procedures”). Expression of pVBA1GFP recovered the defect, albeit incompletely (Fig. 2, A and C, closed triangles). Thus, the Vba1p-GFP fusion protein functions as an amino acid transporter for the vacuole.

Vba1p-GFP localized exclusively to the vacuolar membrane in log-phase \(vba1\) mutant cells (Fig. 3), and GFP fluorescence coincided with that of FM 4–64, which selectively stains the vacuolar membrane (15, 19). These results indicate that Vba1p is a vacuolar membrane protein that, at a minimum, is involved in the transport of basic amino acids into \(S. cerevisiae\) vacuoles.

Uptake Activities of VBA2 (\(YBR293w\)) and VBA3 (\(YCL069w\)) Mutant Vacuolar Membrane Vesicles—VBA2 (\(YBR293w\)) and VBA3 (\(YCL069w\)) mutants (Fig. 4) express candidate genes for histidine transport into vacuoles (Fig. 1 B), so we measured uptake activities of vacuolar membrane vesicles from these cells. ATP-dependent uptake of histidine, arginine, and lysine were all severely impaired in \(\Delta vba2\) mutant vesicles (Fig. 4, A–C, closed circles). Tyrosine uptake also decreased, but to a lesser extent (Fig. 4D). In \(\Delta vba3\) mutant vesicles, uptake of histidine and lysine, but not arginine or tyrosine, was impaired (Fig. 4, A–C, closed triangles). Interestingly, a slight decrease in calcium uptake was observed in VBA3, rather than VBA2, mutant vesicles (Fig. 4E). We concluded that the three genes, VBA1, VBA2, and VBA3, chosen as the candidate transporters in experiments with intact cells are involved in vacuolar uptake of basic amino acids and that VBA1 and VBA3 mediate histidine and lysine uptake, whereas VBA2 mediates histidine, arginine, and lysine uptake.

To determine participation of these VBA genes in total uptake activities in vacuole, we further examined vesicular uptake of mutants deleted in pairs or all three VBA genes (Fig. 5). More or less 20% of the uptake activities of histidine, arginine, and lysine by the parent were all retained in the triple mutant \(\Delta vba1\Delta vba2\Delta vba3\) (\(\Delta ymr088c\::URA3MX4 \Delta ybr293w\::KanMX4 \Delta ycl069w\::NatMX4\)), suggesting the presence of the other system(s) for basic amino acids. Furthermore, tyrosine uptake largely decreased in deleted strains of the VBA1 and VBA2 genes (Fig. 5D). It is also noteworthy that the impairment in calcium transport of the \(\Delta vba3\) mutant was enhanced by combination with a deletion of the VBA1 gene (Fig. 5E).

Phylogenetic Relationship among Vba1p, Vba2p, Vba3p, and Related Open Reading Frames—Fig. 6A shows the alignment of amino acid sequences of Vba1p, Vba2p, and Vba3p. Also shown is the sequence of \(S. pombe\) fnx1, which is reportedly induced upon nitrogen starvation (20). Vba1p (562 residues), Vba2p (474 residues), and Vba3p (458 residues) are predicted to span the membrane 12, 12, and 11 times, respectively (\(S. cerevisiae\) genome database; www.yeastgenome.org/). The alignment revealed the following amino acid identities (and similarities) relative to Vba1p: Vba2p, 28% (48%), Vba3p, 23% (46%), and \(S. pombe\) fnx1, 27% (45%). There are many regions/residues that are highly conserved among these gene products (Fig. 6A, black-shaded).
multidrug permease family in *S. cerevisiae* (Fig. 6B) revealed four closely related gene products: YDR119w (*VBA4*) and YKR105c (*VBA5*), not characterized, and YGR224w (*AZR1*) and YPR198w (*SGE1*), reportedly involved in resistance to several drugs (21, 22).

In sum, our results defined a new VBA transporter family within the multidrug permease family of *S. cerevisiae*. These VBA transporters facilitate the uptake of basic amino acids by vacuoles.

**DISCUSSION**

Active transport systems for amino acids operate in yeast vacuoles. The multiplicity of such systems has been demonstrated by the kinetics of amino acid uptake by vacuolar membrane vesicles (4). Although the AVT genes involved in the transport of glutamine (asparagine), isoleucine (leucine), and tyrosine into vacuoles were recently reported (7), the genes for the transport of basic amino acids have not been determined. In the current study, we found three VBA genes encoding proteins primarily involved in transporting basic amino acids (histidine, lysine, and arginine) into *S. cerevisiae* vacuoles. These VBA transporters represent the main route for uptake of basic amino acids into vacuoles under standard culture conditions. Vba1p and Vba3p transport histidine and lysine, whereas Vba2p transports histidine, arginine, and lysine. Vba2p is also involved in tyrosine transport (Figs. 4D and 5D). Vba3p likely has broad substrate specificity not only for amino acids but also for calcium (Fig. 4E) and other cationic metabolites such as choline or polyamine (23). Another issue to be interpreted concerns why the impairment in calcium transport was enhanced by combination with the absence of Vba1p (Figs. 4E and 5E). Further investigation is required to understand the details of substrate specificity and the physiological roles of VBA transporters in the vacuolar compartment.

We initially examined amino acid uptake in intact vacuolar H^+^-ATPase mutant cells. The amino acid substrates chosen for this experiment (lysine, histidine, arginine, tyrosine, isoleucine, and phenylalanine) accumulate in vacuoles (4), whereas glutamate does not (2). The vacuolar H^+^-ATPase mutant...
VMA1 was defective for the uptake of lysine, arginine, histidine and tyrosine, but not glutamate, whose uptake was unaffected. Uptake of isoleucine and phenylalanine was 50% relative to the control parent strain (data not shown). Although the effect of the VMA1 mutation may not always result solely in the inability to generate the proton electrochemical gradient across the vacuolar membrane, these results suggested that amino acid uptake by intact cells primarily reflects transport into vacuoles. Candidate vacuolar amino acid transporter genes were selected based on this notion. The results obtained from intact cells were consistent with those for vacuolar vesicles. We observed a transient uptake of histidine by vba3 (ycl069w) and vba2 (ybr293w) cells (Fig. 1B), indicating efflux from cells of ninhydrin-reactive material—possibly histidine or another amino acid(s). It has been reported that spermidine is essential for key steps in cell metabolism such as translation initiation (24); when overaccumulated, spermidine is extruded from cells via Tpo1p on the plasma membrane (Tpo1 is a member of the major facilitator superfamily) (25). Therefore it is possible that a pathway involving extrusion of amino acids from the cytoplasm helps to balance the amino acid pool within cells. Although the details of the phenomenon shown in Fig. 1B are unclear, Vba3p and Vba2p, not likely Vba1p (Fig. 1B), may regulate in some fashion amino acid extrusion from cells.

Genes that are phylogenetically related to VBA genes are depicted in Fig. 6. S. pombe fnx1 (Fig. 6A), induced upon nitrogen starvation, is involved in resistance to 3-amino-1,2,4-triazole and 4-nitroquinoline N-oxide (20). The substrate specificity of drug resistance of fnx1 is similar to that of S. cerevisiae Atr1p (20). Although its subcellular localization in S. pombe has not been determined, fnx1 is assumed to function at the plasma membrane (20). Azr1p (encoded by YGR224w, 613 residues), with 13 putative transmembrane spans, reportedly is the plasma membrane protein involved in resistance to azoles such as ketoconazole and fluconazole and to acetic acid (21). Sge1p (encoded by YPR198w, 543 residues), with 14 putative transmembrane spans, is involved in resistance to crystal violet and 10-N-nonyl acridine orange and is purportedly an integral plasma membrane protein (22). Although Vba1p, Vba2p, and Vba3p transporters may function at the vacuolar membrane, we investigated their involvement in drug resistance in S. cerevisiae. However, Δvba1, Δvba2, Δvba3, and parent BY4741 cells showed no difference in sensitivity to the following drugs up to the maximum concentra-

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**Fig. 6.** Alignment and phylogenetic relationships among Vba1p, Vba2p, Vba3p, and related open reading frames. A, the deduced amino acid sequence of VBA1 was aligned with those of VBA2, VBA3, and S. pombe fnx1. Dashes denote gaps introduced to facilitate the alignment. Black boxes denote identical residues; gray boxes indicate chemically similar residues. B, phylogenetic tree for VBA proteins and related S. cerevisiae MFSs. The unweighted pair group method with an arithmetic mean tree was used for the polypeptides, using ClustalW software (www.ddbj.nig.ac.jp/E-mail/clustalw-j.html). The values near branches indicate the branch lengths (the number of amino acid substitutions/site).
tion that allowed cell growth: crystal violet (2 μg/ml), 3-amino-
1,2,4-triazole (100 μM), 4-nitroquinoline N-oxide (2 μM), and
ethidium bromide (10 mM) (data not shown). The functions of
Vba4p (encoded by YDR119w) and Vba5p (encoded by YKR105c)
have not been reported. The uptake of histidine, lysine, or argi-
nine in intact Δvba4 (Δydr119w) and Δvba5 (Δkr105c) mutant
cells was not remarkably different from that of the parent
BY4741. However, global analysis of GFP fusion protein localiza-
tion in S. cerevisiae (26) indicates that Vba4p (768 residues) with
14 putative transmembrane spans is localized to the vacuolar
membrane, likely being involved in the transport of basic amino
acids by vacuoles. Furthermore, whereas VBA1 gene expression
is induced upon nitrogen starvation, VBA4 gene expression is
repressed (Saccharomyces genome data base; www.yeastgenome.
org/). The function and subcellular localization of Vba5p (582
residues), with 14 putative transmembrane spans, is important in
relation to Vba3p, because most of their sequences are conserved
except for the amino-terminal part. It was recently reported that
Bnt1p, an ortholog of the human Batten disease gene CLN3, is
involved in the uptake of arginine into S. cerevisiae vacuoles (27).
The amounts of arginine and lysine in the vacuolar pool severely
decreased in the Δbnt1 mutant (27). Interestingly, Bnt1p is not a
member of the multidrug permease family. We now consider that
the basal uptake activities in vacuoles for basic amino acids
observed by the triple mutant (Fig. 5) arise from Bnt1p as well as
the VBA gene products Vba4p and Vba5p. We are currently
characterizing the vacuolar amino acid transporter at the molecu-
lar level with regard to its multiplicity and regulatory mecha-
nisms, with the goal of understanding how vacuoles contribute to
nitrogen metabolism.

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