Saccharomyces cerevisiae Is Capable of de Novo Pantothenic Acid Biosynthesis Involving a Novel Pathway of β-Alanine Production from Spermine*

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Pantothenic acid and β-alanine are metabolic intermediates in coenzyme A biosynthesis. Using a functional screen in the yeast Saccharomyces cerevisiae, a putative amine oxidase, encoded by FMS1, was found to be rate-limiting for β-alanine and pantothenic acid biosynthesis. Overexpression of FMS1 caused excess pantothenic acid to be excreted into the medium, whereas deletion mutants required β-alanine or pantothenic acid for growth. Furthermore, yeast genes ECM31 and YIL145c, which both have structural homology to genes of the bacterial pantothenic acid pathway, were also required for pantothenic acid biosynthesis. The homology of FMS1 to FAD-containing amine oxidases and its role in β-alanine biosynthesis suggested that its substrates are polyamines. Indeed, we found that all the enzymes of the polyamine pathway in yeast are necessary for β-alanine biosynthesis; spe1Δ, spe2Δ, spe3Δ, and spe4Δ are all β-alanine auxotrophs. Thus, contrary to previous reports, yeast is naturally capable of pantothenic acid biosynthesis, and the β-alanine is derived from methionine via a pathway involving spermine. These findings should facilitate the elucidation of other enzymes and metabolic intermediates involved in polyamine degradation and pantothenic acid biosynthesis in S. cerevisiae and raise questions about these pathways in other organisms.

Pantothenic acid (vitamin B₅) is a metabolic precursor to coenzyme A (CoA) and acyl carrier protein, which are cofactors required by a large number of metabolic enzymes. Biosynthesis of pantothenic acid occurs in microbes and plants only, whereas animals obtain it in their diet. In bacteria, it is synthesized by the condensation of pantoate, derived from 2-oxoisovalerate, an intermediate in valine biosynthesis, and β-alanine, produced by the decarboxylation of L-aspartate (1, 2). Consistent with this, a structural homolog of aspartate-1-decarboxylase is absent from the proteome of yeast (6), whereas structural homologs of all the other enzymes of the pantothenic acid pathway do exist in yeast. The gene ECM31, thought to be involved in cell wall maintenance (7), has homology to panB of Escherichia coli and Aspergillus nidulans (8). The gene YIL145c is a panC ortholog, encoding pantothenate synthase, and has been shown to be functional in E. coli (9). The putative YHR063c gene has structural homology to panE, as noted in the Yeast Proteome Data base (6). Thus, the specific absence of a gene for aspartate-1-decarboxylase may appear to be consistent with the observation, first reported almost 60 years ago, that yeast require exogenous pantothenic acid for growth (4).

Decarboxylation of aspartate is not the only pathway for β-alanine biosynthesis. In some E. coli mutants, the source of β-alanine for pantothenic acid biosynthesis involves reduction of uracil to dihydrouracil followed by hydrolysis first to β-ureidopropionate and second to CO₂, NH₃, and β-alanine (10). In addition, degradation of polyamines by amine oxidases can produce β-alanine (11, 12), effectively making β-alanine from methionine (13). However, polyamine metabolism has never been implicated previously in pantothenic acid biosynthesis. We were therefore interested in the putative amine oxidase encoded by the yeast gene FMS1, which was originally identified as a multicopy suppressor of fen2 pantothenic acid import mutants and encodes a protein of 508 amino acids with sequence homology to FAD-containing amine oxidases (14). Pantothenic acid uptake deficiency in fen2 mutants causes CoA limitation, which affects yeast growth primarily by limiting ergosterol biosynthesis, suggesting a related role for FMS1 (5, 14, 15).

In this report we show that S. cerevisiae can synthesize β-alanine and is therefore capable of de novo biosynthesis of pantothenic acid. Furthermore, the biochemical pathway of β-alanine synthesis differs from that found in bacteria. We have found that β-alanine is formed from spermine via the amine oxidase encoded by FMS1. Thus, the β-alanine moiety of pantothenic acid is derived from methionine via S-adenosylmethionine and the polyamine pathway. These findings should facilitate the elucidation of other enzymes and metabolic intermediates involved in polyamine degradation and pantothenic acid biosynthesis and raise questions about these metabolic pathways in other organisms.

EXPERIMENTAL PROCEDURES

Yeast Strains and Media—The parental yeast strains BY4741 and BY4742 and their gene deletion derivatives (16) from the Saccharomyces Deletion Project were obtained through Research Genetis (Huntsville, AL); these strains are as follows: BY4741 (MATa his3 leu2 met15 ura3); BY4742 (MATa his3 leu2 lys2 ura3); BY4741–0595 and BY4742–10595 (fms1Δ); BY4741–5757 and BY4742–15757 (fen2Δ); BY4741–
FIG. 1. The pantothenic acid pathway in E. coli. The diagram shows the relationship of the E. coli genes and the putative relationships of the yeast genes to the pantothenic acid pathway. ECM31 and panB encode ketopantoate hydroxymethyltransferase (EC 2.1.2.11), YHR063C and panE encode 2-dehydropantoate 2-reductase (EC 1.1.1.169), and YIL145c and panC encode pantoate-β-alanine ligase (EC 6.3.2.1). The yeast genome lacks a panD homolog encoding aspartate 1-decarboxylase (EC 4.1.1.11).IlvGCD, (EC 4.1.3.18, EC 1.1.1.86, EC 4.2.1.9).

3316 and BY4742–13316 (ecm31Δ), BY4741–2304 and BY4742–12304 (YIL145cΔ); BY4741–5034 and BY4742–15034 (spe3Δ), BY4741–1743 and BY4742–11743 (spe2Δ); BY4741–5488 and BY4742–15488 (speFΔ); BY4741–8945 and BY4742–18945 (speΔ). JHT14 (MATa abc1Δ: HIS3 his3 trp1 ura3) was made during this study. The abc1Δ:HIS3 allele was constructed by micro-homologous recombination (17) with a DNA construct made in a single step by the polymerase chain reaction, using oligonucleotide polymerase chain reaction primers (Sigma-Genosys, The Woodlands, Texas) designed as previously described for the trpΔ mutant (18). Growth and manipulation of yeast strains (19, 20) was on “YNB-P” medium, which was mixed from the individual chemicals. YNB-P had the same recipe as “ Yeast Nitrogen Base with ammonium sulfate” (Difco, Detroit, MI), except that pantothenic acid was omitted. Amino acid supplements (18) and 2% glucose were also present in YNB-P medium. Pantothenic acid and other supplements were added to YNB-P as indicated in “Results” and the figure legends.YPD medium was 2% glucose, 2% bactopeptone, and 1% yeast extract (Difco). Pantothenic acid, β-alanine, spermine, spermidine, and putrescine (Sigma) were prepared as stock solutions in water and used in media at the concentrations indicated in the figure legends.

Multicopy Suppressor Screen—Yeast strain JHT14 was transformed with a yeast high copy library (21) and ~5 × 10^9 Ura+ transformants were pooled, divided into aliquots, and stored in 25% glycerol at −70 °C. Transformants were then spread at a density of 10^5 Ura+ cells per 10-cm Petri dish on synthetic agar medium containing 2% glucose, but lacking uracil, adenine, histidine, methionine, and pantothenic acid. After incubation for 3 days at 30 °C, rapidly growing colonies occurred at a frequency of ~1.5 × 10^−4. The rapid growth phenotype of 37 of 55 colonies tested was found to be plasmid-dependent, based on the lack of growth on a selective medium containing 5-fluorouracil and uracil (22). Ten of these plasmids were recovered from yeast by transformation of E. coli and confirmed to confer the rapid growth phenotype on selective medium when reintroduced into yeast strain JHT14. Based on comparison with sequence data in the Saccharomyces Genome Database, six plasmids contained the ABZ1 locus, and four plasmids contained the FMS1 locus. The FMS1 plasmids enhanced growth only because of the low concentration of pantothenic acid used in the medium, and they were not studied further.

Plasmids and DNA Manipulations—E. coli strains DH5α and DH10B (Life Technologies, Inc.) were used for DNA manipulations by standard methods (23). Plasmids were introduced into yeast using lithium acetate isolate (24). Yeast DNA isolation and recovery of plasmids in E. coli was carried out using the Yeast Plasmid Isolation kit (Bio 101, Carlsbad, CA). The FMS1 coding sequence was amplified by polymerase chain reaction using oligonucleotide primers Fms1For-Xho (5′-ctctggatgaacctgcttcagc-3′) and Fms1Rev-Bam (5′-tgtgacctttcagtgaactg-3′) and ligated into the SacI and BamHI sites of YEplac195AC (25) to create the ADH1-FMS1 overexpression vector. The E39Q substitution was made using QuickChange (Stratagene, La Jolla, CA) and mutagenic primers FmsE39QUpper (5′-gtctgttgcgtagcaggctg-3′) and FmsE39QLower (5′-gatcctggctagcaacagac-3′). The DNA sequence of the entire mutant open reading frame was confirmed subsequently.

“Cross-feeding” Experiments—Log phase cultures of strain BY4742–10595 (fms1Δ) or strain BY4742–13316 (ecm31Δ) containing vector YEplac195AC were prepared in synthetic medium lacking uracil and washed by centrifugation in water, and ~10^8 cells were spread on 10-cm Petri dishes containing synthetic agar medium lacking uracil and pantothenic acid. Log phase cultures of strain BY4742 and fen2Δ, fms1Δ, and ecm31Δ deletion derivatives harboring either YEplac195AC or the ADH1-FMS1 overexpression plasmid were prepared in synthetic medium lacking uracil, washed by centrifugation in water, and spotted onto the ecm31Δ and fms1Δ “lawns” at a density of ~10^5 cells per 5 μl. Plates were incubated at 30 °C for 2 days, after which time “halos” of growing lawn cells formed around spots of cells that excreted pantothenic acid or downstream metabolites into the medium.

RESULTS

FMS1 Overexpression Enhances Growth in the Absence of Pantothenic Acid—A high copy yeast genomic DNA library was screened for genes that enhanced growth in the absence of pantothenic acid, and plasmids containing genomic DNA in the region of the FMS1 locus were found. To determine whether FMS1, rather than other DNA sequences in these plasmids, was responsible for the enhanced growth, the FMS1 open reading frame was subcloned into an expression vector under the control of the ADH1 promoter and confirmed to have a DNA sequence identical to the published sequence (Ref. 14, GenBank™ accession number X81848). This plasmid was introduced into yeast, and it was found that ADH1-FMS1, but not the empty vector, could enhance the growth of yeast on medium lacking pantothenic acid (Fig. 2).

FMS1, ECM31, and YIL145c Are Required for Pantothenic Acid Production in Yeast—As shown above, yeast grew well in the absence of yeast when FMS1 was overexpressed. This finding prompted us to test the currently available deletion strains, fms1Δ, ecm31Δ, YIL145cΔ, and fen2Δ for pantothenic acid and β-alanine auxotrophy (see Fig. 1). The deletion strains and parental strain BY4742 were plated on medium lacking pantothenic acid and β-alanine or on medium supplemented with these compounds (Fig. 3A). The fms1Δ strain required either pantothenic acid or β-alanine for growth. This is consistent with the results for overexpression of FMS1; overexpression of FMS1 enhanced growth in the absence of pantothenic acid/β-alanine, whereas the fms1Δ deletion totally abolished growth in the absence of pantothenic acid/β-alanine.

In the same experiment, the ecm31Δ and YIL145cΔ strains could utilize pantothenic acid but differed from the fms1Δ strain because they could not grow on β-alanine. Neither the fen2Δ nor the parental strain required these supplements. Other potential metabolites, including β-ureidopropionate, 5,6-dihydrouracil, 1-aspartic acid, and 1,3-diaminopropane (100)}
mM) did not support growth of the deletion strains (data not shown). The same results were also obtained using a different parental strain, BY4741, and its deletion derivatives (data not shown). Thus, based on the auxotrophic phenotypes, \( \text{FMS1} \) is required for \( \beta \)-alanine production, whereas \( \text{ECM31} \) and \( \text{YIL145c} \) are required downstream in the pantothenic acid pathway (Fig. 1).

Further evidence that \( \text{FMS1} \) functions in the same pathway as \( \text{ECM31} \) was obtained from a complementation analysis using the \( \text{ADH1-FMS1} \) overexpression plasmid. This plasmid was introduced into \( \text{fms1}^{-} \), \( \text{ecm31}^{-} \), and \( \text{fen2}^{-} \) strains, which were then tested for growth in the absence of \( \beta \)-alanine (Fig. 3B). Growth occurred in the \( \text{fms1}^{-} \) and \( \text{fen2}^{-} \) strains, but not the \( \text{ecm31}^{-} \) strain, indicating that \( \text{FMS1} \) is dependent on \( \text{ECM31} \) for pantothenic acid biosynthesis. Thus, \( \text{S. cerevisiae} \) does not require exogenous pantothenic acid or \( \beta \)-alanine in the medium for growth, and \( \text{FMS1} \) activity is rate-limiting for \( \beta \)-alanine biosynthesis under the conditions used.

Overexpression of \( \text{FMS1} \) Results in Excretion of Excess Metabolites—Dramatically increased metabolic activity in the pantothenic acid pathway caused by \( \text{FMS1} \) overexpression can be detected in cross-feeding experiments, in which cells excret-
of either ecm31Δ or fms1Δ cells on medium lacking pantothenic acid (Fig. 4). After incubation, halos formed around each of the FMS1-overexpressing strains, with the exception of the ecm31Δ strain, on both lawns. No halos formed around strains harboring empty vector. The simplest explanation for the halos is that FMS1 overexpression results in excretion of excess pantothenic acid, which is then taken up by the lawn cells, allowing them to grow. Overexpression of FMS1 in the ecm31Δ strain did not result in a halo, further confirming that FMS1 and ECM31 function in the same pathway.

The FAD-binding Domain of Fms1p Is Necessary for β-Alanine Production—Although it is required for β-alanine production, FMS1 encodes a protein that has no structural homology to bacterial aspartate-1-decarboxylases. Instead, Fms1p has homology to FAD-containing amine oxidases (14) and likewise contains a GXGXXG dinucleotide-binding motif similar, for example, to Candida albicans Cbp1p, human monoamine oxidases A and B (human), and acetylspermidine oxidase Aso1p of Candida boidinii (Fig. 5A). To assess the role of FAD in β-alanine production, we made the E39Q substitution mutant, equivalent to the substitution that was shown to abolish FAD binding and catalytic activity of monoamine oxidase B (26–28). The resulting ADH1-fms1Δ(E39Q) expression plasmid was introduced into the fms1Δ strain, and transformants were tested for growth in the absence of β-alanine and pantothenic acid (Fig. 5B). The E39Q mutant did not complement the β-alanine and pantothenic acid auxotrophy of the fms1Δ strain, consistent with a role for FAD in the mechanism of β-alanine production.

FMS1 Links Polyamine Biosynthesis with Pantothenic Acid Production in Yeast—The sequence homology of Fms1p to amine oxidases and the apparent role of FAD in β-alanine production by Fms1p suggested that polyamines could provide the substrates for Fms1p. We therefore tested deletion mutants of the polyamine pathway (29, 30) for β-alanine auxotrophy. Parental, spe1Δ, spe2Δ, spe3Δ, spe4Δ, fms1Δ, and ecm31Δ strains were plated on medium lacking pantothenic acid, β-alanine, and polyamines or on medium supplemented with pantothenic acid and β-alanine or onto the same medium supplemented with pantothenic acid or β-alanine (0.1 mM), as indicated. Incubation was for 3 days at 30 °C.
one of the compounds spermine, β-alanine, or pantothenic acid was added to the medium. In addition, spe1Δ and spe3Δ could also grow on spermidine, and spe1Δ could grow on putrescine. As expected, the fms1Δ and ecm31Δ strains could grow on pantothenic acid but could not utilize any of the polyamine compounds. Thus, biosynthesis of β-alanine and pantothenic acid is dependent on the polyamine biosynthetic pathway, consistent with production of β-alanine via polyamine degradation (11–13). The source of the carbon atoms in β-alanine would therefore be from methionine via spermine. Based on these results, the relationship of the polyamine pathway to pantothenic acid biosynthesis and the key genes involved are illustrated in Fig. 7.

DISCUSSION

*S. cerevisiae Can Synthesize β-Alanine and Pantothenic Acid*—Yeast have been reported to require a supplement of either pantothenic acid or β-alanine, from which it has been inferred that they cannot synthesize pantothenic acid de novo (4, 5). Contrary to this, we found that overexpression of the yeast gene FMS1, encoding a putative amine oxidase, allowed strong growth on medium lacking pantothenic acid. Furthermore, when FMS1 was overexpressed under the control of the ADH1 promoter, excess pantothenic acid was excreted from the cells. Thus, yeast clearly have the capacity to synthesize pantothenic acid de novo when FMS1 is overexpressed. To eliminate the possibility that the pantothenic acid biosynthesis was a metabolic abnormality caused by FMS1 overexpression, we analyzed gene deletion mutants. The fms1Δ strains were auxotrophic for β-alanine and could grow when supplemented with either β-alanine or pantothenic acid. Deletions in genes that have structural homology to the bacterial genes of the pantothenic acid pathway, ECM31 and YIL145c (see Fig. 1), caused pantothenic acid auxotrophy, but these strains did not grow on a β-alanine supplement, indicating that these genes are downstream in the pathway (see Fig. 1). These auxotrophic phenotypes indicate that FMS1, ECM31, and YIL145c are normally involved in pantothenic acid biosynthesis. Direct evidence that FMS1 and ECM31 are in the same pathway came from the finding that FMS1 requires ECM31 activity to make pantothenic acid; the ecm31Δ deletion eliminated both the ability of FMS1 to enhance growth in the absence of pantothenic acid and also eliminated its ability to cause pantothenic acid excre-
tion. Thus, pantothenic acid biosynthesis is a natural part of metabolism in *S. cerevisiae*, and production of the β-alanine required involves a putative amine oxidase, encoded by *FMS1*.

**Spermine Is Required for β-Alanine Biosynthesis in Yeast—**

Three different enzymatic pathways have been shown to produce β-alanine: decarboxylation of aspartate (1, 2), degradation of pyrimidines (10), and degradation of polyanines (13). The polyanine pathway has not been implicated previously in pantothenic acid biosynthesis, and spermine, in particular, has no previously identified physiological function in yeast (31). The involvement of the polyanine pathway is suggested by the Fms1p amino acid sequence, which has structural homology to FAD-containing amine oxidases (14), some of which are involved in the oxidative degradation of polyanines (4). In addition, we showed that a FAD binding site mutant of *FMS1*, E39Q, did not complement the *fms1Δ* mutant, consistent with a role for oxidation by the Fms1p protein. We therefore investigated deletion mutants of the polyanine pathway to see whether this pathway is required for β-alanine synthesis. Indeed, *spe1Δ*, *spe2Δ*, *spe3Δ*, and *spe4Δ* mutants were all auxotrophic for β-alanine on a medium that lacked polyanines. This showed that synthesis of spermine is required for β-alanine biosynthesis in yeast. A more detailed analysis of which polyanine pathway intermediates could support growth of the *speΔ* and *fms1Δ* mutants confirmed this conclusion (Fig. 6). Thus, in yeast, β-alanine is derived from methionine via spermine, making polyanine degradation part of pantothenic acid biosynthesis (Fig. 7).

We found that the auxotrophic phenotypes of the *speΔ* mutants for polyanines were readily observable on minimal synthetic medium in the absence of β-alanine or pantothenic acid (Fig. 6). This contrasts with previous reports, in which special precautions in medium preparation were required, such as HCl washing of glassware and avoidance of autoclave use, to eliminate contaminating amines, and in which many cell divisions were required to deplete intracellular pools of polyanines (32). The difference is simply in the presence or absence of β-alanine or pantothenic acid; in their absence, a relatively high level of polyanine metabolism is required to meet β-alanine requirements, such that contaminated glassware and intracellular pools do not make a significant contribution. In the presence of β-alanine or pantothenic acid, as customary in yeast media, low levels of contaminating polyanines are sufficient for essential processes, such as hypusine synthesis (33), which are unrelated to the polyanine pathway.

**The Pathway from Spermine to β-Alanine—**

Amide oxidases have been shown to catalyze a number of different degradation reactions for polyanines, producing various aldehydes and amines, such as 3-aminopropanal and 1,3-diaminopropane, respectively (13). Thus, the simplest hypothesis is that the Fms1p enzyme converts spermine to 3-aminopropanal and spermidine and that aldehyde dehydrogenases, for which there are seven genes in yeast (34), would be required to convert the 3-aminopropanal to β-alanine. A less direct route between spermine and β-alanine could, in principle, involve the intermediate 1,3-diaminopropane (13). However, this compound was not able to support growth of the *speΔ* mutants in the absence of β-alanine and therefore appears not to be on the pathway in yeast. The simple phenotype of β-alanine auxotrophy in yeast will help identify the metabolic intermediates and additional enzymes involved.

**Regulation of FMS1 Activity—**

It may seem unexpected that yeast would have the capacity to make pantothenic acid and yet require a supplement for efficient growth on customary yeast media. In fact, on medium containing glycerol or acetate as the sole carbon source, we found that pantothenic acid and β-alanine were not rate-limiting for growth (data not shown). Thus, *FMS1* activity is growth-limiting only on glucose medium. This simple observation may explain the carbon source-dependent phenotype (catabolite repression) reported for the *fen2* pantothenate transporter mutant (15). In the light of the finding that pantothenic acid biosynthesis is a natural part of yeast metabolism, we propose that growth of the *fen2* mutant, which cannot absorb pantothenic acid from the medium, depends on pantothenic acid synthesis inside the yeast cells. The *fen2* mutant would therefore be growth-limited on glucose because of insufficient *FMS1* expression caused by the presence of glucose. Likewise, wild-type strains would depend on internal synthesis when pantothenic acid was absent from the medium and would be growth-limited by insufficient *FMS1* expression on glucose medium. These observations suggest that *FMS1* activity is regulated and raise questions concerning the mechanism of regulation of the pantothenic acid pathway in yeast.

**β-Alanine Biosynthesis in Other Organisms—**

The finding that β-alanine biosynthesis is different between yeast and bacteria raises questions as to how other organisms, such as fungi and plants, make β-alanine. At the present time in the public sequence data bases there are over a dozen identifiable aspartate-1-decarboxylase genes from different prokaryotic species, whereas this enzyme does not appear to be present in eukaryotic species. In contrast, proteins of significant sequence homology to Fms1p can be found in eukaryotes, in particular in plants, but not in prokaryotes. The closest sequence similarity to Fms1p is in Cbp1p from the yeast *C. albicans*, a protein with steroid binding activity (14, 35). This suggests that plants and lower eukaryotes generally produce β-alanine and hence CoA by a polyanine degradation pathway, as described here for yeast.

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