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Vitamin requirements and biosynthesis in *Saccharomyces cerevisiae*

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Abstract

Chemically defined media for yeast cultivation (CDMY) were developed to support fast growth, experimental reproducibility, and quantitative analysis of growth rates and biomass yields. In addition to mineral salts and a carbon substrate, popular CDMYs contain seven to nine B-group vitamins, which are either enzyme cofactors or precursors for their synthesis. Despite the widespread use of CDMY in fundamental and applied yeast research, the relation of their design and composition to the actual vitamin requirements of yeasts has not been subjected to critical review since their first development in the 1940s. Vitamins are formally defined as essential organic molecules that cannot be synthesized by an organism. In yeast physiology, use of the term "vitamin" is primarily based on essentiality for humans, but the genome of the *Saccharomyces cerevisiae* reference strain S288C harbours most of the structural genes required for synthesis of the vitamins included in popular CDMY. Here, we review the biochemistry and genetics of the biosynthesis of these compounds by *S. cerevisiae* and, based on a comparative genomics analysis, assess the diversity within the *Saccharomyces* genus with respect to vitamin prototrophy.

KEYWORDS

fermentation, growth requirements, *Saccharomyces cerevisiae*, synthetic media, vitamin biosynthesis

1 | INTRODUCTION

"No animal can live on only pure protein, fat, and carbohydrates, but other dietary factors are required for life" (Gowland Hopkins, 1906). This observation eventually led to the vitamine (later changed to vitamin) theory established by Casimir Funk (Funk, 1922). An organic compound is defined as a vitamin if it is essential, cannot be synthesized by the organism itself, and therefore needs to be taken up from the environment (Combs, 2008). Whether a compound is a vitamin therefore depends on the organism studied and, potentially, on growth conditions.

Chemically defined media for cultivation of yeasts (CDMY) are essential for fundamental as well as applied research. In contrast to complex media, which contain nondefined components such as yeast extract and/or peptone, defined media enable the generation of highly reproducible data, independent variation of the concentrations of individual nutrients, and, in applied settings, design of balanced media

Thomas Perli and Anna K. Wronska contributed equally to this publication and should be considered co-first authors.

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for high-biomass-density cultivation and application of defined nutrient limitation regimes. The use of CDMY prevents thus unwanted variations. Lot to lot variation of the complex raw materials as yeast extract may lead to up to 50% difference in growth rate and biomass levels (Potvin, Fonchy, Conway, & Champagne, 1997; Zhang, Reddy, Buckland, & Greasham, 2003). The control of process variability is not only crucial to be in line with FDA regulations but also for maintining high productivity and maximize process economics (Dahod, Greasham, & Kennedy, 2010). The CDMY that are now used in yeast research laboratories around the world are based on an early investigation of the requirements for riboflavin (B_2), biotin (B_7), thiamine (B_1), pyridoxine (B_6), inositol (B_8), nicotinic acid (B_3), and pantothenate (B_5) of over a hundred yeast species (Burkholder, McVeigh, & Moyer, 1944). With the exception of riboflavin, which could be universally omitted, yeast species exhibited diverse auxotrophy patterns for the remaining six compounds, which were therefore included in the first CDMY. *para*-Aminobenzoic acid (*p*ABA, formerly referred to as vitamin B_{10}) was later added as it was found to stimulate growth of brewing yeasts (Cutts & Rainbow, 1950). These seven compounds with riboflavin (vitamin B_2) and folate (vitamin B_9) are still included in the widely used CDMY known as Yeast Nitrogen Base (YNB; Table 1; Sherman, Fink, & Hicks, 1987; Wickerham, 1951). The concentration of the vitamins contained in YNB has been empirically defined but without quantitative assessment of the exact yeast requirement (Wickerham, 1946). In another popular CDMY, often referred to as Verduyn medium (Table 1), concentrations of media components were adjusted to support yeast biomass concentrations up to 10 g L^{-1} in aerobic, glucose-limited cultures that exhibit a fully respiratory metabolism (Bruinenberg, van Dijken, & Scheffers, 1983; Verduyn et al., 1992).

Although meant to suit all *Saccharomyces cerevisiae* strains, it may happen that in specific growth conditions or for specific strains, these recipes have to be adjusted. Strains of the popular *S. cerevisiae* BY lineage (Brachmann et al., 1998) require additional inositol to support fast growth until glucose exhaustion in YNB medium (Hanscho et al., 2012). Inositol concentration represents one of main difference between the YNB and the Verduyn medium, the latest containing an inositol (B_8) concentration 12.5-fold higher to prevent occurrence of

TABLE 1 Composition of Yeast Nitrogen Base (Wickerham, 1946; Guthrie & Fink, 1991) and synthetic medium (Verduyn, Postma, Scheffers, & Van Dijken, 1992) for aerobic growth. Values are for 1 L of media

Composition		Yeast Nitrogen Base w/out amino acids	Verduyn Synthetic Media
Nitrogen source	Ammonium sulphate ($(NH_4)_2SO_4$)	5 g	5 g
Salts	Potassium phosphate monobasic (KH_2PO_4)	850 mg	3 g
	Potassium phosphate dibasic (K_2HPO_4)	150 mg	
	Sodium chloride (NaCl)	100 mg	
	Calcium chloride ($CaCl_2$)	100 mg	3.39 mg
	Boric acid (H_3BO_3)	0.5 mg	1 mg
	Copper sulphate ($CuSO_4$)	0.04 mg	0.19 mg
	Cobalt chloride ($CoCl_2$)		0.16 mg
	Potassium iodide (KI)	0.1 mg	0.1 mg
	Ferric chloride ($FeCl_3$)	0.2 mg	
	Iron sulphate heptahydrate ($FeSO_4 \cdot 7\ H_2O$)		3 mg
	Magnesium sulphate ($MgSO_4$)	0.5 g	0.244 g
	Manganese chloride ($MnCl_2$)		0.64 mg
	Manganese sulphate ($MnSO_4$)	0.4 mg	
	Sodium molybdate (Na_2MoO_4)	0.2 mg	0.34 mg
	Zinc sulphate ($ZnSO_4$)	0.4 mg	2.53 mg
	EDTA		15 mg
Growth factors	Biotin	0.002 mg	0.05 mg
	Calcium pantothenate	0.4 mg	1 mg
	Folic acid	0.002 mg	
	Inositol	2 mg	25 mg
	Nicotinic acid	0.4 mg	1 mg
	para-Aminobenzoic acid	0.2 mg	0.2 mg
	Pyridoxine	0.4 mg	0.82 mg
	Riboflavin	0.2 mg	
	Thiamine	0.32 mg	0.79 mg

undesired growth limitation. (Table 1). Information of yeast biomass vitamin content (per $gram_{DW}$) would allow to prepare tailor-made media based on exact nutritional requirements. However, data of intracellular vitamin concentrations remain scarce and difficult to compare. As an example, the range of measured intracellular biotin concentration in *S. cerevisiae* varies by order of magnitude likely influenced by the used detection method that oscilates between bioassay based on growth of an auxotroph organism (1.4–1.5 μg/g; Emery, McLeod, & Robinson, 1946), imunodetection (0.053–0.004 ng/g; Pirner & Stolz, 2006), or liquid chromatography. It is obvious that more complete and accurate quantitative information regarding intracellular vitamin concentration is needed. This knowledge will be the key to further understand the physiological role of class B vitamin in yeast metabolism.

Based on their essentiality in the human diet, the molecules precedently mentioned belong to the class B vitamins, which are water-soluble compounds involved in cell metabolism. However, as will be discussed below, they have widely different chemical structures and roles in cellular metabolism (Combs, 2008). Early studies already demonstrated that growth of some yeasts, including *Saccharomyces* species, was not strictly dependent on addition of all of these compounds, although omission of individual compounds might result in suboptimal growth (Burkholder, 1943; de Kock, du Preez, & Kilian, 2000; Rogosa, 1944). These observations suggested that these yeast strains could *de novo* synthesize some of these compounds, in which cases they should formally not be referred to as vitamins but, if their addition leads to improved growth, as growth factors.

It is well established that vitamin and/or growth factor requirements of yeasts are not only species dependent but can also strongly vary with growth conditions. In particular, ergosterol and unsaturated fatty acids, whose synthesis by *S. cerevisiae* requires molecular oxygen, are routinely included in CDMY for anaerobic yeast cultivation (Andreasen & Stier, 1953; Andreasen & Stier, 1954). These anaerobic nutritional requirements of yeasts are addressed in several dedicated reviews (Rosenfeld & Beauvoit, 2003; Snoek & Steensma, 2006) and will not be discussed here. For information on the applications and physiological impacts of artificially introduced auxotrophic requirements in *S. cerevisiae*, readers are referred to a previous published minireview (Pronk, 2002).

The present paper aims to review current knowledge on the capability of *S. cerevisiae* for *de novo* synthesis of the seven "vitamins" that are commonly added to CDMY and on the pathways and genes involved in their biosynthesis. Riboflavin (B_2) and folic acid (B_9) that are only present in YNB will not be discussed further. *S. cerevisiae* and more generally Saccharomycotina yeasts are B_2 prototroph under both aerobic and anaerobic conditions (Burkholder et al., 1944). Folic acid (B_9) synthesis depends on *p*ABA as a rate limiting precursor, whose *de novo* synthesis and metabolic implication are reviewed below. In addition, based on the existing knowledge on *S. cerevisiae* and a comparative analysis of the genomes of *Saccharomyces* species, we present a brief assessment of the distribution of these metabolic pathways across *Saccharomyces* species.

2 | VITAMINS THAT ACT AS ENZYME COFACTORS

2.1 | Pyridoxine (B6)

Pyridoxine (PN), pyridoxal (PL), pyridoxamine (PM), and their phosphorylated derivatives pyridoxine 5'-phosphate (PNP) and pyridoxamine 5'-phosphate (PMP) can be interconverted intracellularly and together form the B_6 vitamers. A vitamer is defined as a molecule having a similar structure and the same nutritional impact as the biologically active form of the vitamin. Pyridoxine was isolated and synthesized after its identification as a substance preventing dermatitis in rats (Harris & Folkers, 1939; Keresztesy & Stevens, 1938; Lepkovsky, 1938). Its chemical structure is characterized by a tetrasubstituted pyrimidine ring with one methyl, one hydroxyl, and two methyl–hydroxyl groups (Figure 1). Pyridoxine was first reported to stimulate yeast growth in 1939 (Schultz, Atkin, & Frey, 1939). Although mainly supplied to CDMY as the vitamer pyridoxine, pyridoxal 5'-phosphate (PLP) is the active form. PLP serves as coenzyme and/or substrate for at least 50 *S. cerevisiae* enzymes involved in amino-acid, glucose, and lipid metabolism, as well as in thiamine biosynthesis and regulation (Table 2).

PLP formation from PM, PN, or PL involves a salvage pathway that is widespread in nature (di Salvo, Contestabile, & Safo, 2011). These three vitamers can be imported in *S. cerevisiae* by the high-affinity proton symporter Tpn1 (Stolz & Vielreicher, 2003). In the yeast cytosol, PN, PM, and PL are phosphorylated to form PNP, PMP, and PLP, respectively, most probably by the putative pyridoxine kinase Bud16. PNP and PMP are subsequently oxidized to PLP by the pyridoxine oxidase Pdx3 (Loubbardi, Marcireau, Karst, & Guilloton, 1995).

De novo synthesis of PLP by *S. cerevisiae* (Dong, Sueda, Nikawa, & Kondo, 2004) involves a single reaction catalyzed by PLP synthase, which is a heterodimeric enzyme (Raschle, Amrhein, & Fitzpatrick, 2005; Figure 1). Its glutamine–hydrolase subunit (Sno) catalyzes the hydrolysis of L-glutamine, producing L-glutamate and ammonia (Bauer, Bennett, Begley, & Ealick, 2004). Ammonia generated in this reaction is not released from the enzyme but channelled to the active site of the synthase subunit (Snz), which condenses it with D-ribulose 5-phosphate and D-glyceraldehyde 3-phosphate to yield PLP (Hanes et al., 2008). The Snz protein not only catalyzes PLP formation but also isomerizes dihydroxyacetone-phosphate and ribose-5-phosphate to glyceraldehyde-phosphate and ribulose-5-phosphate, respectively, with the latter being the favoured substrate for PLP formation (Zhang et al., 2010).

The *S. cerevisiae* genome carries three members of the *SNO* and *SNZ* genes familes (*SNO1,2, and 3*, *SNZ1,2, and 3*). These *SNO* and *SNZ* genes form colocalized gene pairs, each expressed from a single bidirectional promoter. The *SNZ1/SNO1* pair has been shown to be involved in *de novo* PLP biosynthesis, and its transcription is activated in late stationary phase (Padilla, Fuge, Crawford, Errett, & Werner-Washburne, 1998). Transcriptional activation of *SNZ1/SNO1* under amino acid starvation, mediated by the Gcn4 master regulator, is

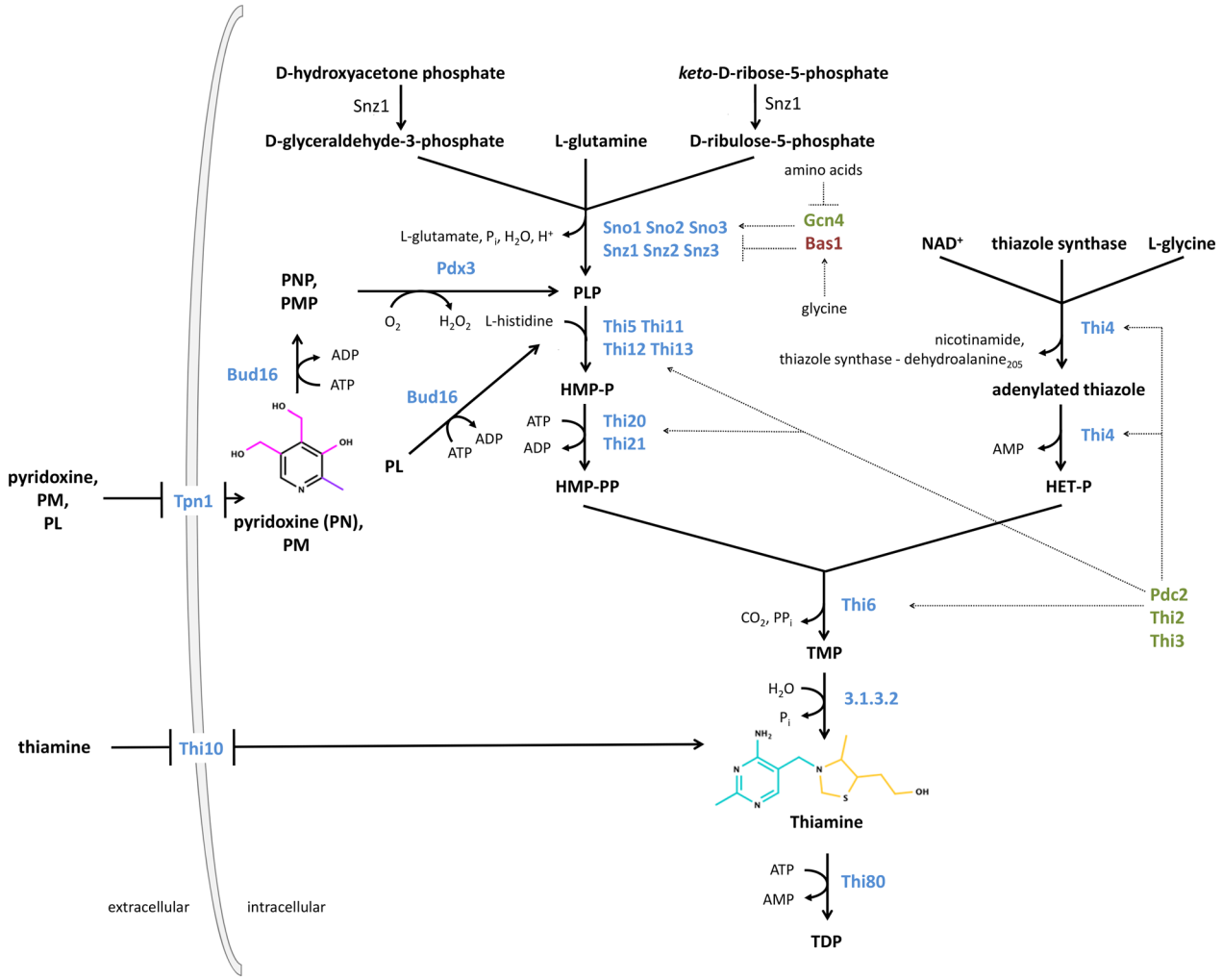

FIGURE 1 PLP and TDP *de novo* synthesis pathway in *Saccharomyces cerevisiae*. D-glyceraldehyde 3-phosphate, L-glutamine, and keto-D-ribose 5-phosphate are converted to PLP by the catalytic activity of the *SNO1,2,3* and *SNZ1,2,3* gene products . Gcn4 acts as positive regulator of *de novo* PLP biosynthesis, whereas Bas1 acts as an inhibitor. Gcn4 is inhibited by amino acids and activated under amino-acid starvation. Bas1 instead is upregulated in the presence of glycine. PN, PM, and PL are imported by Tpn1. PN is converted at the expense of ATP to PNP by Bud16 whereupon Pdx3, produces PLP and hydrogen peroxide in an oxygen-dependent reaction. Similarly, PLP can be formed starting from PM in two steps by action of Bud16 and Pdx3, with PMP as intermediate. Moreover, PL can also be converted to PLP by action of Bud16. PLP is used as cofactor or converted to HMP-P by one of the four homologous enzymes Thi5, Thi11, Thi12, and Thi13, under consumption of L-histidine. HMP-P is the intermediate for the formation of the pyrimidyl moiety of thiamine (shown in cyan). Thi20 and Thi21 further phosphorylate HMP-P to HMP-PP. The thiazole moiety (shown in yellow) is synthesized by activity of Thi4 in a suicide mechanism, leading to HET-P. HMP-PP and HET-P are merged by the gene product of *THI6* to TMP. The following reaction catalyzed by an acid phosphatase (EC number 3.1.3.2) yields thiamine. Thiamine can be taken up with the aid of the transporter Thi10. Finally, thiamine is converted to its biologically active form TDP under consumption of ATP by Thi80. Pdc2, Thi2, and Thi3 are responsible for the upregulation of transcription of *THI5/11/12/13*, *THI20/21*, *THI6 and THI4*. Alcohol and methyl substitutions on the pyridoxine pyrimide ring are shown in magenta and purple, respectively. Metabolites, proteins, and positive regulators are shown in bold, blue, and green, respectively. ATP, adenosine triphosphate; HET-P, 5-(2-hyroxylethyl)-4-methylthiazole phosphate; HMP-P, 4-amino-2-methyl-5-pyrimidine phosphate; HMP-PP, 4-amino-2-methyl-5-pyrimidine diphosphate; PL, pyridoxal; PLP, pyridoxal-5'-phosphate; PM, pyridoxamine; PMP, pyridoxamine-5'-phosphate; PN, pyridoxine; PNP, pyridoxine-5'-phosphate; TDP, thiamine diphosphate; TMP, thiamine phosphate [Colour figure can be viewed at wileyonlinelibrary.com]

consistent with the PLP requirement of aminotransferases (Natarajan et al., 2001). The *SNZ1/SNO1* gene pair is coregulated by the adenine and histidine biosynthesis transcription factor Bas1 (Daignan-Fornier & Fink, 1992; Mieczkowski et al., 2006; Tice-Baldwin, Fink, & Arndt, 1989) in the presence of glycine (Subramanian et al., 2005). In contrast to the *SNZ1/SNO1* gene pair, which is located in the middle of the right arm of CHRXIII, *SNZ2/SNO2* and *SNZ3/SNO3* are found in subtelomeric regions of CHRXIV and VI, respectively, and are flanked by the thiamine biosynthetic genes *THI12* and *THI5*, respectively. Their increased expression upon thiamine depletion is consistent with the role of PLP in thiamine biosynthesis (Paxhia & Downs, 2019). The demonstration that Snz proteins can directly interact with Thi5 proteins (Rodriguez-Navarro et al., 2002) further shows the interaction of pyridoxine and thiamine biosynthesis (Figure 1).

TABLE 2 *Saccharomyce cerevisiae* S288C proteins requiring pyridoxal-5-phosphate, thiamine diphosphate and biotin as cofactor or as substrate

Cofactor	Protein	Protein name
Pyridoxal-5-phosphate	Uga1	4-aminobutyrate aminotransferase (Andersen, Andersen, Dobritzsch, Schnackerz, & Piskur, 2007)
	Hem1	5-aminolevulinate synthase (Volland & Felix, 1984)
	Arg8	Acetylornithine aminotransferase* (Hilger & Mortimer, 1980)
	Bio3	Adenosylmethionine-8-amino-7-oxononanoate aminotransferase (Phalip, Kuhn, Lemoine, & Jeltsch, 1999)
	Agx1	Alanine-glyoxylate aminotransferase 1 (Takada & Noguchi, 1985)
	Abz2	Aminodeoxychorismate lyase (Dai et al., 2013)
	Aro9	Aromatic amino acid aminotransferase 2 (Zhang, Yang, Shen, & Tong, 2003)
	Aro8	Aromatic/aminoadipate aminotransferase (Karsten, Reyes, Bobyk, Cook, & Chooback, 2011)
	Aat2	Aspartate aminotransferase 2 (Yagi & Kagamiyama, 1982)
	Aat1	Aspartate aminotransferase 1 (Morin, Subramanian, & Gilmore, 1992)
	Bat2	Branched-chain-amino-acid aminotransferase 2 (Eden, Simchen, & Benvenisty, 1996)
	Bat1	Branched-chain-amino-acid aminotransferase 1 (Eden et al., 1996)
	Cha1	Catabolic L-serine/threonine dehydratase (Bornaes, Petersen, & Holmberg, 1992)
	Str3	Cystathionine beta-lyase (Holt et al., 2011)
	Cys4	Cystathionine beta-synthase (Jhee, McPhie, & Miles, 2000)
	Cys3	Cystathionine gamma-lyase (Messerschmidt et al., 2003)
	Str2	Cystathionine gamma-synthase (Hansen & Johannesen, 2000)
	Nfs1	Cysteine desulfurase (Pandey, Golla, Yoon, Dancis, & Pain, 2012)
	Dsd1	D-serine dehydratase (Ito, Hemmi, Kataoka, Mukai, & Yoshimura, 2008)
	Gad1	Glutamate decarboxylase (Coleman, Fang, Rovinsky, Turano, & Moye-Rowley, 2001)
	Gcv2	Glycine dehydrogenase (Sinclair, Hong, & Dawes, 1996)
	Gph1	Glycogen phosphorylase (Becker, Wingender-Drissen, & Schiltz, 1983)
	His5	Histidinol-phosphate aminotransferase (Alifano et al., 1996)
	Met17	Homocysteine/cysteine synthase (Yamagata & Takeshima, 1976)
	Bna5	Kynureninase* (Panozzo et al., 2002)
	Sry1	L-threo-3-hydroxyaspartate ammonia-lyase (Wada, Nakamori, & Takagi, 2003)
	Gly1	Low specificity L-threonine aldolase (Liu et al., 1997)
	Car2	Ornithine aminotransferase (Degols, Jauniaux, & Wiame, 1987)
	Spe1	Ornithine decarboxylase (Tyagi, Tabor, & Tabor, 1981)
	Ser1	Phosphoserine aminotransferase* (Melcher, Rose, Kunzler, Braus, & Entian, 1995)
	Alt2	Probable alanine aminotransferase 2 (Garcia-Campusano et al., 2009)
	Alt1	Probable alanine aminotransferase 1 (Duff et al., 2012)
	Bna3	Probable kynurenine-oxoglutarate transaminase (Wogulis, Chew, Donohoue, & Wilson, 2008)
	Irc7	Putative cystathionine beta-lyase* (Wogulis et al., 2008)
	Yll058w	Putative cystathionine gamma-synthase (Zhang et al., 2001)
	Yml082w	Putative cystathionine gamma-synthase (Hansen & Johannesen, 2000)
	Mcy1	Putative cysteine synthase* (Hughes, Hughes, Henderson, Yazvenko, & Gottschling, 2016)
	Shm2	Serine hydroxymethyltransferase 2 (Nakamura, Trewyn, & Parks, 1973)
	Shm1	Serine hydroxymethyltransferase 1 (Nakamura et al., 1973)
	Lcb1	Serine palmitoyltransferase 1 (Perry, 2002)
	Lcb2	Serine palmitoyltransferase 2 (Perry, 2002)
	Dpl1	Sphingosine-1-phosphate lyase (Saba, Nara, Bielawska, Garrett, & Hannun, 1997)
	Ilv1	Threonine dehydratase (Karassevitch & Robichon-Szulmajster, 1972)
	Thr4	Threonine synthase* (Parsot, 1986)

(Continues)

TABLE 2 (Continued)

Cofactor	Protein	Protein name
	Trp5	Tryptophan synthase (Bartholmes, Boker, & Jaenicke, 1979)
	Yhr112c	Uncharacterized trans-sulfuration enzyme (Arlt, Perz, & Ungermann, 2011)
	Thi5	4-amino-5-hydroxymethyl-2-methylpyrimidine phosphate (HMP-P) synthase (Coquille, Roux, Fitzpatrick, & Thore, 2012)
	Thi11	4-amino-5-hydroxymethyl-2-methylpyrimidine phosphate (HMP-P) synthase (Coquille et al., 2012)
	Thi12	4-amino-5-hydroxymethyl-2-methylpyrimidine phosphate (HMP-P) synthase (Coquille et al., 2012)
	Thi13	4-amino-5-hydroxymethyl-2-methylpyrimidine phosphate (HMP-P) synthase (Coquille et al., 2012)
Thiamine diphosphate	Kgd1	2-oxoglutarate dehydrogenase (Repetto & Tzagoloff, 1989)
	Ilv2	Acetolactate synthase catalytic subunit (Falco, Dumas, & Livak, 1985)
	Pxp1	Putative 2-hydroxyacyl-CoA lyase (Notzel, Lingner, Klingenberg, & Thoms, 2016)
	Pdc1	Pyruvate decarboxylase isozyme 1 (Schmitt, Ciriacy, & Zimmermann, 1983)
	Pdc5	Pyruvate decarboxylase isozyme 2 (Hohmann & Cederberg, 1990)
	Pdc6	Pyruvate decarboxylase isozyme 3 (Hohmann, 1991)
	Pda1	Pyruvate dehydrogenase E1 component subunit alpha (Zeeman et al., 1998)
	Pdb1	Pyruvate dehydrogenase E1 component subunit beta (Miran, Lawson, & Reed, 1993)
	Thi3	Thiamine metabolism regulatory protein THI3 (Nishimura, Kawasaki, Kaneko, Nosaka, & Iwashima, 1992b)
	Aro10	Transaminated amino acid decarboxylase (Vuralhan, Morais, Tai, Piper, & Pronk, 2003)
	Tkl1	Transketolase 1 (Kochetov & Sevostyanova, 2005)
	Tkl2	Transketolase 2 (Schaaff-Gerstenschlager, Mannhaupt, Vetter, Zimmermann, & Feldmann, 1993)
Biotin	Acc1	Acetyl-CoA carboxylase (Zhang, Yang, et al., 2003)
	Hfa1	Acetyl-CoA carboxylase, mitochondrial (Hoja et al., 2004)
	Bpl1	Biotin protein ligase (Cronan & Wallace, 1995)
	Pyc1	Pyruvate carboxylase 1 (Walker, Val, Rohde, Devenish, & Wallace, 1991)
	Pyc2	Pyruvate carboxylase 2 (Walker et al., 1991)
	Dur1,2	Urea amidolyase (Genbauffe & Cooper, 1991)

TABLE 3 *Saccharomyces* species used in a comparative analysis of the presence of annotated vitamin biosynthesis genes

Taxid	Species	Strain	Other Identifiers	Reference	Biosample
1080349	*Saccharomyces eubayanus*	CBS12357^T	NBRC111513^T	(Baker et al., 2015)	NA
226127	*Saccharomyces uvarum*	CBS7001^T	MCYC623^T	(Scannell et al., 2011)	SAMN13069661
1160507	*Saccharomyces arboricola*	CBS10644^T	H-6^T	(Liti et al., 2013)	SAMN13069660
226230	*Saccharomyces kudriavzevii*	CBS8840^T	IFO1802^T	(Scannell et al., 2011)	NA
226126	*Saccharomyces mikatae*	CBS8839^T	IFO1815^T	(Scannell et al., 2011)	SAMN13069662
1987369	*Saccharomyces jurei*	CBS14759^T	NCYC3947^T	(Naseeb et al., 2017)	SAMN13069663
226125	*Saccharomyces paradoxus*	CBS432^T	NRRLY-17217^T	(Yue et al., 2017)	SAMN13069659
559292	*Saccharomyces cerevisiae*	S288C	CBS8803	(Goffeau et al., 1996)	NA
889517	*S. cerevisiae*	CEN.PK113-7D	CBS8340	(Salazar et al., 2017)	SAMN13069664

Note. Biosamples can be accessed under bioproject accession PRJNA578688 (https://www.ncbi.nlm.nih.gov/bioproject).

2.2 | Thiamine (B_1)

Thiamine, also known as vitamin B_1, was first isolated by Jansen and Donath (Jansen & Donath, 1926) and later obtained in sufficient amounts for extended chemical analysis (Williams, Waterman, & Keresztesy, 1934). In animals, which cannot synthesize thiamine, a lack of dietary supply causes beriberi, a disease affecting the nervous system (Weiss & Wilkins, 1937). Thiamine is essential for cellular energy metabolism, and its major biologically active derivative thiamine diphosphate (TDP) serves as cofactor for a variety of enzymes, including pyruvate and oxoglutarate dehydrogenases, transketolases, 2-hydroxy-3-oxoadipate synthase, acetolactate synthase, and 2-oxo

acid decarboxylases (Table 2). As an electrophilic cofactor, TDP forms covalent intermediates with enzyme substrates. Thiamine can also perform intramolecular proton transfers, which is a rare function among cofactors (Nemeria, Chakraborty, Balakrishnan, & Jordan, 2009). It has been proposed that a general stress-protective role of thiamine in *S. cerevisiae* is partially unrelated to its role as a cofactor (Wolak, Kowalska, Kozik, & Rapala-Kozik, 2014). Thiamine is synthesized *de novo* by plants and many microorganisms including yeast species.

Thiamine consists of two substituted aromatic moieties, 4-amino-2-methyl-5-pyrimidyl (HMP) and 5-(2-hydroxylethyl)-4-methylthiazolium, which are connected by a methylene bridge (Figure 1). In addition to free thiamine and the biologically active form TDP, thiamine monophosphate (TMP), and thiamine triphosphate are also found intracellularly. All thiamine-prototrophic organisms synthesize TDP via condensation of the precursors 5-(2-hydroxylethyl)-4-methyl thiazole phosphate and 4-amino-2-methyl-5-pyrimidine diphosphate (HMP-PP) to TMP by TMP diphosphorylase (Thi6 in *S. cerevisiae*; Figure 1). Although bacteria can synthesize TDP from TMP in a single reaction, catalyzed by a TMP kinase, eukaryotes utilize a pathway in which TMP is first dephosphorylated to thiamine, which is then pyrophosphorylated to TDP by a thiamine pyrophosphokinase (Thi80 in *S. cerevisiae*; Muller et al., 2009). Two transporters involved in the acquisition of exogenous thiamine have been identified in *S. cerevisiae*: a high-affinity transporter encoded by *THI10* (Enjo, Nosaka, Ogata, Iwashima, & Nishimura, 1997) and a periplasmic acid phosphatase encoded by *PHO3* that releases thiamine from thiamine phosphates (Nosaka, Kaneko, Nishimura, & Iwashima, 1989).

In *S. cerevisiae*, the thiamin precursor HMP-PP is synthesized in two steps. First, 4-amino-2-methyl-5-pyrimidine phosphate (HMP-P) is formed from pyridoxal-5-phosphate and histidine. The histidine used for HMP-P synthesis is provided from the active site of HMP-P synthase in a suicide reaction (Coquille et al., 2012; Lai et al., 2012). HMP-P synthase is encoded by four highly similar *S. cerevisiae* genes (*THI5*, *THI11*, *THI12*, and *THI13*). These genes are located in subtelomeric regions of different chromosomes, suggesting that an increased copy number conferred a selective advantage in thiamine-poor environments (Wightman & Meacock, 2003). In a second step, HMP-P is phosphorylated to HMP-PP by HMP-P kinase in an adenosine triphosphate-dependent reaction (Kawasaki, Onozuka, Mizote, & Nosaka, 2005). The *S. cerevisiae* genome harbours two paralogous genes encoding HMP-P kinase, *THI20*, and *THI21*, of which the former encodes the major isoform (Wightman & Meacock, 2003). Thi20 is a trifunctional protein that displays thiamine biosynthesis and thiamine degradation activities in a single protein. Its N-terminal domain is active as HMP and HMP-P kinase, whereas its C-terminal domain has thiaminase II activity (Haas, Laun, & Begley, 2005). Although molecular oxygen is not directly required for HMP biosynthesis, activity of this branch of the thiamine biosynthetic pathway was shown to be oxygen dependent (Wightman & Meacock, 2003). However, based on gene deletion studies, it has been proposed that *S. cerevisiae* can still synthesize the pyrimidyl moiety under anaerobic conditions via an alternative, as yet unidentified, pathway (Tanaka, Tazuya, Yamada, & Kumaoka, 2000).

For the synthesis of the thiazole moiety, eukaryotic cells use a single enzyme to form 5-(2-hydroxylethyl)-4-methyl thiazole phosphate from glycine and nicotinamide adenine dinucleotide (NAD^+), encoded by *THI4* in *S. cerevisiae* (Praekelt, Byrne, & Meacock, 1994). Thi4 acts as a substrate in the reaction by providing the sulphur atom needed for thiazole formation in an iron-dependent sulphide transfer from a conserved cysteine. Therefore, similar to Thi5, Thi4 acts as a suicide enzyme undergoing only a single catalytic turnover (Chatterjee et al., 2011; Chatterjee, Jurgenson, Schroeder, Ealick, & Begley, 2007; Chatterjee, Schroeder, Jurgenson, Ealick, & Begley, 2008). Under thiamine-depleted conditions, Thi5 and Thi4 are among the most abundant proteins in *S. cerevisiae* (Muller et al., 1999). Strains harbouring a *THI4* deletion have an increased sensitivity to DNA damaging agents such as ultraviolet light and methyl methanesulfonate. The mechanism of this protection is not fully understood (Machado et al., 1997; Wightman & Meacock, 2003).

Involvement of two suicide enzymes makes *de novo* thiamine biosynthesis in yeast an energetically very expensive process: For each molecule of thiamine produced, two complete proteins (Thi4 and Thi5/11/12/13) have to be synthesized and degraded. Tight regulation of thiamine synthesis occurs mainly at the transcriptional level (Hohmann & Meacock, 1998; Nosaka, 2006). As a result, the *THI* regulon is repressed in the presence of high intracellular levels of TDP. A strain carrying a partially inactivated form of Thi80 was shown to constitutively express the *THI* genes, suggesting that TDP is the molecule acting in this negative feedback regulation loop (Nishimura, Kawasaki, Nosaka, Kaneko, & Iwashima, 1991). Three positive regulators for thiamine biosynthesis have been identified to date: Thi2, Thi3, and Pdc2 (Hohmann, 1993; Nishimura et al., 1992b; Nishimura, Kawasaki, Kaneko, Nosaka, & Iwashima, 1992a). Elimination of any of these three proteins abolishes *THI* genes expression. The expression of *THI2* and *THI3*, but not *PDC2*, strongly increased under thiamine-depleted conditions (Nosaka et al., 2005). Deletion of *THI2* results in repression of all *THI* genes except for *THI10*, whereas deletion of *THI3* causes repression of all *THI* genes. Thi3, which binds TDP, was originally proposed to also act as a 2-oxo acid decarboxylase involved in the Ehrlich for fusel alcohol biosynthesis (Dickinson et al., 1997), but this conclusion was later refuted (Hazelwood, Daran, van Maris, Pronk, & Dickinson, 2008; Romagnoli, Luttik, Kotter, Pronk, & Daran, 2012; Vuralhan et al., 2005). A strain that only carried a *thi3* allele encoding a protein unable to bind TDP showed constitutive expression of *THI* genes in thiamine-containing medium, suggesting that Thi3 acts as a TDP sensor. However, Thi3 lacks a clear DNA-binding motif and is likely to act through interaction with other proteins, such as Thi2 and Pdc2. Pdc2 is a transcriptional regulator that activates both *THI* genes and *PDC* genes encoding pyruvate decarboxylases (Hohmann, 1993; Mojzita & Hohmann, 2006). These regulatory proteins therefore provide an interesting link between the biosynthesis of pyruvate decarboxylase, the most highly expressed TDP-dependent enzyme in *S. cerevisiae*, and its cofactor. A regulatory link between the biosynthesis of thiamine and that of nicotinic acid, another member of the B-complex

vitamins, was demonstrated when the NAD^+-dependent histone deacetylase Hst1 was found to act as a repressor of basal *THI*-gene expression (Li et al., 2010).

2.3 | BIOTIN (B_7)

During the first half of the 20th century, biotin was discovered as an essential growth factor for various organisms (Gyorgy, Melville, Burk, & V, D. U. V., 1940; Kogl & Kostermans, 1935). Biotin plays an important role as coenzyme in carboxylases involved in fatty acid synthesis, sugar, and amino acid metabolism (Lardy, Potter, & Harris, 1949). The cytosolic (Acc1; Wakil, Titchener, & Gibson, 1958) and mitochondrial (Hfa1) acetyl-CoA carboxylases (Hoja et al., 2004), pyruvate carboxylase (Pyc1,2; Morris, Lim, & Wallace, 1987), urea carboxylase (Dur1,2; Roon, Hampshire, & Levenberg, 1972), and a tRNA-aminoacylation cofactor (Arc1; Kim, Hoja, Stolz, Sauer, & Schweizer, 2004) are the only biotin-dependent enzymatic activities in *S. cerevisiae* (Table 2). Covalent linkage of the carboxyl group of biotin to an ε-lysine residue of apo-Acc1 and apo-Pyc1 and 2 is catalyzed by the biotin protein ligase, Bpl1 (Cronan & Wallace, 1995; Mishina, Roggenkamp, & Schweizer, 1980). Although not characterized, a similar mechanism is likely to occur for the mitochondrial acetyl-CoA carboxylase (Hoja, Wellein, Greiner, & Schweizer, 1998; Suomi et al., 2014). Biotin can be taken up via the proton symporter Vht1 (Stolz, Hoja, Meier, Sauer, & Schweizer, 1999). Alternatively, the biotin intermediates 8-amino-7-oxonanote (KAPA) and 7,8-diaminopelargonate (DAPA) can be transported into yeast via the Bio5 membrane protein (Phalip et al., 1999).

The molecular structure of biotin is characterized by an imidazole, or ureido ring, fused with a sulphur-containing tetrahydrothiophene ring, substituted with a valeric acid chain (Figure 2). The reactions involved in the formation of the ring structures of biotin from KAPA are highly conserved among yeast and bacteria and require three steps starting with the conversion of KAPA to DAPA. This reaction is catalyzed by Bio3, a DAPA aminotransferase that requires S-adenosyl-methionine and PLP as cofactors. The following step, catalyzed by the dethiobiotin synthetase Bio4, converts DAPA to dethiobiotin at the expense of adenosine triphosphate (Phalip et al., 1999). In the final step, the biotin synthase Bio2, a mitochondrial

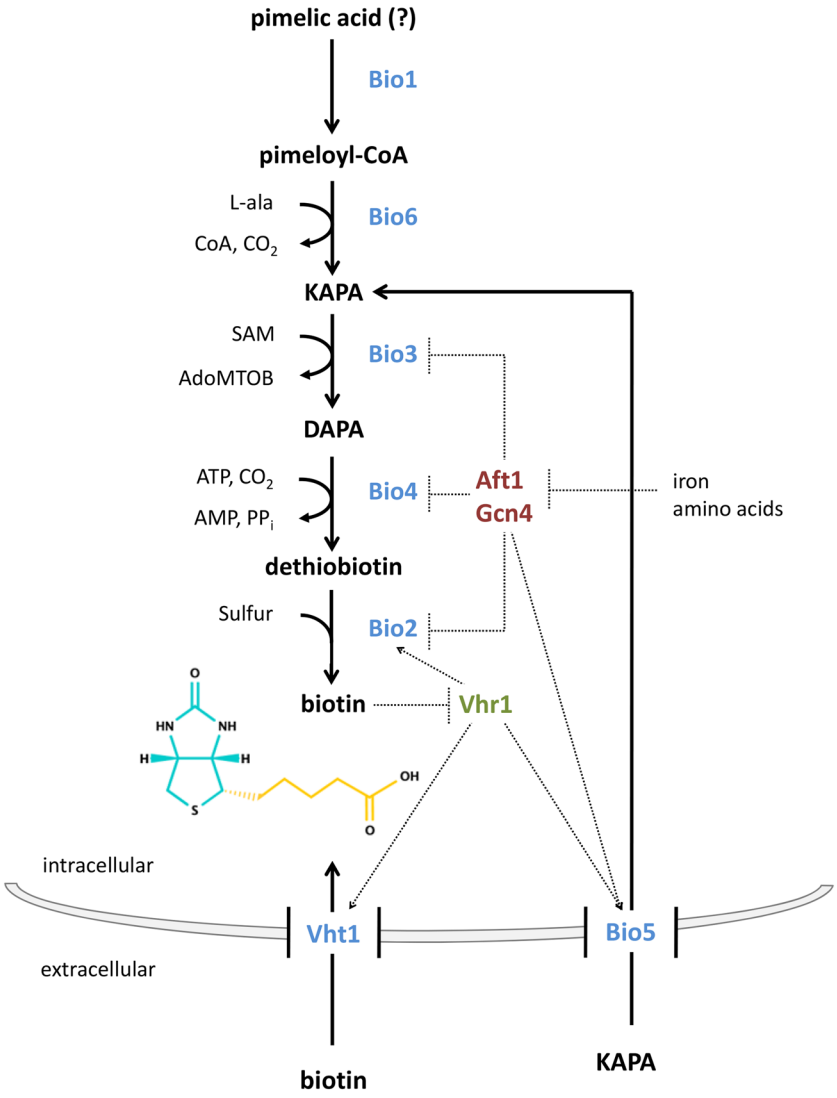

FIGURE 2 Biotin *de novo* biosynthesis pathway in *Saccharomyces cerevisiae*. Biotin is composed of an ureido and a tetrahydrothiophene ring (shown in cyan) fused to a valeric acid chain (shown in yellow). The five final steps of *de novo* biotin synthesis are carried out by Bio1, Bio6, Bio3, Bio4, and Bio2. Origin of pimelic acid remains elusive in *S. cerevisiae* (indicated by question mark(?)). Pimeloyl-CoA formed by Bio1 is converted via 8-amino-7-oxonanoate (KAPA) to 7,8-diaminopelargonate (DAPA) by Bio6 and Bio3. DAPA is subsequently converted by Bio4 to dethiobiotin and finally to biotin by Bio2. The intermediate KAPA and biotin can be imported via the membrane transporters Bio5 and Vht1, respectively. In the absence of biotin, the regulator Vhr1 upregulates expression of genes encoding the transporters Vht1 and Bio5 as well as Bio2. In iron and amino acid rich conditions the transcriptional regulator genes *AFT1* and *GCN4* are transcriptionally repressed, which under iron and amino-acid scarce conditions would not activate transcription of *BIO3*, *BIO4*, and *BIO2* and relieve *BIO5* expression. Metabolites, proteins, positive, and negative regulators are shown in bold, blue, green, and red, respectively [Colour figure can be viewed at wileyonlinelibrary.com]

iron–sulphur–cluster protein, converts dethiobiotin to biotin by incorporating a sulphur atom (Berkovitch, Nicolet, Wan, Jarrett, & Drennan, 2004), presumably acting as a suicide enzyme (Jarrett, 2005).

The pathway for synthesis of the valeric acid side chain of biotin remains elusive and probably involves Bio1 and Bio6, both of which are required for biotin-independent growth of *S. cerevisiae* (Hall & Dietrich, 2007). Presence of BIO1 and BIO6 is straindependent. For example, the reference strain S288C (Goffeau et al., 1996) lacks these two genes and is unable to grow on CDMY lacking biotin (Nijkamp et al., 2012). In contrast, sake strains of *S. cerevisiae* (Wu, Ito, & Shimoi, 2005), *S. cerevisiae* strains isolated from cachaça fermentations (Barbosa et al., 2018), and the laboratory strains A364a (Hall & Dietrich, 2007) and CEN.PK113-7D (Bracher et al., 2017; Nijkamp et al., 2012) do carry these two genes and exhibit growth, albeit very slowly, on CDMY without biotin. *BIO6* has been proposed to have evolved from a duplication and neofunctionalization of *BIO3*, after *BIO3* and *BIO4* had been simultaneously acquired by horizontal gene transfer, with *BIO1* similarly having evolved from duplication and neofunctionalization of the uncharacterized ORF *YJR154W* (Hall & Dietrich, 2007).

In view of its 55% amino-acid sequence similarity with *Escherichia coli* BioA, *BIO6* probably encodes an adenosylmethionine-8-amino-7-oxononanoate transaminase (Wu et al., 2005). The initial formation of the pimeloyl thioester in *S. cerevisiae* remains unclear. Hall and Dietrich (2007) proposed that *BIO1* encodes a coenzyme A (CoA) ligase that activates pimelic acid, a C7 dicarboxylic acid, to pimeloyl-CoA. Although such a CoA ligase (BioW) was identified in the gram-positive bacterium *Bacillus subtilis* (Manandhar & Cronan, 2017), *S. cerevisiae* Bio1 protein does not show similarity to that enzyme. Additionally, biosynthesis of pimelic acid by *S. cerevisiae* has not been reported, and pimelic acid feeding to a strain carrying the full biotin biosynthesis pathway was not able to stimulate growth on medium lacking biotin (Ohsugi & Imanishi, 1985).

Laboratory evolution studies highlighted the role of the enigmatic Bio1 protein in biotin prototrophy of *S. cerevisiae*. Prolonged cultivation of the laboratory strain CEN.PK113-7D in biotin-free accelerostats yielded an evolved strain that showed the same high specific growth rate (0.36 hr^{-1}) in the absence and presence of biotin. Whole-genome resequencing of evolved isolates revealed a massive 20- to 40-fold amplification of the physically linked *BIO1* and *BIO6* gene copies (Bracher et al., 2017). Overexpression of *BIO1*, but not *BIO6*, from a multicopy plasmid sufficed to increase specific growth rates of the nonevolved strain on biotin-free CDMY without biotin from 0.01 to 0.15 hr^{-1}. Despite its unknown function, these results show that *BIO1* is a key bottleneck of *de novo* biotin synthesis in *S. cerevisiae* (Bracher et al., 2017). Strategies to generate biotin-prototrophic *S. cerevisiae* strains are likely to benefit from elucidation of the reaction catalyzed by Bio1.

The biotin biosynthetic genes *BIO5*, *BIO2*, *BIO4*, *BIO3*, *BIO6*, *VHT1*, and *BPL1* showed a concerted upregulation during biotin starvation (Pirner & Stolz, 2006; Wu et al., 2005). The promoter regions of *BIO5*, *VHT1*, *BIO2*, and *BPL1* contain an upstream activating element that, in the absence of biotin, is bound by the transcription factor Vhr1, which upregulates transcription. This activation ensures expression of biotin and DAPA transporters, *de novo* biotin synthesis and enzyme biotinylation (Weider, Machnik, Klebl, & Sauer, 2006). The transcriptional regulation of the biotin permease gene *VHT1* is additionally controlled by the transcription factors Aft1 and Gcn4, which are involved in iron homeostasis and global control of nitrogen metabolism, respectively. Downregulation of biotin biosynthesis genes and a parallel upregulation of biotin transport upon low availability of iron and/or nitrogen (Shakoury-Elizeh et al., 2004) has been interpreted as a strategy to decrease the metabolic burden of *de novo* biotin synthesis under these conditions (Pirner & Stolz, 2006).

3 | VITAMINS THAT ACT AS METABOLIC PRECURSORS FOR COFACTOR BIOSYNTHESIS

3.1 | Pantothenic Acid (B_5)

Vitamin B_5 was discovered by 1933 (Williams, Lyman, Goodyear, Truesdail, & Holaday, 1933) and, based on its presence in all animal tissues, named pantothenate (παντοθεν, from everywhere). Pantothenate is not a cofactor, but a key precursor for synthesis of CoA and acyl carrier protein, which play key roles in metabolism. When supplied to media, pantothenate is imported into *S. cerevisiae* by the plasma-membrane pantothenate-proton symporter Fen2 (Stolz & Vielreicher, 2003). Only plants and microorganisms, including fungi, can perform *de novo* pantothenate biosynthesis. However, most sake strains of *S. cerevisiae* strains are entirely auxotrophic for pantothenate when grown in media that exclusively contain organic nitrogen sources and, in some cases, also when an inorganic nitrogen source is provided (Sugama, 1965). Many *S. cerevisiae* strains can synthesize pantothenic acid. In such strains, removal of the molecule from the medium typically results in impaired growth on glucose, but not on glycerol or acetate (White, Gunyuzlu, & Toyn, 2001).

Panothenate is formed by fusion of pantoate and β-alanine, in a reaction catalyzed by pantoate-beta-alanine ligase (Pan6 in *S. cerevisiae*, Figure 3). In *S. cerevisiae*, β-alanine is produced from spermine in two steps (White et al., 2001). The first step is catalyzed by the polyamine oxidase Fms1, which produces 3-aminopropanal from spermine. 3-Aminopropanal is then oxidized to β-alanine by the cytosolic aldehyde dehydrogenases Ald2 and Ald3. The reaction catalyzed by Fms1 has been reported to be rate limiting for pantothenate biosynthesis, and Fms1 overexpression results in the secretion of pantothenic acid (Schadeweg & Boles, 2016). Pantoate is synthesized in *S. cerevisiae* from 2-*keto*-isovalerate, an intermediate of the valine biosynthesis. After conversion of 2-keto-isovalerate into 2-dehydropantoate (Lussier et al., 1997) by keto-pantoate hydroxymethyltransferase (Ecm31), 2-dehydropantoate is transformed into pantoate by 2-dehydropantoate 2-reductase (Pan5) in a NADPH-dependent reduction (Patil & Nielsen, 2005).

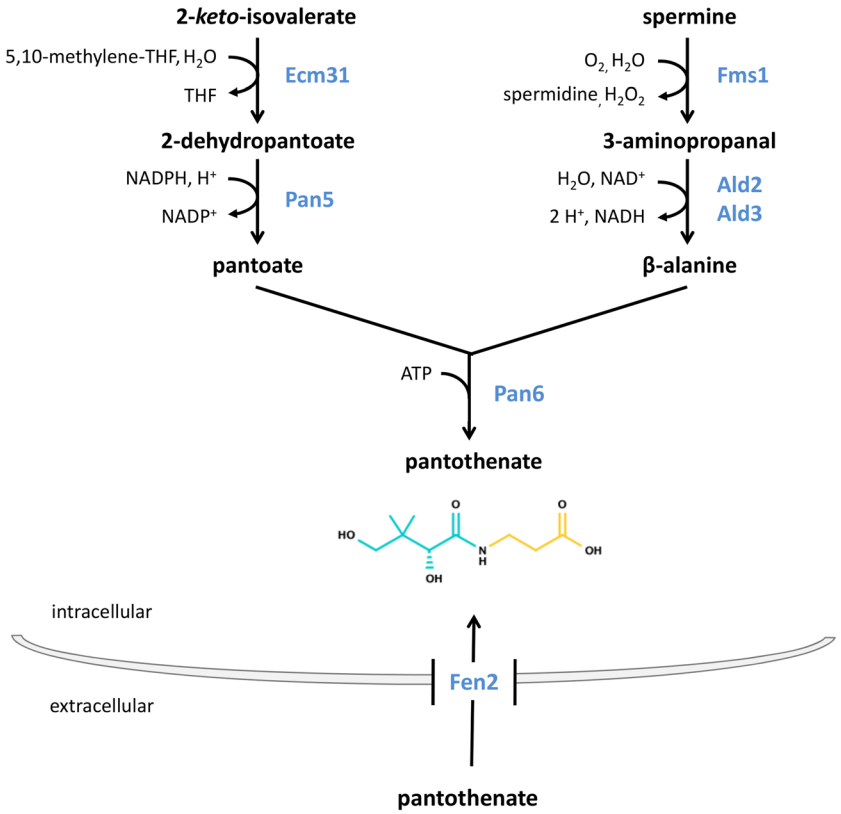

FIGURE 3 Pantothenate *de novo* synthesis pathway in *Saccharomyces cerevisiae* and transcription profiles of pantothenate biosynthetic genes under different growth conditions. Pantothenate can be imported by the proton symporter Fen2 or synthesized *de novo* by condensation of pantoate (shown in cyan) and β-alanine (shown in yellow) in an ATP-dependent reaction catalyzed by Pan6. Pantoate is formed in a two-step pathway from 2-keto-isovalerate catalyzed by Ecm31 and Pan5 with 2-dehydropantoate as intermediate. β-alanine is formed starting from spermine by the enzymes Fms1 and Ald2-3 via 3-aminopropanal. ATP, adenosine triphosphate; $NADP^+$, nicotinamide adenine dinucleotide phosphate [Colour figure can be viewed at wileyonlinelibrary.com]

In comparison with the regulation of the other biosynthetic pathways discussed in this review, regulation of pantothenate acid biosynthesis in *S. cerevisiae* has not been intensively studied and, therefore, is still incompletely understood. Expression of *ECM31* and *PAN6* was shown to be low, constititutive, and unaffected by extracellular panthotenate concentrations (Olzhausen, Schubbe, & Schuller, 2009), whereas transcript levels of the pantothenic acid biosynthetic genes (*ECM31*, *PAN5*, *FMS1*, *ALD2*, *ALD3*, and *PAN6*) across 55 different culture conditions (Knijnenburg et al., 2007; Knijnenburg et al., 2009; Figure 4) did not reveal indications for coregulation.

3.2 | *p*ABA (B_{10})

*p*ABA, also known as vitamin B_{10}, is a water-soluble B complex vitamin. It was discovered in 1920s (Behaghel, Rothman, & Schultze, 1928; Rothman, 1926). A temporary sunscreen application after the WW2 was soon withdrawn as it caused dermatitis and autoimmune responses (Mackie & Mackie, 1999; Rothman & Rubin, 1942). *p*ABA is an important intermediate in the biosynthesis of folates, a class of cofactors involved in transfer of C1-units in nucleic acid and amino-acid metabolism, as well as in ubiquinone biosynthesis (Brown, Weisman, & Molnar, 1961; Pierrel et al., 2010). Folates result from the association of three precursors *p*ABA (B_{10}), GTP, and glutamate, out of which *p*ABA is the less abundant intracellularly and limit folic acid (B_9) synthesis. Additionally, growth deficiency in the presence of *p*ABA and absence of folic acid has not been reported before, making this vitamin dispensable for CDMY.

In *S. cerevisiae*, *p*ABA biosynthesis starts from chorismate which, as indicated by its name (χωρίζω; to separate), is located at the intersection of the biosynthesis of (a) tyrosine and phenylalanine, (b) tryptophan, and (c) *p*ABA and folates. Conversion of chorismate in to *p*ABA involves two enzyme reactions (Figure 5a). First, amino-deoxy-chorismate synthase (Abz1) uses glutamine as amino donor to produce 4-amino-4-deoxy-chorismate. Subsequently, amino-deoxy-chorismate lyase (Abz2) removes the pyruvate moiety of chorismate, resulting in *p*ABA (Marbois et al., 2010). Chorismate is a key intermediate of the shikimate pathway for aromatic amino-acid biosynthesis. The shikimate pathway is tightly regulated, not only transcriptionally but also by allosteric feedback regulation of its first committed enzyme, 3-Deoxy-D-arabinoheptulosonate 7-phosphate synthase. *S. cerevisiae* contains two isoenzymes of 3-Deoxy-D-arabinoheptulosonate 7-phosphate, Aro3 and Aro4, which are feedback inhibited by phenylalanine and tyrosine, respectively (Braus, 1991; Luttik et al., 2008). This regulation ensures that intracellular chorismate availability is strongly influenced by aromatic amino-acid concentrations. *ABZ1* and *ABZ2*, which encode the key enzymes of the *p*ABA pathway, are transcribed constitutively (Ambroset et al., 2011), suggesting that any regulation of *p*ABA biosynthesis occurs is post-transcriptional.

Rates of fermentation and nitrogen assimilation of *S. cerevisiae* strains have been correlated with specific alleles of *ABZ1*, thereby linking *p*ABA synthesis to overall strain performance (Ambroset et al.,

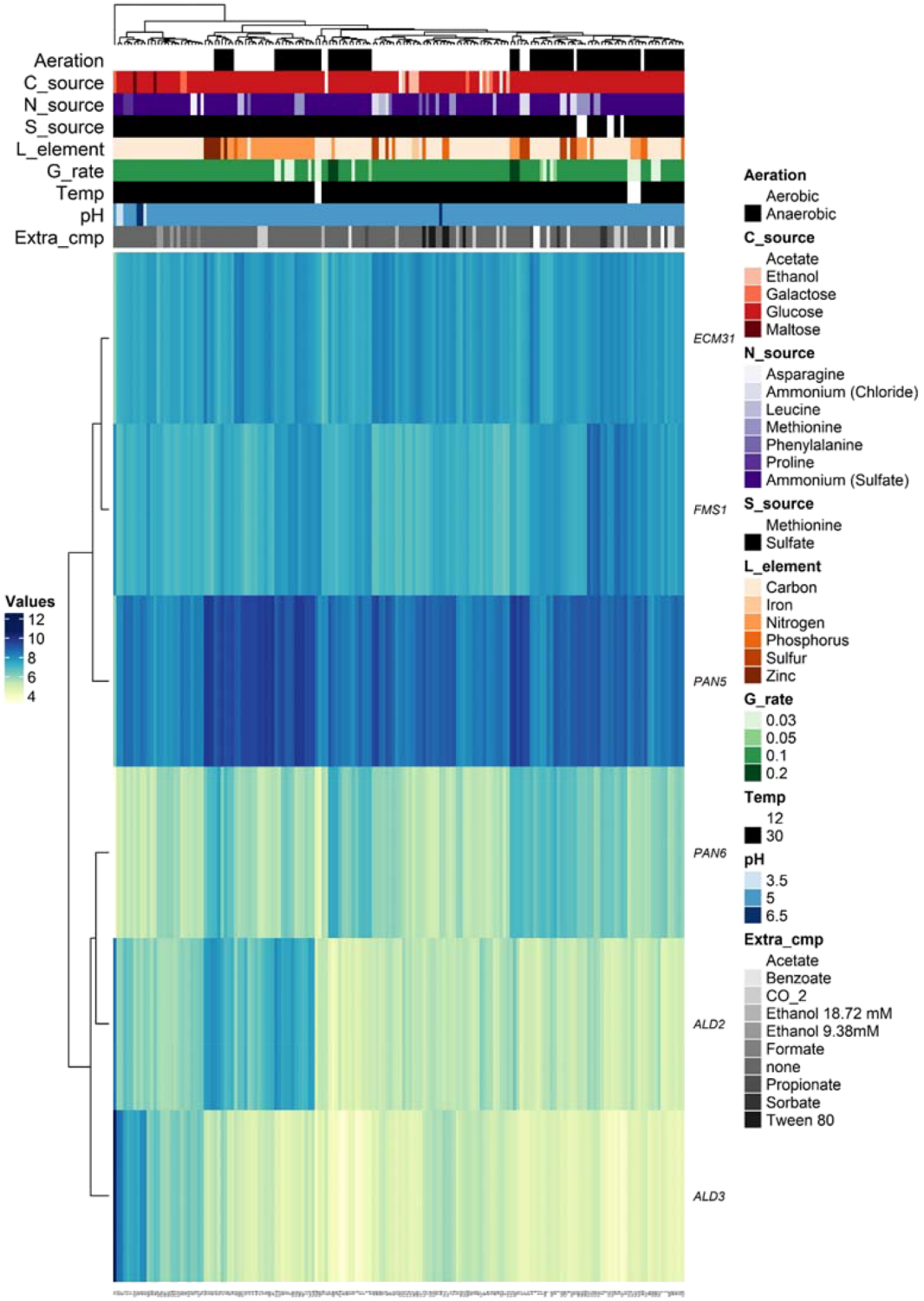

FIGURE 4 Heatmap showing mRNA levels for pantothenate biosynthetic genes measured under 70 different conditions in chemostat cultures. Each row shows a gene involved in *de novo* pantothenate biosynthesis, whereas each column represents one condition. Data are derived from (Knijnenburg et al., 2007; Knijnenburg et al., 2009), and code for generating this plot is available at https://gitlab.tudelft.nl/rortizmerino/sacch_vitamins [Colour figure can be viewed at wileyonlinelibrary.com]

2011; Steyer et al., 2012). This genetic heterogeneity has been exploited to engineer *S. cerevisiae* for *p*ABA production by over-expressing *ABZ1-2* alleles from wine strains that encode highly active enzymes (Averesch, Winter, & Kromer, 2016).

3.3 | Nicotinic acid (B_3)

Nicotinic acid, also known as niacin, was first isolated from liver in 1937 and was identified as "pellagra-preventing factor" and "anti-

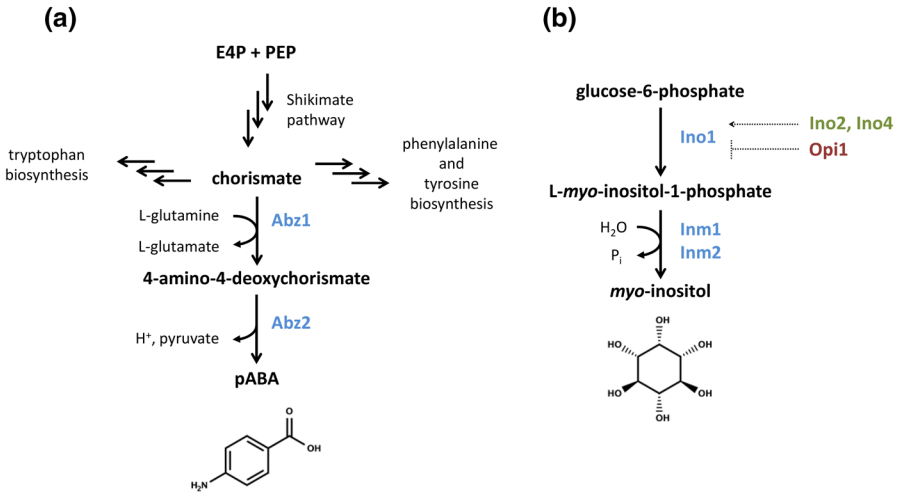

FIGURE 5 *p*ABA and *myo*-inositol *de novo* synthesis pathways in *Saccharomyces cerevisiae*. (a) The genes *ABZ1* and *ABZ2* code for a two-step pathway producing *p*ABA from chorismate via the intermediate 4-amino-4-deoxychorismate. Chorismate is synthesized from erythrose-4-phosphate and phosphoenolpyruvate via the shikimate pathway. In addition to being precursor for *p*ABA biosynthesis, chorismate also serves as precursor for tryptophan, phenylalanine and tyrosine biosynthesis. (b) *myo*-Inositol is formed from glucose-6-phosphate via Ino1 yielding L-myo-inositol-1-phosphate, which is in a second step converted to *myo*-inositol by Inm1 or Inm2. *INO2*, *INO4* genes encode *INO1* transcriptional activators while *OPI1* encodes the antagonist regulator of the gene encoding the initial step of inositol synthesis. Metabolites, proteins, positive regulators, and positive regulators are shown in bold, blue, green, and red, respectively. *p*ABA, *para*-Aminobenzoic acid [Colour figure can be viewed at wileyonlinelibrary.com]

black tongue factor" (Elvehjem, Madden, Strong, & Woolley, 1938). Together with nicotinamide, it makes up the vitamin B_3 complex. Nicotinic acid is an important precursor for the essential redox cofactors NAD^+ and nicotinamide adenine dinucleotide phosphate ($NADP^+$).

S. cerevisiae can either obtaine NAD^+ from *de novo* biosynthesis or from salvage routes that regenerate NAD^+ from its nicotinamide degradation products (Bedalov, Hirao, Posakony, Nelson, & Simon, 2003; Lin & Guarente, 2003; Figure 4). These pathways converge at the level of nicotinic acid mononucleotide (NaMN) and share the last two reactions towards NAD^+ formation.

In the *de novo* biosynthesis pathway, NaMN is synthesized from L-tryptophan in a series of six enzymatic reactions (catalyzed by Bna1-2 and Bna4-7) and one spontaneous reaction (Figure 5). Three of the enzymes involved in the *de novo* biosynthesis pathway, indoleamine 2,3 dioxygenase (Bna2), kynurenine 3-monooxygenase (Bna4), and 3-hydroxyanthranilate 3,4-dioxygenase (Bna1), require molecular oxygen as a substrate, thereby explaining the strict requirement of anaerobic *S. cerevisiae* cultures for nicotinic acid supplementation (Panozzo et al., 2002). In the salvage pathway, nicotinamide and nicotinic acid are converted to NaMN via the so-called Preiss–Handler pathway I (Preiss & Handler, 1957; Preiss & Handler, 1958), which involves Pnc1 and Npti1 as key enzymes. Extracellular nicotinic acid can be imported into yeast cells by the plasma-membrane transporter Tna1 and then used to form NAD^+ through the salvage pathway (Klebl, Zillig, & Sauer, 2000; Llorente & Dujon, 2000).

In yeast, there are other four additional pathways for NAD^+ biosynthesis: two salvage pathways from nicotinamide riboside (NR) and two salvage pathways from nicotinic acid riboside (Belenky et al., 2007; Bieganowski & Brenner, 2004; Tempel et al., 2007). Three of these salvage pathways converge first with the Preiss–Handler NAD^+ salvage pathway and then with the *de novo* NAD pathway (Figure 4). In the NR salvage pathway I, which is not connected to the other pathways, NR is first phosphorylated to nicotinamide nucleotide by the Nrk1 kinase and then adenylated to NAD^+ by Nma1 or Nma2 (Figure 6).

NAD^+ and $NADP^+$ are essential redox cofactors for many oxidoreductases (Voet, Voet, & Pratt, 2006). In addition to its role as a redox cofactor, NAD^+ is a substrate for several enzymes in yeast including sirtuin protein deacetylases (Sir2, Hst1-4) and cyclic ADP-ribose synthases (Tpt1; Culver, McCraith, Consaul, Stanford, & Phizicky, 1997; Wierman & Smith, 2014). These enzymes have important roles in the maintenance and regulation of chromatin structure, calcium signalling, life-span and DNA repair (Bürkle, 2005; Chini, 2009; Kato & Lin, 2014; Lin & Guarente, 2003; Rusche, Kirchmaier, & Rine, 2003). NAD^+ is also a precursor for $NADP^+$ which, like NAD^+, is involved in many cellular redox reactions (Kawai, Suzuki, Mori, & Murata, 2001). Intracellular NAD^+ levels are controlled by a complex regulation network. Hst1 (Homologue of Sir2) acts as a NAD^+ sensor that represses *BNA* genes when NAD^+ is abundant. Hst1 does not bind the DNA directly but interacts with Rfm1 and Sum1 to form a repressor complex. Mac1, which was previously characterized as a copper-sensing transcription factor, has been shown to also be involved in regulation of *BNA* genes, together with Hst1 (Bedalov et al., 2003; James Theoga Raj et al., 2019; Laurenson & Rine, 1991; McCord et al., 2003). When NA is abundantly available, NA salvage metabolism is preferred over use of the *de novo* biosynthetic pathway, which is repressed by Hst1 (Bedalov et al., 2003; James Theoga Raj et al., 2019). In *S. cerevisiae*, NAD^+

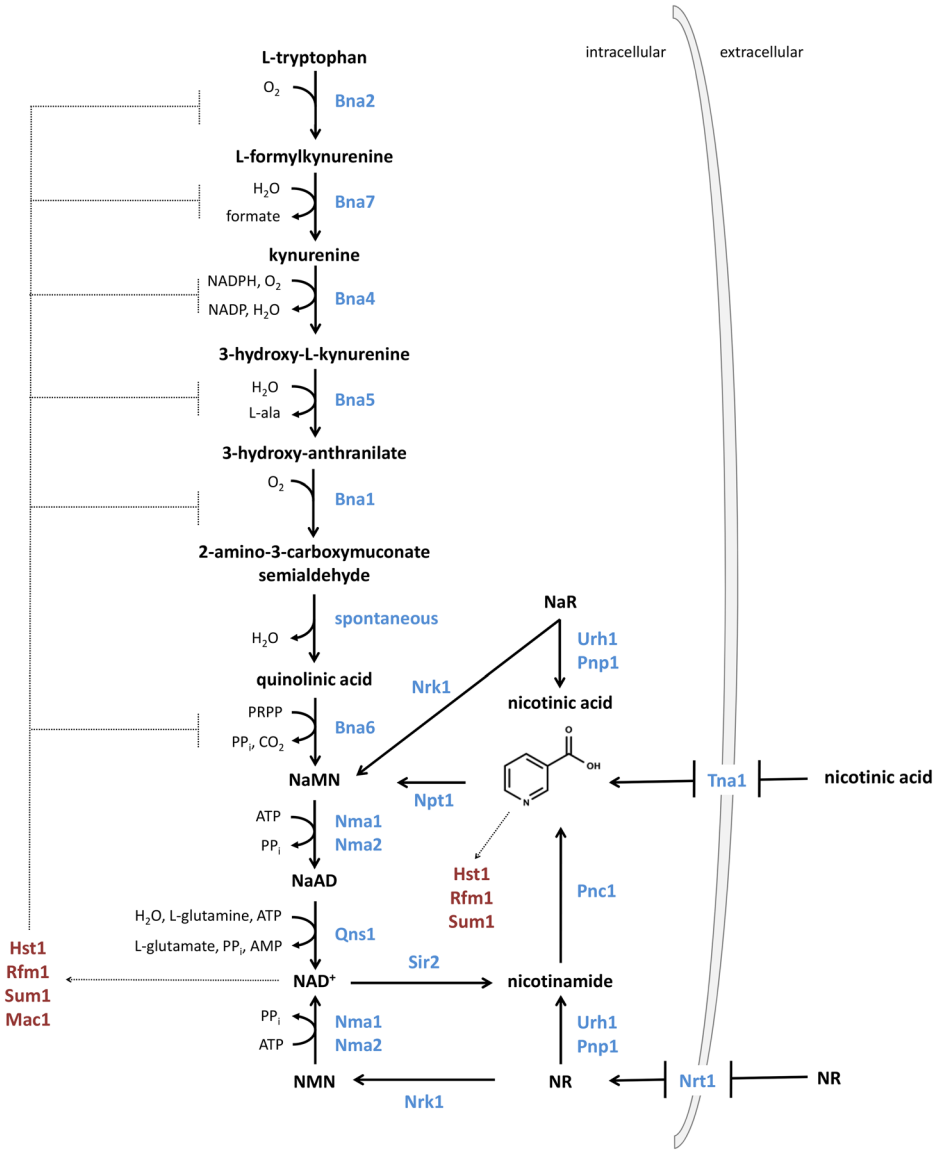

FIGURE 6 Nicotinic acid *de novo* synthesis and salvage pathway in *Saccharomyces cerevisiae*. NAD^+ is *de novo* synthesized from L-tryptophan in nine catalytic steps involving the Bna enzyme family and enzymes Nma1, Nma2, and Qns1. Nicotinic acid can be imported into the cell via Tna1 and enters the NAD synthesis pathway as NaMN by catalytic activity of Npt1. Similarly, NaR can be salvaged by catalytic activity of Nrk1 to form NaMN. NaR can be also converted to nicotinic acid by Urh1 and Pnp1. Nrk1 also converts NR into NMN subsequently converted to NAD^+ by Nma1 and Nma2. NR is imported by activity of Nrt1 transporter and might be used by Pnp1 or Urh1 to form nicotinamide. Alternatively, nicotinamide can be synthesized via Sir2 from NAD^+. Pnc1 uses nicotinamide to form nicotinic acid. The regulators Hst1 (with aid of Rfm1 and Sum1) and Mac1 repress the expression of genes encoding Bna enzymes upon binding to NAD^+ and nicotinic acid. Metabolites, proteins and negative regulators are shown in bold, blue and red respectively. NAD^+, nicotinamide adenine dinucleotide; NaMN, nicotinic acid mononucleotide; NAR, nicotinamide riboside; NMN, nicotinamide nucleotide; NR, nicotinamide riboside [Colour figure can be viewed at wileyonlinelibrary.com]

metabolism is regulated together with phosphate and purine nucleotide metabolism, although the exact mechanisms remain uncharacterized (Lu & Lin, 2010; Pinson, Ceschin, Saint-Marc, & Daignan-Fornier, 2019). NR can be produced and stored in vacuoles and then released into the cytosol by the Fun26 transporter, thereby enabling cells to feed NR stores into NAD^+ synthesis (Boswell-Casteel et al., 2014; Lu & Lin, 2011).

3.4 | INOSITOL (B_8)

Of the seven organic supplements that are added to commonly used CDMY, only inositol (Table 1) is not a cofactor or cofactor precursor. First isolated in 1928 (Eastcott, 1928), inositol is a polyol (cyclohexane-1,2,3,4,5,6-hexol) that serves as precursor for phosphatidylinositol, a main constituent of phospholipid membranes (White, Lopes, & Henry, 1991). Upon its cleavage into inositol phosphate and diacylglycerol by phospholipase C, phosphatidylinositol also plays a central role in inositol-phosphate signalling (Yoko-o et al., 1993). Moreover, inositol is a precursor for the synthesis of glycosylphosphatidylinositol anchor proteins (Pittet & Conzelmann, 2007).

Myo-inositol is physiologically the most common stereoisomer among the eight possible inositol enantiomers. In organisms capable of synthesizing *myo*-inositol, it is formed from glucose-6-phosphate via two enzyme-catalyzed reactions. The genes involved in the *S. cerevisiae* inositol biosynthesis pathway were discovered by complementation of inositol-requiring mutants (Culbertson, Donahue, & Henry, 1976; Figure 5a). First, L-*myo*-inositol 1-phosphate is generated from glucose-6-phosphate by L-*myo*-inositol 1-phosphate synthase (Ino1; Donahue & Henry, 1981). Subsequently, *myo*-inositol is generated by dephosphorylation of L-*myo*-inositol 1-phosphate by the heterodimeric enzyme inositol 3-phosphate monophosphatase (Inm1/Inm2 Murray & Greenberg, 2000).

Lipid metabolism in eukaryotic cells, including yeasts, is rigourously regulated. Yeast cells continuously monitor lipid status and quickly respond to alterations by a dual regulatory control. Many insights into how the yeast cells regulate their phospholipid metabolism derive from research on regulatory responses to variations in the inositol content of growth media (Henry, Gaspar, & Jesch, 2014). Analysis of inositol-auxotrophic *S. cerevisiae* strains enabled discovery of *INO2* and *INO4*, which encode positive transcriptional regulators for *INO1* and a large number of other genes involved in phospholipid synthesis (Henry, Kohlwein, & Carman, 2012). A key negative feedback mechanism for transcriptional regulation was discovered by the characterization of mutants able to secrete inositol, a phenotype also referred to as the opi$^-$ phenotype (Greenberg, Reiner, & Henry, 1982). The transcriptional factor Opi1 was shown to act as a negative regulator in the presence of inositol, with some and mutations in *OPI1* resulting in constitutive *INO1* expression. The Opi$^-$ phenotype has also been useful for identifying other *S. cerevisiae* genes involved in phospholipid biosynthesis, transcription, protein processing, and trafficking (Hancock, Behta, & Lopes, 2006).

4 | SYSTEMATIC SEARCH FOR COMPONENTS OF THE CLASS B VITAMIN BIOSYNTHESIS PATHWAYS IN *SACCHAROMYCES* SPECIES

Although strain-to-strain differences occur, the *S. cerevisiae* pangenome harbors all necessary genetic information to synthesize inositol, biotin, thiamine, nicotinic acid, panthotenate, pyridoxine, and *p*ABA. Since the work of Burkholder, McVeigh and Moyer in 1944, no systematic analysis has been performed to assess growth factor requirements of different species within the *Saccharomyces* genus. To explore this issue, we screened the genomes of the type strains of *Saccharomyces* species for annotated sequences homologous to the structural genes encoding enzymes involved in biosynthesis of class B vitamins in *S. cerevisiae* (Jelier, Semple, Garcia-Verdugo, & Lehner, 2011). Based on this screen, the genomes of most *Saccharomyces* type strains encode complete biosynthetic pathways for these compounds (Figure 7). Two notable exceptions are *Saccharomyces arboricola*, which misses key genes required for biosynthesis of pyridoxine, thiamine, and biotin (*SNO2/3*, *SNZ2/3*, *THI5-13*, *BIO1*) and *Saccharomyces kudriavzevii*, which lacks genes involved in biosynthesis of pyridoxine, pantothenate, *p*ABA, and inositol (*SNO1*, *FMS1*, *PAN6*, *ABZ1/2*, *INO1*). Absence of *SNO2/3* in *Saccharomyces paradoxus* should not compromise its pyridoxine prototrophy as its genome does harbour the main paralog *SNO1*.

Some *Saccharomyces* species show higher copy numbers for individual vitamin biosynthesis genes than *S. cerevisiae*. In particular, *Saccharomyces jurei* harbors additional copies of *SNO2/3*, *SNZ2/3*, *THI5*, and *THI11-13*, whereas *S. paradoxus* carries two copies of *BIO1* and *BIO6*. These genes are all located in subtelomeric regions in *S. cerevisiae*. Subtelomeric regions are known hotspots for genetic plasticity that contain many gene families involved in interaction between the cell and its environment (Winzeler et al., 2003). Assuming conserved synteny within the *Saccharomyces* genus, these gene amplifications may therefore reflect evolutionary adaptations to the environmental conditions these different species were exposed to.

5 | OUTLOOK

The information presented in this review is now at hand for future research on vitamin metabolism in *S. cerevisiae* and might be extrapolated to other members of the *Saccharomyces* genus or other yeasts. Although representing only a small sample of the potential biodiversity within the *Saccharomyces* genus, the observed differences in vitamin biosynthetic genes between type strains indicate that further genomic, physiological, and ecological studies can contribute to our understanding of the adaptation of *Saccharomyces* species to their habitats.

Another more practical aspect is that yeast cultivations in research and industry often require supplementation of vitamins, because endogenous synthesis does not always meet the demands for fast growth and high product titres. Gaining understanding of the biochemistry and genetics of vitamin metabolism is of high relevance for optimization of vitamin *de novo* synthesis. Design of prototrophic strains can be informed by genetic and physiological analysis of fully prototrophic strains and species as well as by evolutionary engineering of strains for fast growth in the absence of growth factors (Bracher et al., 2017; Mans, Daran, & Pronk, 2018). Knowledge derived from such studies may, ultimately, enable the construction of yeast cell factories for vitamin production.

Availability of vitamin prototrophic *S. cerevisiae*, would allow costs reduction for preparation of (semi-) defined industrial growth media. One example could be processes based on feedstocks whose preparation requires heating and/or acid-treatment steps (e.g., lignocellulosic hydrolysates; Jansen et al., 2017; Lynd, 1996) that inactivate specific vitamins. Moreover, vitamin starvation has been proven to affect ethanol yields and cell viability and be the cause of stuck fermentation in a nitrogen-dependent manner (Alfenore et al., 2002; Duc et al., 2017). Strains with optimized vitamin metabolism could result in higher performance and increase process robustness. In addition, processes based on vitamin-independent yeast strains may be less susceptible to contamination by vitamin-auxotrophic microorganisms (e.g., lactic acid bacteria; Skinner & Leathers, 2004). Whether the engineered prototrophic strain would be able to secrete class B vitamins resulting in cross-feeding of the auxotrophic species as previously shown for the case of amino acids would have to be tested (Ponomarova et al., 2017). Furthermore, future research focusing on precise quantification of vitamins consumption rates and intracellular vitamin concentrations under industrially relevant conditions could generate useful information for medium optimization or for the integration of vitamin metabolism in the current yeast metabolic models.

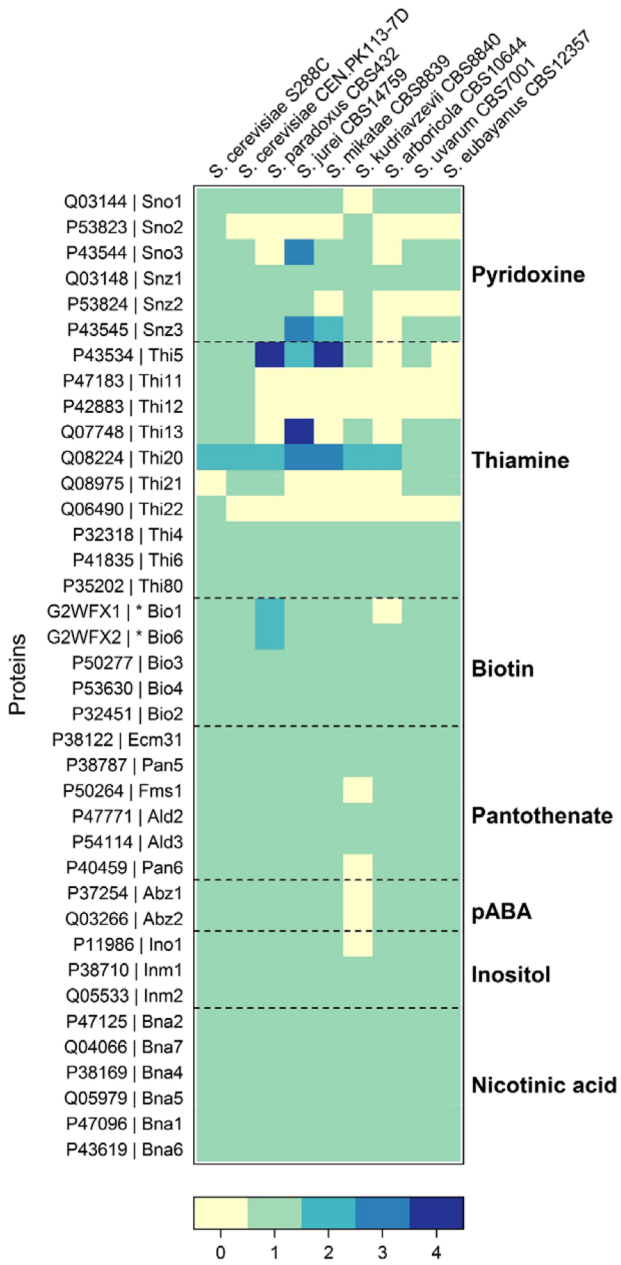

FIGURE 7 Occurrence of vitamin biosynthesis annotated genes in *Saccharomyces* species. A homology search was conducted using HMMER v3 (Eddy, 2011) with *Saccharomyces cerevisiae* S288C proteins as queries (left side row names) against a database of annotated proteins from the *Saccharomyces* species listed in the column headers. For *BIO1* and*BIO6*, *S. cerevisiae* K7 proteins were used as queries (indicated with *) because S288C is known to lack such proteins. Available genome annotations from species in the monophyletic *Saccharomyces* clade (formely known as sensu stricto; Table 3) were used to build a protein sequence database. Besides *S. cerevisiae* S288C and CEN.PK113-7D, sequences in the database belong to type strains. This database was then searched for sequence homologs using the queries listed on the left-hand side. Queries are grouped and labelled on the right-hand side and depending on the biosynthetic pathway they are involved in. Boxes are coloured depending on the number of hits (e-value > 1e-5, percentage of alignment > 75%) obtained by each query on each strain. The colour code is shown at the bottom. Hits from queries belonging to the same biosynthetic pathway were ranked according to lowest e-value then highest percentage of alignment and best hits were uniquely assigned to each query (i.e., a sequence considered as best hit is never used more than once and best hits with a count >1 are all identical). This last step accounts for the presence of paralogs and the high level of similarity between proteins in the same pathway, especially in the pyridoxine and thiamine pathways (see Thi5 and Thi20 for instance). Code for this search is available in https://gitlab.tudelft.nl/rortizmerino/sacch_vitamins and sequences are deposited under BioProject accession PRJNA578688 as indicated in Table 3 [Colour figure can be viewed at wileyonlinelibrary.com]

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interests.

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REFERENCES

Alfenore, S., Molina-Jouve, C., Guillouet, S. E., Uribelarrea, J. L., Goma, G., & Benbadis, L. (2002). Improving ethanol production and viability of *Saccharomyces cerevisiae* by a vitamin feeding strategy during fed-batch process. *Applied Microbiology and Biotechnolology*, *60*, 67–72.

Alifano, P., Fani, R., Lio, P., Lazcano, A., Bazzicalupo, M., Carlomagno, M. S., & Bruni, C. B. (1996). Histidine biosynthetic pathway and genes: Structure, regulation, and evolution. *Microbiology Reviews*, *60*, 44–69.

Ambroset, C., Petit, M., Brion, C., Sanchez, I., Delobel, P., Guerin, C., … Blondin, B. (2011). Deciphering the molecular basis of wine yeast fermentation traits using a combined genetic and genomic approach. *G3 (Bethesda)*, *1*, 263–281.

Andersen, G., Andersen, B., Dobritzsch, D., Schnackerz, K. D., & Piskur, J. (2007). A gene duplication led to specialized γ-aminobutyrate and β-alanine aminotransferase in yeast. *FEBS Journal*, *274*, 1804–1817.

Andreasen, A. A., & Stier, T. J. (1953). Anaerobic nutrition of *Saccharomyces cerevisiae*. I. Ergosterol requirement for growth in a defined medium. *Journal of Cellular and Comparative Physiology*, *41*, 23–36.

Andreasen, A. A., & Stier, T. J. (1954). Anaerobic nutrition of *Saccharomyces cerevisiae*. II. Unsaturated fatty acid requirement for growth in a defined medium. *Journal of Cellular and Comparative Physiology*, *43*, 271–281.

Arlt, H., Perz, A., & Ungermann, C. (2011). An overexpression screen in *Saccharomyces cerevisiae* identifies novel genes that affect endocytic protein trafficking. *Traffic*, *12*, 1592–1603.

Averesch, N. J., Winter, G., & Kromer, J. O. (2016). Production of *para*-aminobenzoic acid from different carbon-sources in engineered *Saccharomyces cerevisiae*. *Microbial Cell Factories*, *15*, 89. https://doi.org/10.1186/s12934-016-0485-8

Baker, E., Wang, B., Bellora, N., Peris, D., Hulfachor, A. B., Koshalek, J. A., … Hittinger, C. T. (2015). The genome sequence of *Saccharomyces eubayanus* and the domestication of lager-brewing yeasts. *Molecular Biology and Evolution*, *32*, 2818–2831.

Barbosa, R., Pontes, A., Santos, R. O., Montandon, G. G., de Ponzzes-Gomes, C. M., Morais, P. B., … Sampaio, J. P. (2018). Multiple rounds of artificial selection promote microbe secondary domestication—The case of cachaça yeasts. *Genome Biology and Evolution*, *10*, 1939–1955.

Bartholmes, P., Boker, H., & Jaenicke, R. (1979). Purification of tryptophan synthase from *Saccharomyces cerevisiae* and partial activity of its nicked subunits. *European Journal of Biochemistry*, *102*, 167–172.

Bauer, J. A., Bennett, E. M., Begley, T. P., & Ealick, S. E. (2004). Three-dimensional structure of YaaE from *Bacillus subtilis*, a glutaminase implicated in pyridoxal-5'-phosphate biosynthesis. *Journal of Biological Chemistry*, *279*, 2704–2711.

Becker, J. U., Wingender-Drissen, R., & Schiltz, E. (1983). Purification and properties of phosphorylase from baker's yeast. *Archives in Biochemistry and Biophysics*, *225*, 667–678.

Bedalov, A., Hirao, M., Posakony, J., Nelson, M., & Simon, J. A. (2003). NAD^+-dependent deacetylase Hst1p controls biosynthesis and cellular NAD^+ levels in *Saccharomyces cerevisiae*. *Molecular and Cellular Biology*, *23*, 7044–7054.

Behaghel, O., Rothman, S., & Schultze, W. (1928). Beziehungen zwischen selektiver Ultraviolett-Absorption mit chemischer Konstitution. *Strahlentherapie*, *28*, 110–114.

Belenky, P., Racette, F. G., Bogan, K. L., McClure, J. M., Smith, J. S., & Brenner, C. (2007). Nicotinamide riboside promotes Sir2 silencing and extends lifespan via Nrk and Urh1/Pnp1/Meu1 pathways to NAD^+. *Cell*, *129*, 473–484.

Berkovitch, F., Nicolet, Y., Wan, J. T., Jarrett, J. T., & Drennan, C. L. (2004). Crystal structure of biotin synthase, an S-adenosylmethionine-dependent radical enzyme. *Science*, *303*, 76–79.

Bieganowski, P., & Brenner, C. (2004). Discoveries of nicotinamide riboside as a nutrient and conserved *NRK* genes establish a Preiss-Handler independent route to NAD^+ in fungi and humans. *Cell*, *117*, 495–502.

Bornaes, C., Petersen, J. G., & Holmberg, S. (1992). Serine and threonine catabolism in *Saccharomyces cerevisiae*: The *CHA1* polypeptide is homologous with other serine and threonine dehydratases. *Genetics*, *131*, 531–539.

Boswell-Casteel, R. C., Johnson, J. M., Duggan, K. D., Roe-Zurz, Z., Schmitz, H., Burleson, C., & Hays, F. A. (2014). *FUN26* (function unknown now 26) protein from *Saccharomyces cerevisiae* is a broad selectivity, high affinity, nucleoside and nucleobase transporter. *Journal of Biological Chemistry*, *289*, 24440–24451.

Bracher, J. M., de Hulster, E., Koster, C. C., van den Broek, M., Daran, J. G., van Maris, A. J. A., & Pronk, J. T. (2017). Laboratory evolution of a biotin-requiring *Saccharomyces cerevisiae* strain for full biotin prototrophy and identification of causal mutations. *Applied and Environmental Microbiology*, *83*, 1–16.

Brachmann, C. B., Davies, A., Cost, G. J., Caputo, E., Li, J., Hieter, P., & Boeke, J. D. (1998). Designer deletion strains derived from *Saccharomyces cerevisiae* S288C: A useful set of strains and plasmids for PCR-mediated gene disruption and other applications. *Yeast*, *14*, 115–132.

Braus, G. H. (1991). Aromatic amino acid biosynthesis in the yeast *Saccharomyces cerevisiae*: A model system for the regulation of a eukaryotic biosynthetic pathway. *Microbiological Reviews*, *55*, 349–370.

Brown, G. M., Weisman, R. A., & Molnar, D. A. (1961). The biosynthesis of folic acid: I. Substrate and cofactor requirements for enzymatic synthesis by cell-free extracts of *Escherichia coli*. *Journal of Biological Chemistry*, *236*, 2534–2543.

Bruinenberg, P. M., van Dijken, J. P., & Scheffers, W. A. (1983). An enzymic analysis of NADPH production and consumption in *Candida utilis*. *Journal of General Microbiology*, *129*, 965–971.

Burkholder, P. R. (1943). Vitamin deficiencies in yeasts. *American Journal of Botany*, *30*, 206–211.

Burkholder, P. R., McVeigh, I., & Moyer, D. (1944). Studies on some growth factors of yeasts. *Journal of Bacteriology*, *48*, 385–391.

Bürkle, A. (2005). Poly (ADP-ribose). The most elaborate metabolite of NAD^+. *FEBS Journal*, *272*, 4576–4589.

Chatterjee, A., Abeydeera, N. D., Bale, S., Pai, P. J., Dorrestein, P. C., Russell, D. H., … Begley, T. P. (2011). *Saccharomyces cerevisiae* THI4p is a suicide thiamine thiazole synthase. *Nature*, *478*, 542–546.

Chatterjee, A., Jurgenson, C. T., Schroeder, F. C., Ealick, S. E., & Begley, T. P. (2007). Biosynthesis of thiamin thiazole in eukaryotes: Conversion of NAD to an advanced intermediate. *Journal of the American Chemical Society*, *129*, 2914–2922.

Chatterjee, A., Schroeder, F. C., Jurgenson, C. T., Ealick, S. E., & Begley, T. P. (2008). Biosynthesis of the thiamin-thiazole in eukaryotes: Identification of a thiazole tautomer intermediate. *Journal of the American Chemical Society*, *130*, 11394–11398.

Chini, E. N. (2009). CD38 as a regulator of cellular NAD: A novel potential pharmacological target for metabolic conditions. *Current Pharmaceutical Design*, *15*, 57–63.

Coleman, S. T., Fang, T. K., Rovinsky, S. A., Turano, F. J., & Moye-Rowley, W. S. (2001). Expression of a glutamate decarboxylase homologue is required for normal oxidative stress tolerance in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *276*, 244–250.

Combs, G. F. (2008). *The vitamins: Fundamental aspects in nutrition and health* (3rd ed.). Elsevier Academic Press.

Coquille, S., Roux, C., Fitzpatrick, T. B., & Thore, S. (2012). The last piece in the vitamin B1 biosynthesis puzzle: Structural and functional insight into yeast 4-amino-5-hydroxymethyl-2-methylpyrimidine phosphate (HMP-P) synthase. *Journal of Biological Chemistry*, *287*, 42333–42343.

Cronan, J. E. Jr., & Wallace, J. C. (1995). The gene encoding the biotin-apoprotein ligase of *Saccharomyces cerevisiae*. *FEMS Microbiology Letters*, *130*, 221–229.

Culbertson, M. R., Donahue, T. F., & Henry, S. A. (1976). Control of inositol biosynthesis in *Saccharomyces cerevisiae*; inositol-phosphate synthetase mutants. *Journal of Bacteriology*, *126*, 243–250.

Culver, G. M., McCraith, S. M., Consaul, S. A., Stanford, D. R., & Phizicky, E. M. (1997). A 2'-phosphotransferase implicated in tRNA splicing is essential in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *272*, 13203–13210.

Cutts, N. S., & Rainbow, C. (1950). Studies of a yeast exacting towards *para*-aminobenzoic acid. *Journal of General Microbiology*, *4*, 150–155.

Dahod, S. K., Greasham, R., & Kennedy, M. (2010). Raw materials selection and medium development for industrial fermentation processes. In *Manual of Industrial Microbiology and Biotechnology* (Third ed.) (pp. 659–668).

Dai, Y. N., Chi, C. B., Zhou, K., Cheng, W., Jiang, Y. L., Ren, Y. M., … Zhou, C. Z. (2013). Structure and catalytic mechanism of yeast 4-amino-4-deoxychorismate lyase. *Journal of Biological Chemistry*, *288*, 22985–22992.

Daignan-Fornier, B., & Fink, G. R. (1992). Coregulation of purine and histidine biosynthesis by the transcriptional activators *BAS1* and *BAS2*. *Proceedings of the National Academy of Sciences, USA*, *89*, 6746–6750.

de Kock, S. H., du Preez, J. C., & Kilian, S. G. (2000). The effect of vitamins and amino acids on glucose uptake in aerobic chemostat cultures of three *Saccharomyces cerevisiae* strains. *Systematic and Applied Microbiology*, *23*, 41–46.

Degols, G., Jauniaux, J. C., & Wiame, J. M. (1987). Molecular characterization of transposable-element-associated mutations that lead to constitutive L-ornithine aminotransferase expression in *Saccharomyces cerevisiae*. *European Journal of Biochemistry*, *165*, 289–296.

di Salvo, M. L., Contestabile, R., & Safo, M. K. (2011). Vitamin B6 salvage enzymes: Mechanism, structure and regulation. *Biochimica et Biophysica Acta*, *1814*, 1597–1608.

Dickinson, J. R., Lanterman, M. M., Danner, D. J., Pearson, B. M., Sanz, P., Harrison, S. J., & Hewlins, M. J. (1997). A ^{13}C nuclear magnetic resonance investigation of the metabolism of leucine to isoamyl alcohol in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *272*, 26871–26878.

Donahue, T. F., & Henry, S. A. (1981). myo-Inositol-1-phosphate synthase. Characteristics of the enzyme and identification of its structural gene in yeast. *Journal of Biological Chemistry*, *256*, 7077–7085.

Dong, Y. X., Sueda, S., Nikawa, J., & Kondo, H. (2004). Characterization of the products of the genes *SNO1* and *SNZ1* involved in pyridoxine synthesis in *Saccharomyces cerevisiae*. *European Journal of Biochemistry*, *271*, 745–752.

Duc, C., Pradal, M., Sanchez, I., Noble, J., Tesniere, C., & Blondin, B. (2017). A set of nutrient limitations trigger yeast cell death in a nitrogen-dependent manner during wine alcoholic fermentation. *PLoS ONE*, *12*, e0184838. https://doi.org/10.1371/journal.pone

Duff, S. M., Rydel, T. J., McClerren, A. L., Zhang, W., Li, J. Y., Sturman, E. J., … Evdokimov, A. (2012). The enzymology of alanine aminotransferase (AlaAT) isoforms from *Hordeum vulgare* and other organisms, and the HvAlaAT crystal structure. *Archives of Biochemistry and Biophysics*, *528*, 90–101.

Eastcott, E. V. (1928). Wildiers' bios—The isolation and identification of "bios I". *Journal of Physical Chemistry*, *32*, 1094–1111.

Eddy, S. R. (2011). Accelerated Profile HMM Searches. *PLoS Computational Biology*, *7*, e1002195. https://doi.org/10.1371/journal.pcbi.1002195

Eden, A., Simchen, G., & Benvenisty, N. (1996). Two yeast homologs of *ECA39*, a target for c-Myc regulation, code for cytosolic and mitochondrial branched-chain amino acid aminotransferases. *Journal of Biological Chemistry*, *271*, 20242–20245.

Elvehjem, C. A., Madden, R. J., Strong, F. M., & Woolley, D. W. (1938). The isolation and identification of the anti-black tongue factor. *Journal of Biological Chemistry*, *123*, 137–149.

Emery, W. B., McLeod, N., & Robinson, F. A. (1946). Comparative microbiological assays of members of the vitamin B complex in yeast and liver extracts. *Biochemical Journal*, *40*, 426–432.

Enjo, F., Nosaka, K., Ogata, M., Iwashima, A., & Nishimura, H. (1997). Isolation and characterization of a thiamin transport gene, *THI10*, from *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *272*, 19165–19170.

Falco, S. C., Dumas, K. S., & Livak, K. J. (1985). Nucleotide sequence of the yeast *ILV2* gene which encodes acetolactate synthase. *Nucleic Acids Research*, *13*, 4011–4027.

Funk, C. (1922). *The vitamines* (2nd ed.). Williams & Wilkins Company: Baltimore.

Garcia-Campusano, F., Anaya, V. H., Robledo-Arratia, L., Quezada, H., Hernandez, H., Riego, L., & Gonzalez, A. (2009). *ALT1*-encoded alanine aminotransferase plays a central role in the metabolism of alanine in *Saccharomyces cerevisiae*. *Canadian Journal of Microbiology*, *55*, 368–374.

Genbauffe, F. S., & Cooper, T. G. (1991). The urea amidolyase (*DUR1,2*) gene of *Saccharomyces cerevisiae*. *DNA Sequence*, *2*, 19–32.

Goffeau, A., Barrell, B. G., Bussey, H., Davis, R. W., Dujon, B., Feldmann, H., … Oliver, S. G. (1996). Life with 6000 genes. *Science*, *274*(546), 563–567.

Gowland Hopkins, F. (1906). The analyst and the medical man. *Analyst*, *31*, 385b–404b.

Greenberg, M. L., Reiner, B., & Henry, S. A. (1982). Regulatory mutations of inositol biosynthesis in yeast: isolation of inositol-excreting mutants. *Genetics*, *100*, 19–33.

Guthrie, C., & Fink, G. R. (1991). Getting started with yeast. *Methods in Enzymology*, *194*, 3–21.

Gyorgy, P., Melville, D. B., Burk, D., & V, D. U. V. (1940). The possible identity of vitamin H with biotin and coenzyme R. *Science*, *91*, 243–245.

Haas, A. L., Laun, N. P., & Begley, T. P. (2005). Thi20, a remarkable enzyme from *Saccharomyces cerevisiae* with dual thiamin biosynthetic and degradation activities. *Bioorganic Chemistry*, *33*, 338–344.

Hall, C., & Dietrich, F. S. (2007). The reacquisition of biotin prototrophy in *Saccharomyces cerevisiae* involved horizontal gene transfer, gene duplication and gene clustering. *Genetics*, *177*, 2293–2307.

Hancock, L. C., Behta, R. P., & Lopes, J. M. (2006). Genomic analysis of the Opi$^-$ phenotype. *Genetics*, *173*, 621–634.

Hanes, J. W., Burns, K. E., Hilmey, D. G., Chatterjee, A., Dorrestein, P. C., & Begley, T. P. (2008). Mechanistic studies on pyridoxal phosphate synthase: The reaction pathway leading to a chromophoric intermediate. *Journal of the American Chemical Society*, *130*, 3043–3052.

Hanscho, M., Ruckerbauer, D. E., Chauhan, N., Hofbauer, H. F., Krahulec, S., Nidetzky, B., … Natter, K. (2012). Nutritional

requirements of the BY series of *Saccharomyces cerevisiae* strains for optimum growth. *FEMS Yeast Research*, *12*, 796–808.

Hansen, J., & Johannesen, P. F. (2000). Cysteine is essential for transcriptional regulation of the sulfur assimilation genes in *Saccharomyces cerevisiae*. *Molecular and General Genetics*, *263*, 535–542.

Harris, S. A., & Folkers, K. (1939). Synthesis of vitamin B6. *Journal of the American Chemical Society*, *61*, 1245–1247.

Hazelwood, L. A., Daran, J. M., van Maris, A. J., Pronk, J. T., & Dickinson, J. R. (2008). The Ehrlich pathway for fusel alcohol production: A century of research on *Saccharomyces cerevisiae* metabolism. *Applied and Environmental Microbiology*, *74*, 2259–2266.

Henry, S. A., Gaspar, M. L., & Jesch, S. A. (2014). The response to inositol: regulation of glycerolipid metabolism and stress response signaling in yeast. *Chemistry and Physics of Lipids*, *180*, 23–43.

Henry, S. A., Kohlwein, S. D., & Carman, G. M. (2012). Metabolism and regulation of glycerolipids in the yeast *Saccharomyces cerevisiae*. *Genetics*, *190*, 317–349.

Hilger, F., & Mortimer, R. K. (1980). Genetic mapping of *ARG1* and *ARG8* in *Saccharomyces cerevisiae* by trisomic analysis combined with interallelic complementation. *Journal of Bacteriology*, *141*, 270–274.

Hohmann, S. (1991). Characterization of *PDC6*, a third structural gene for pyruvate decarboxylase in *Saccharomyces cerevisiae*. *Journal of Bacteriology*, *173*, 7963–7969.

Hohmann, S. (1993). Characterisation of *PDC2*, a gene necessary for high level expression of pyruvate decarboxylase structural genes in *Saccharomyces cerevisiae*. *Molecular and General Genetics*, *241*, 657–666.

Hohmann, S., & Cederberg, H. (1990). Autoregulation may control the expression of yeast pyruvate decarboxylase structural genes *PDC1* and *PDC5*. *European Journal of Biochemistry*, *188*, 615–621.

Hohmann, S., & Meacock, P. A. (1998). Thiamin metabolism and thiamin diphosphate-dependent enzymes in the yeast *Saccharomyces cerevisiae*: genetic regulation. *Biochimica et Biophysica Acta*, *1385*, 201–219.

Hoja, U., Marthol, S., Hofmann, J., Stegner, S., Schulz, R., Meier, S., … Schweizer, E. (2004). *HFA1* encoding an organelle-specific acetyl-CoA carboxylase controls mitochondrial fatty acid synthesis in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *279*, 21779–21786.

Hoja, U., Wellein, C., Greiner, E., & Schweizer, E. (1998). Pleiotropic phenotype of acetyl-CoA-carboxylase-defective yeast cells—Viability of a *BPL1*-amber mutation depending on its readthrough by normal tRNA (Gln)(CAG). *European Journal of Biochemistry*, *254*, 520–526.

Holt, S., Cordente, A. G., Williams, S. J., Capone, D. L., Jitjaroen, W., Menz, I. R., … Anderson, P. A. (2011). Engineering *Saccharomyces cerevisiae* to release 3-Mercaptohexan-1-ol during fermentation through overexpression of an *S. cerevisiae* gene, *STR3*, for improvement of wine aroma. *Applied and Environmental Microbiology*, *77*, 3626–3632.

Hughes, A. L., Hughes, C. E., Henderson, K. A., Yazvenko, N., & Gottschling, D. E. (2016). Selective sorting and destruction of mitochondrial membrane proteins in aged yeast. *eLife*, *5*. https://doi.org/10.7554/eLife.13943

Ito, T., Hemmi, H., Kataoka, K., Mukai, Y., & Yoshimura, T. (2008). A novel zinc-dependent D-serine dehydratase from *Saccharomyces cerevisiae*. *Biochemical Journal*, *409*, 399–406.

James Theoga Raj, C., Croft, T., Venkatakrishnan, P., Groth, B., Dhugga, G., Cater, T., & Lin, S. J. (2019). The copper-sensing transcription factor Mac1, the histone deacetylase Hst1, and nicotinic acid regulate *de novo* NAD^+ biosynthesis in budding yeast. *Journal of Biological Chemistry*, *294*, 5562–5575.

Jansen, B. C. P., & Donath, W. F. (1926). On the isolation of the anti-beriberi vitamin. *Proceedings of the Koninklijke Akademie Van Wetenschappen Te Amsterdam*, *29*, 1390–1400.

Jansen, M. L. A., Bracher, J. M., Papapetridis, I., Verhoeven, M. D., de Bruijn, H., de Waal, P. P., … Pronk, J. T. (2017). *Saccharomyces cerevisiae* strains for second-generation ethanol production: From academic exploration to industrial implementation. *FEMS Yeast Research*, *17*, fox04. https://doi.org/10.1093/femsyr/fox044

Jarrett, J. T. (2005). The novel structure and chemistry of iron-sulfur clusters in the adenosylmethionine-dependent radical enzyme biotin synthase. *Archives in Biochemistry and Biophysics*, *433*, 312–321.

Jelier, R., Semple, J. I., Garcia-Verdugo, R., & Lehner, B. (2011). Predicting phenotypic variation in yeast from individual genome sequences. *Nature Genetics*, *43*, 1270–1274.

Jhee, K. H., McPhie, P., & Miles, E. W. (2000). Domain architecture of the heme-independent yeast cystathionine β-synthase provides insights into mechanisms of catalysis and regulation. *Biochemistry*, *39*, 10548–10556.

Karassevitch, Y., & Robichon-Szulmajster, H. (1972). Reversible dissociation of threonine deaminase in an *ilvl* mutant of *Saccharomyces cerevisiae*. *Molecular and General Genetics*, *117*, 113–123.

Karsten, W. E., Reyes, Z. L., Bobyk, K. D., Cook, P. F., & Chooback, L. (2011). Mechanism of the aromatic aminotransferase encoded by the *ARO8* gene from *Saccharomyces cerevisiae*. *Archives in Biochemistry and Biophysics*, *516*, 67–74.

Kato, M., & Lin, S. J. (2014). Regulation of NAD^+ metabolism, signaling and compartmentalization in the yeast *Saccharomyces cerevisiae*. *DNA Repair*, *23*, 49–58.

Kawai, S., Suzuki, S., Mori, S., & Murata, K. (2001). Molecular cloning and identification of *UTR1* of a yeast *Saccharomyces cerevisiae* as a gene encoding an NAD kinase. *FEMS Microbiology Letters*, *200*, 181–184.

Kawasaki, Y., Onozuka, M., Mizote, T., & Nosaka, K. (2005). Biosynthesis of hydroxymethylpyrimidine pyrophosphate in *Saccharomyces cerevisiae*. *Current Genetics*, *47*, 156–162.

Keresztesy, J. C., & Stevens, J. R. (1938). Vitamin B6. *Journal of the American Chemical Society*, *60*, 1267–1268.

Kim, H. S., Hoja, U., Stolz, J., Sauer, G., & Schweizer, E. (2004). Identification of the tRNA-binding protein Arc1p as a novel target of *in vivo* biotinylation in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *279*, 42445–42452.

Klebl, F., Zillig, M., & Sauer, N. (2000). Transcription of the yeast *TNA1* gene is not only regulated by nicotinate but also by *p*-aminobenzoate. *FEBS Letters*, *481*, 86–87.

Knijnenburg, T. A., Daran, J. M., van den Broek, M. A., Daran-Lapujade, P. A., de Winde, J. H., Pronk, J. T., … Wessels, L. F. (2009). Combinatorial effects of environmental parameters on transcriptional regulation in *Saccharomyces cerevisiae*: A quantitative analysis of a compendium of chemostat-based transcriptome data. *BMC Genomics*, *10*, 53. https://doi.org/10.1186/1471-2164-10-53

Knijnenburg, T. A., de Winde, J. H., Daran, J. M., Daran-Lapujade, P., Pronk, J. T., Reinders, M. J., & Wessels, L. F. (2007). Exploiting combinatorial cultivation conditions to infer transcriptional regulation. *BMC Genomics*, *8*, 25. https://doi.org/10.1186/1471-2164-8-25

Kochetov, G., & Sevostyanova, I. A. (2005). Binding of the coenzyme and formation of the transketolase active center. *IUBMB Life*, *57*, 491–497.

Kogl, F., & Kostermans, D. G. F. B. (1935). The consitutition-specificity of the hetero-auxins. 16. Announcement on the plant growth materials. *Hoppe-Seylers Zeitschrift Fur Physiologische Chemie*, *235*, 201–216.

Lai, R. Y., Huang, S., Fenwick, M. K., Hazra, A., Zhang, Y., Rajashankar, K., … Begley, T. P. (2012). Thiamin pyrimidine biosynthesis in *Candida albicans*: A remarkable reaction between histidine and pyridoxal phosphate. *Journal of the American Chemical Society*, *134*, 9157–9159.

Lardy, H. A., Potter, R. L., & Harris, R. H. (1949). Metabolic functions of biotin; the role of biotin in bicarbonate utilization by *Lactobacillus arabinosus* studied with ^{14}C. *Journal of Biological Chemistry*, *179*, 721–731.

Laurenson, P., & Rine, J. (1991). *SUM1-1*: a suppressor of silencing defects in *Saccharomyces cerevisiae*. *Genetics*, *129*, 685–696.

Lepkovsky, S. (1938). Crystalline Factor I. *Science*, *87*, 169–170.

Li, M., Petteys, B. J., McClure, J. M., Valsakumar, V., Bekiranov, S., Frank, E. L., & Smith, J. S. (2010). Thiamine biosynthesis in

Saccharomyces cerevisiae is regulated by the NAD^+-dependent histone deacetylase Hst1. *Molecular and Cellular Biology*, *30*, 3329–3341.

Lin, S. J., & Guarente, L. (2003). Nicotinamide adenine dinucleotide, a metabolic regulator of transcription, longevity and disease. *Current Opinion in Cell Biology*, *15*, 241–246.

Liti, G., Nguyen Ba, A. N., Blythe, M., Muller, C. A., Bergstrom, A., Cubillos, F. A., … Nieduszynski, C. A. (2013). High quality *de novo* sequencing and assembly of the *Saccharomyces arboricolus* genome. *BMC Genomics*, *14*, 69. https://doi.org/10.1186/1471-2164-14-69

Liu, J. Q., Nagata, S., Dairi, T., Misono, H., Shimizu, S., & Yamada, H. (1997). The *GLY1* gene of *Saccharomyces cerevisiae* encodes a low-specific L-threonine aldolase that catalyzes cleavage of L-allo-threonine and L-threonine to glycine—expression of the gene in *Escherichia coli* and purification and characterization of the enzyme. *European Journal of Biochemistry*, *245*, 289–293.

Llorente, B., & Dujon, B. (2000). Transcriptional regulation of the *Saccharomyces cerevisiae DAL5* gene family and identification of the high affinity nicotinic acid permease *TNA1* (YGR260w). *FEBS Letters*, *475*, 237–241.

Loubbardi, A., Marcireau, C., Karst, F., & Guilloton, M. (1995). Sterol uptake induced by an impairment of pyridoxal phosphate synthesis in *Saccharomyces cerevisiae*: Cloning and sequencing of the *PDX3* gene encoding pyridoxine (pyridoxamine) phosphate oxidase. *Journal of Bacteriology*, *177*, 1817–1823.

Lu, S. P., & Lin, S. J. (2010). Regulation of yeast sirtuins by NAD^+ metabolism and calorie restriction. *Biochimica et Biophysica Acta*, *1804*, 1567–1575.

Lu, S. P., & Lin, S. J. (2011). Phosphate-responsive signaling pathway is a novel component of NAD^+ metabolism in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *286*, 14271–14281.

Lussier, M., White, A. M., Sheraton, J., di Paolo, T., Treadwell, J., Southard, S. B., … Bussey, H. (1997). Large scale identification of genes involved in cell surface biosynthesis and architecture in *Saccharomyces cerevisiae*. *Genetics*, *147*, 435–450.

Luttik, M. A., Vuralhan, Z., Suir, E., Braus, G. H., Pronk, J. T., & Daran, J. M. (2008). Alleviation of feedback inhibition in *Saccharomyces cerevisiae* aromatic amino acid biosynthesis: Quantification of metabolic impact. *Metabolic Engineering*, *10*, 141–153.

Lynd, L. R. (1996). Overview and evaluation of fuel ethanol from cellulosic biomass: Technology, economics, the environment, and policy. *Annual Review of Energy and the Environment*, *21*, 403–465.

Machado, C. R., Praekelt, U. M., de Oliveira, R. C., Barbosa, A. C., Byrne, K. L., Meacock, P. A., & Menck, C. F. (1997). Dual role for the yeast *THI4* gene in thiamine biosynthesis and DNA damage tolerance. *Journal of Molecular Biology*, *273*, 114–121.

Mackie, B. S., & Mackie, L. E. (1999). The PABA story. *Australasian Journal of Dermatology*, *40*, 51–53.

Manandhar, M., & Cronan, J. E. (2017). Pimelic acid, the first precursor of the *Bacillus subtilis* biotin synthesis pathway, exists as the free acid and is assembled by fatty acid synthesis. *Molecular Microbiology*, *104*, 595–607.

Mans, R., Daran, J. G., & Pronk, J. T. (2018). Under pressure: Evolutionary engineering of yeast strains for improved performance in fuels and chemicals production. *Current Opinion in Biotechnology*, *50*, 47–56.

Marbois, B., Xie, L. X., Choi, S., Hirano, K., Hyman, K., & Clarke, C. F. (2010). *para*-Aminobenzoic acid is a precursor in coenzyme Q6 biosynthesis in *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *285*, 27827–27838.

McCord, R., Pierce, M., Xie, J., Wonkatal, S., Mickel, C., & Vershon, A. K. (2003). Rfm1, a novel tethering factor required to recruit the Hst1 histone deacetylase for repression of middle sporulation genes. *Molecular and Cellular Biology*, *23*, 2009–2016.

Melcher, K., Rose, M., Kunzler, M., Braus, G. H., & Entian, K. D. (1995). Molecular analysis of the yeast *SER1* gene encoding 3-phosphoserine aminotransferase: Regulation by general control and serine repression. *Current Genetics*, *27*, 501–508.

Messerschmidt, A., Worbs, M., Steegborn, C., Wahl, M. C., Huber, R., Laber, B., & Clausen, T. (2003). Determinants of enzymatic specificity in the Cys-Met-metabolism PLP-dependent enzymes family: crystal structure of cystathionine γ-lyase from yeast and intrafamiliar structure comparison. *Biological Chemistry*, *384*, 373–386.

Mieczkowski, P. A., Dominska, M., Buck, M. J., Gerton, J. L., Lieb, J. D., & Petes, T. D. (2006). Global analysis of the relationship between the binding of the Bas1p transcription factor and meiosis-specific double-strand DNA breaks in *Saccharomyces cerevisiae*. *Molecular and Cellular Biology*, *26*, 1014–1027.

Miran, S. G., Lawson, J. E., & Reed, L. J. (1993). Characterization of *PDH* β1, the structural gene for the pyruvate dehydrogenase β-subunit from *Saccharomyces cerevisiae*. *Proceedings of the national Academy of Sciences, USA*, *90*, 1252–1256.

Mishina, M., Roggenkamp, R., & Schweizer, E. (1980). Yeast mutants defective in acetyl-coenzyme A carboxylase and biotin: Apocarboxylase ligase. *European Journal of Biochemistry*, *111*, 79–87.

Mojzita, D., & Hohmann, S. (2006). Pdc2 coordinates expression of the *THI* regulon in the yeast *Saccharomyces cerevisiae*. *Molecular Genetics and Genomics*, *276*, 147–161.

Morin, P. J., Subramanian, G. S., & Gilmore, T. D. (1992). *AAT1*, a gene encoding a mitochondrial aspartate aminotransferase in *Saccharomyces cerevisiae*. *Biochimica et Biophysica Acta*, *1171*, 211–214.

Morris, C. P., Lim, F., & Wallace, J. C. (1987). Yeast pyruvate carboxylase: gene isolation. *Biochemical and Biophysical Research Communications*, *145*, 390–396.

Muller, E. H., Richards, E. J., Norbeck, J., Byrne, K. L., Karlsson, K. A., Pretorius, G. H., … Hohmann, S. (1999). Thiamine repression and pyruvate decarboxylase autoregulation independently control the expression of the *Saccharomyces cerevisiae PDC5* gene. *FEBS Letters*, *449*, 245–250.

Muller, I. B., Bergmann, B., Groves, M. R., Couto, I., Amaral, L., Begley, T. P., … Wrenger, C. (2009). The vitamin B1 metabolism of *Staphylococcus aureus* is controlled at enzymatic and transcriptional levels. *PLoS ONE*, *4*, e7656. https://doi.org/10.1371/journal.pone.0007656

Murray, M., & Greenberg, M. L. (2000). Expression of yeast *INM1* encoding inositol monophosphatase is regulated by inositol, carbon source and growth stage and is decreased by lithium and valproate. *Molecular Microbiology*, *36*, 651–661.

Nakamura, K. D., Trewyn, R. W., & Parks, L. W. (1973). Purification and characterization of serine transhydroxy-methylase from *Saccharomyces cerevisiae*. *Biochimica et Biophysica Acta*, *327*, 328–335.

Naseeb, S., James, S. A., Alsammar, H., Michaels, C. J., Gini, B., Nueno-Palop, C., … Delneri, D. (2017). *Saccharomyces jurei* sp. nov., isolation and genetic identification of a novel yeast species from *Quercus robur*. *International Journal of Systematic and Evolutionary Microbiology*, *67*, 2046–2052.

Natarajan, K., Meyer, M. R., Jackson, B. M., Slade, D., Roberts, C., Hinnebusch, A. G., & Marton, M. J. (2001). Transcriptional profiling shows that Gcn4p is a master regulator of gene expression during amino acid starvation in yeast. *Molecular and Cellular Biology*, *21*, 4347–4368.

Nemeria, N. S., Chakraborty, S., Balakrishnan, A., & Jordan, F. (2009). Reaction mechanisms of thiamin diphosphate enzymes: Defining states of ionization and tautomerization of the cofactor at individual steps. *FEBS Journal*, *276*, 2432–2446.

Nijkamp, J. F., van den Broek, M., Datema, E., de Kok, S., Bosman, L., Luttik, M. A., … Daran, J. M. (2012). *De novo* sequencing, assembly and analysis of the genome of the laboratory strain *Saccharomyces*

cerevisiae CEN.PK113-7D, a model for modern industrial biotechnology. *Microbial Cell Factories*, *11*, 36. https://doi.org/10.1186/1475-2859-11-36

Nishimura, H., Kawasaki, Y., Kaneko, Y., Nosaka, K., & Iwashima, A. (1992a). Cloning and characteristics of a positive regulatory gene, *THI2* (*PHO6*), of thiamin biosynthesis in *Saccharomyces cerevisiae*. *FEBS Letters*, *297*, 155–158.

Nishimura, H., Kawasaki, Y., Kaneko, Y., Nosaka, K., & Iwashima, A. (1992b). A positive regulatory gene, *THI3*, is required for thiamine metabolism in *Saccharomyces cerevisiae*. *Journal of Bacteriology*, *174*, 4701–4706.

Nishimura, H., Kawasaki, Y., Nosaka, K., Kaneko, Y., & Iwashima, A. (1991). A constitutive thiamine metabolism mutation, thi80, causing reduced thiamine pyrophosphokinase activity in *Saccharomyces cerevisiae*. *Journal of Bacteriology*, *173*, 2716–2719.

Nosaka, K. (2006). Recent progress in understanding thiamin biosynthesis and its genetic regulation in *Saccharomyces cerevisiae*. *Applied Microbiology and Biotechnology*, *72*, 30–40.

Nosaka, K., Kaneko, Y., Nishimura, H., & Iwashima, A. (1989). A possible role for acid phosphatase with thiamin-binding activity encoded by *PHO3* in yeast. *FEMS Microbiology Letters*, *51*, 55–59.

Nosaka, K., Onozuka, M., Konno, H., Kawasaki, Y., Nishimura, H., Sano, M., & Akaji, K. (2005). Genetic regulation mediated by thiamin pyrophosphate-binding motif in *Saccharomyces cerevisiae*. *Molecular Microbiology*, *58*, 467–479.

Notzel, C., Lingner, T., Klingenberg, H., & Thoms, S. (2016). Identification of new fungal peroxisomal matrix proteins and revision of the *PTS1* consensus. *Traffic*, *17*, 1110–1124.

Ohsugi, M., & Imanishi, Y. (1985). Microbiological activity of biotin-vitamers. *Journal of Nutritional Science and Vitaminology (Tokyo)*, *31*, 563–572.

Olzhausen, J., Schubbe, S., & Schuller, H. J. (2009). Genetic analysis of coenzyme A biosynthesis in the yeast *Saccharomyces cerevisiae*: Identification of a conditional mutation in the pantothenate kinase gene *CAB1*. *Current Genetics*, *55*, 163–173.

Padilla, P. A., Fuge, E. K., Crawford, M. E., Errett, A., & Werner-Washburne, M. (1998). The highly conserved, coregulated *SNO* and *SNZ* gene families in *Saccharomyces cerevisiae* respond to nutrient limitation. *Journal of Bacteriology*, *180*, 5718–5726.

Pandey, A., Golla, R., Yoon, H., Dancis, A., & Pain, D. (2012). Persulfide formation on mitochondrial cysteine desulfurase: Enzyme activation by a eukaryote-specific interacting protein and Fe-S cluster synthesis. *Biochemical Journal*, *448*, 171–187.

Panozzo, C., Nawara, M., Suski, C., Kucharczyka, R., Skoneczny, M., Becam, A. M., … Herbert, C. J. (2002). Aerobic and anaerobic NAD^+ metabolism in *Saccharomyces cerevisiae*. *FEBS Letters*, *517*, 97–102.

Parsot, C. (1986). Evolution of biosynthetic pathways: A common ancestor for threonine synthase, threonine dehydratase and D-serine dehydratase. *EMBO Journal*, *5*, 3013–3019.

Patil, K. R., & Nielsen, J. (2005). Uncovering transcriptional regulation of metabolism by using metabolic network topology. *Proceedings of the national Academy of Sciences, USA*, *102*, 2685–2689.

Paxhia, M. D., & Downs, D. M. (2019). *SNZ3* encodes a PLP synthase involved in thiamine synthesis in *Saccharomyces cerevisiae*. *Genes|Genomes|Genetics (Bethesda)*, *9*, 335–344.

Perry, D. K. (2002). Serine palmitoyltransferase: Role in apoptotic *de novo* ceramide synthesis and other stress responses. *Biochimica et Biophysica Acta*, *1585*, 146–152.

Phalip, V., Kuhn, I., Lemoine, Y., & Jeltsch, J. M. (1999). Characterization of the biotin biosynthesis pathway in *Saccharomyces cerevisiae* and evidence for a cluster containing *BIO5*, a novel gene involved in vitamer uptake. *Gene*, *232*, 43–51.

Pierrel, F., Hamelin, O., Douki, T., Kieffer-Jaquinod, S., Muhlenhoff, U., Ozeir, M., … Fontecave, M. (2010). Involvement of mitochondrial ferredoxin and *para*-aminobenzoic acid in yeast coenzyme Q biosynthesis. *Chemical Biology*, *17*, 449–459.

Pinson, B., Ceschin, J., Saint-Marc, C., & Daignan-Fornier, B. (2019). Dual control of NAD^+ synthesis by purine metabolites in yeast. *eLife*, *8*. https://doi.org/10.7554/eLife.43808

Pirner, H. M., & Stolz, J. (2006). Biotin sensing in *Saccharomyces cerevisiae* is mediated by a conserved DNA element and requires the activity of biotin-protein ligase. *Journal of Biological Chemistry*, *281*, 12381–12389.

Pittet, M., & Conzelmann, A. (2007). Biosynthesis and function of GPI proteins in the yeast *Saccharomyces cerevisiae*. *Biochimica et Biophysica Acta*, *1771*, 405–420.

Ponomarova, O., Gabrielli, N., Sevin, D. C., Mulleder, M., Zirngibl, K., Bulyha, K., … Patil, K. R. (2017). Yeast creates a niche for symbiotic lactic acid bacteria through nitrogen overflow. *Cell Systems*, *5*, 345–357 e6.

Potvin, J., Fonchy, E., Conway, J., & Champagne, C. P. (1997). An automatic turbidimetric method to screen yeast extracts as fermentation nutrient ingredients. *Journal of Microbiological Methods*, *29*, 153–160.

Praekelt, U. M., Byrne, K. L., & Meacock, P. A. (1994). Regulation of *THI4* (*MOL1*), a thiamine-biosynthetic gene of *Saccharomyces cerevisiae*. *Yeast*, *10*, 481–490.

Preiss, J., & Handler, P. (1957). Enzymatic synthesis of nicotinamide mononucleotide. *Journal of Biological Chemistry*, *225*, 759–770.

Preiss, J., & Handler, P. (1958). Biosynthesis of diphosphopyridine nucleotide. I. Identification of intermediates. *Journal of Biological Chemistry*, *233*, 488–492.

Pronk, J. T. (2002). Auxotrophic yeast strains in fundamental and applied research. *Applied and Environmental Microbiology*, *68*, 2095–2100.

Raschle, T., Amrhein, N., & Fitzpatrick, T. B. (2005). On the two components of pyridoxal 5'-phosphate synthase from *Bacillus subtilis*. *Journal of Biological Chemistry*, *280*, 32291–32300.

Repetto, B., & Tzagoloff, A. (1989). Structure and regulation of *KGD1*, the structural gene for yeast α-ketoglutarate dehydrogenase. *Molecular and Cellular Biology*, *9*, 2695–2705.

Rodriguez-Navarro, S., Llorente, B., Rodriguez-Manzaneque, M. T., Ramne, A., Uber, G., Marchesan, D., … Perez-Ortin, J. E. (2002). Functional analysis of yeast gene families involved in metabolism of vitamins B1 and B6. *Yeast*, *19*, 1261–1276.

Rogosa, M. (1944). Vitamin requirements of lactose-fermenting and certain other yeasts. *Journal of Bacteriology*, *47*, 159–170.

Romagnoli, G., Luttik, M. A., Kotter, P., Pronk, J. T., & Daran, J. M. (2012). Substrate specificity of thiamine pyrophosphate-dependent 2-oxo-acid decarboxylases in *Saccharomyces cerevisiae*. *Applied and Environmental Microbiology*, *78*, 7538–7548.

Roon, R. J., Hampshire, J., & Levenberg, B. (1972). Urea amidolyase. The involvement of biotin in urea cleavage. *Journal of Biological Chemistry*, *247*, 7539–7545.

Rosenfeld, E., & Beauvoit, B. (2003). Role of the non-respiratory pathways in the utilization of molecular oxygen by *Saccharomyces cerevisiae*. *Yeast*, *20*, 1115–1144.

Rothman, S. (1926). Die Beeinflussung der Lichentzündung und der Pigmentierung durch Novokain-Einspritzungen. *Strahlentherapie*, *22*, 729–735.

Rothman, S., & Rubin, J. (1942). Sunburn and *para*-aminobenzoic acid. *Journal of Investigative Dermatology*, *5*, 445–457.

Rusche, L. N., Kirchmaier, A. L., & Rine, J. (2003). The establishment, inheritance, and function of silenced chromatin in *Saccharomyces cerevisiae*. *Annual Review of Biochemistry*, *72*, 481–516.

Saba, J. D., Nara, F., Bielawska, A., Garrett, S., & Hannun, Y. A. (1997). The *BST1* gene of *Saccharomyces cerevisiae* is the sphingosine-1-phosphate lyase. *Journal of Biological Chemistry*, *272*, 26087–26090.

Salazar, A. N., Gorter de Vries, A. R., van den Broek, M., Wijsman, M., de la Torre Cortes, P., Brickwedde, A., … Abeel, T. (2017). Nanopore sequencing enables near-complete *de novo* assembly of *Saccharomyces*

cerevisiae reference strain CEN.PK113-7D. *FEMS Yeast Research*, *17*, fox074. https://doi.org/10.1093/femsyr/fox074

Scannell, D. R., Zill, O. A., Rokas, A., Payen, C., Dunham, M. J., Eisen, M. B., … Hittinger, C. T. (2011). The awesome power of yeast evolutionary genetics: New genome sequences and strain resources for the *Saccharomyces sensu stricto* genus. *Genes|Genomes|Genetics (Bethesda)*, *1*, 11–25.

Schaaff-Gerstenschlager, I., Mannhaupt, G., Vetter, I., Zimmermann, F. K., & Feldmann, H. (1993). *TKL2*, a second transketolase gene of *Saccharomyces cerevisiae*. Cloning, sequence and deletion analysis of the gene. *European Journal of Biochemistry*, *217*, 487–492.

Schadeweg, V., & Boles, E. (2016). Increasing n-butanol production with *Saccharomyces cerevisiae* by optimizing acetyl-CoA synthesis, NADH levels and trans-2-enoyl-CoA reductase expression. *Biotechnology for Biofuels*, *9*, 257. https://doi.org/10.1186/s13068-016-0673-0

Schmitt, H. D., Ciriacy, M., & Zimmermann, F. K. (1983). The synthesis of yeast pyruvate decarboxylase is regulated by large variations in the messenger RNA level. *Molecular and General Genetics*, *192*, 247–252.

Schultz, A. S., Atkin, L., & Frey, C. N. (1939). Vitamin B6 a growth promoting factor for yeast. *Journal of the American Chemical Society*, *61*, 1931–1931.

Shakoury-Elizeh, M., Tiedeman, J., Rashford, J., Ferea, T., Demeter, J., Garcia, E., … Philpott, C. C. (2004). Transcriptional remodeling in response to iron deprivation in *Saccharomyces cerevisiae*. *Molecular Biology of the Cell*, *15*, 1233–1243.

Sherman, F., Fink, G. R., & Hicks, J. (1987). *Methods in yeast genetics: A laboratory course manual*. Cold Spring Harbor: Cold Spring Harbor Laboratory Press.

Sinclair, D. A., Hong, S. P., & Dawes, I. W. (1996). Specific induction by glycine of the gene for the P-subunit of glycine decarboxylase from *Saccharomyces cerevisiae*. *Molecular Microbiology*, *19*, 611–623.

Skinner, K. A., & Leathers, T. D. (2004). Bacterial contaminants of fuel ethanol production. *Journal of Industrial Microbiology and Biotechnology*, *31*, 401–408.

Snoek, I. S., & Steensma, H. Y. (2006). Why does *Kluyveromyces lactis* not grow under anaerobic conditions? Comparison of essential anaerobic genes of *Saccharomyces cerevisiae* with the *Kluyveromyces lactis* genome. *FEMS Yeast Research*, *6*, 393–403.

Steyer, D., Ambroset, C., Brion, C., Claudel, P., Delobel, P., Sanchez, I., … Legras, J. L. (2012). QTL mapping of the production of wine aroma compounds by yeast. *BMC Genomics*, *13*, 573. https://doi.org/10.1186/1471-2164-13-573

Stolz, J., Hoja, U., Meier, S., Sauer, N., & Schweizer, E. (1999). Identification of the plasma membrane H^+-biotin symporter of *Saccharomyces cerevisiae* by rescue of a fatty acid-auxotrophic mutant. *Journal of Biological Chemistry*, *274*, 18741–18746.

Stolz, J., & Vielreicher, M. (2003). Tpn1p, the plasma membrane vitamin B6 transporter of *Saccharomyces cerevisiae*. *Journal of Biological Chemistry*, *278*, 18990–18996.

Subramanian, M., Qiao, W. B., Khanam, N., Wilkins, O., Der, S. D., Lalich, J. D., & Bognar, A. L. (2005). Transcriptional regulation of the one-carbon metabolism regulon in *Saccharomyces cerevisiae* by Bas1p. *Molecular Microbiology*, *57*, 53–69.

Sugama, S. (1965). Sake brewery yeast (II): Requirement of pantothenic acid in a medium containing inorganic nitrogen source. *Journal of the Brewing Society of Japan*, *60*, 453–456.

Suomi, F., Menger, K. E., Monteuuis, G., Naumann, U., Kursu, V. A., Shvetsova, A., & Kastaniotis, A. J. (2014). Expression and evolution of the non-canonically translated yeast mitochondrial acetyl-CoA carboxylase Hfa1p. *PLoS ONE*, *9*, e114738. https://doi.org/10.1371/journal.pone.0114738

Takada, Y., & Noguchi, T. (1985). Characteristics of alanine: glyoxylate aminotransferase from *Saccharomyces cerevisiae*, a regulatory enzyme in the glyoxylate pathway of glycine and serine biosynthesis from tricarboxylic acid-cycle intermediates. *Biochemical Journal*, *231*, 157–163.

Tanaka, K., Tazuya, K., Yamada, K., & Kumaoka, H. (2000). Biosynthesis of thiamin under anaerobic conditions in *Saccharomyces cerevisiae*. *Biological & Pharmaceutical Bulletin*, *23*, 108–111.

Tempel, W., Rabeh, W. M., Bogan, K. L., Belenky, P., Wojcik, M., Seidle, H. F., … Brenner, C. (2007). Nicotinamide riboside kinase structures reveal new pathways to NAD^+. *PLoS Biology*, *5*, e263. https://doi.org/10.1371/journal.pbio.0050263

Tice-Baldwin, K., Fink, G. R., & Arndt, K. T. (1989). *BAS1* has a Myb motif and activates *HIS4* transcription only in combination with *BAS2*. *Science*, *246*, 931–935.

Tyagi, A. K., Tabor, C. W., & Tabor, H. (1981). Ornithine decarboxylase from *Saccharomyces cerevisiae*. Purification, properties, and regulation of activity. *Journal of Biological Chemistry*, *256*, 12156–12163.

Verduyn, C., Postma, E., Scheffers, W. A., & Van Dijken, J. P. (1992). Effect of benzoic acid on metabolic fluxes in yeasts: A continuous-culture study on the regulation of respiration and alcoholic fermentation. *Yeast*, *8*, 501–517.

Voet, D., Voet, J. G., & Pratt, C. W. (2006). *Fundamentals of biochemistry life at the molecular level*. Hoboken, NJ: John Wiley and Sons.

Volland, C., & Felix, F. (1984). Isolation and properties of 5-aminolevulinate synthase from the yeast *Saccharomyces cerevisiae*. *European Journal of Biochemistry*, *142*, 551–557.

Vuralhan, Z., Luttik, M. A., Tai, S. L., Boer, V. M., Morais, M. A., Schipper, D., … Pronk, J. T. (2005). Physiological characterization of the *ARO10*-dependent, broad-substrate-specificity 2-oxo acid decarboxylase activity of *Saccharomyces cerevisiae*. *Applied and Environmental Microbiology*, *71*, 3276–3284.

Vuralhan, Z., Morais, M. A., Tai, S. L., Piper, M. D., & Pronk, J. T. (2003). Identification and characterization of phenylpyruvate decarboxylase genes in *Saccharomyces cerevisiae*. *Applied and Environmental Microbiology*, *69*, 4534–4541.

Wada, M., Nakamori, S., & Takagi, H. (2003). Serine racemase homologue of *Saccharomyces cerevisiae* has L-threo-3-hydroxyaspartate dehydratase activity. *FEMS Microbiology Letters*, *225*, 189–193.

Wakil, S. J., Titchener, E. B., & Gibson, D. M. (1958). Evidence for the participation of biotin in the enzymic synthesis of fatty acids. *Biochimica et Biophysica Acta*, *29*, 225–226.

Walker, M. E., Val, D. L., Rohde, M., Devenish, R. J., & Wallace, J. C. (1991). Yeast pyruvate carboxylase: Identification of two genes encoding isoenzymes. *Biochemical and Biophysical Research Communications*, *176*, 1210–1217.

Weider, M., Machnik, A., Klebl, F., & Sauer, N. (2006). Vhr1p, a new transcription factor from budding yeast, regulates biotin-dependent expression of *VHT1* and *BIO5*. *Journal of Biological Chemistry*, *281*, 13513–13524.

Weiss, S., & Wilkins, R. W. (1937). The nature of the cardiovascular disturbances in nutritional deficiency states (beriberi). *Annals of Internal Medicine*, *11*, 104–148.

White, M. J., Lopes, J. M., & Henry, S. A. (1991). Inositol metabolism in yeasts. *Advances in Microbial Physiology*, *32*, 1–51.

White, W. H., Gunyuzlu, P. L., & Toyn, J. H. (2001). *Saccharomyces cerevisiae* is capable of *de novo* pantothenic acid biosynthesis involving a novel pathway of β-alanine production from spermine. *Journal of Biological Chemistry*, *276*, 10794–10800.

Wickerham, L. J. (1946). A critical evaluation of the nitrogen assimilation tests as commonly used in the classification of the yeasts. *Journal of Bacteriology*, *51*, 6–6.

Wickerham, L. J. (1951). *Taxonomy of yeasts* (Vol. 1029). Washington DC: Technical Bulletin U.S. Dept. Agriculture.

Wierman, M. B., & Smith, J. S. (2014). Yeast sirtuins and the regulation of aging. *FEMS Yeast Research*, *14*, 73–88.

Wightman, R., & Meacock, P. A. (2003). The *THI5* gene family of *Saccharomyces cerevisiae*: Distribution of homologues among

the hemiascomycetes and functional redundancy in the aerobic biosynthesis of thiamin from pyridoxine. *Microbiology*, *149*, 1447–1460.

Williams, R. J., Lyman, C. M., Goodyear, G. H., Truesdail, J. H., & Holaday, D. (1933). "Pantothenic acid", a growth determinant of universal biological occurrence. *Journal of the American Chemical Society*, *55*, 2912–2927.

Williams, R. R., Waterman, R. E., & Keresztesy, J. C. (1934). Larger yields of crystalline antineuritic vitamin. *Journal of the American Chemical Society*, *56*, 1187–1191.

Winzeler, E. A., Castillo-Davis, C. I., Oshiro, G., Liang, D., Richards, D. R., Zhou, Y. Y., & Hartl, D. L. (2003). Genetic diversity in yeast assessed with whole-genome oligonucleotide arrays. *Genetics*, *163*, 79–89.

Wogulis, M., Chew, E. R., Donohoue, P. D., & Wilson, D. K. (2008). Identification of formyl kynurenine formamidase and kynurenine aminotransferase from *Saccharomyces cerevisiae* using crystallographic, bioinformatic and biochemical evidence. *Biochemistry*, *47*, 1608–1621.

Wolak, N., Kowalska, E., Kozik, A., & Rapala-Kozik, M. (2014). Thiamine increases the resistance of baker's yeast *Saccharomyces cerevisiae* against oxidative, osmotic and thermal stress, through mechanisms partly independent of thiamine diphosphate-bound enzymes. *FEMS Yeast Research*, *14*, 1249–1262.

Wu, H., Ito, K., & Shimoi, H. (2005). Identification and characterization of a novel biotin biosynthesis gene in *Saccharomyces cerevisiae*. *Applied and Environmental Microbiology*, *71*, 6845–6855.

Yagi, T., & Kagamiyama, H. (1982). Aspartate: 2-oxoglutarate aminotransferase from bakers' yeast: crystallization and characterization. *Journal of Biochemistry*, *92*, 35–43.

Yamagata, S., & Takeshima, K. (1976). O-acetylserine and O-acetylhomoserine sulfhydrylase of yeast—Further purification and characterization as a pyridoxal enzyme. *Journal of Biochemistry*, *80*, 777–785.

Yoko-o, T., Matsui, Y., Yagisawa, H., Nojima, H., Uno, I., & Toh-e, A. (1993). The putative phosphoinositide-specific phospholipase C gene, *PLC1*, of the yeast *Saccharomyces cerevisiae* is important for cell growth. *Proceedings of the national Academy of Sciences, USA*, *90*, 1804–1808.

Yue, J. X., Li, J., Aigrain, L., Hallin, J., Persson, K., Oliver, K., … Liti, G. (2017). Contrasting evolutionary genome dynamics between domesticated and wild yeasts. *Nature Genetics*, *49*, 913–924.

Zeeman, A. M., Luttik, M. A., Thiele, C., van Dijken, J. P., Pronk, J. T., & Steensma, H. Y. (1998). Inactivation of the *Kluyveromyces lactis KlPDA1* gene leads to loss of pyruvate dehydrogenase activity, impairs growth on glucose and triggers aerobic alcoholic fermentation. *Microbiology*, *144*, 3437–3446.

Zhang, H., Yang, Z., Shen, Y., & Tong, L. (2003). Crystal structure of the carboxyltransferase domain of acetyl-coenzyme A carboxylase. *Science*, *299*, 2064–2067.

Zhang, J., Reddy, J., Buckland, B., & Greasham, R. (2003). Toward consistent and productive complex media for industrial fermentations: Studies on yeast extract for a recombinant yeast fermentation process. *Biotechnology and Bioengineering*, *82*, 640–652.

Zhang, N., Merlotti, C., Wu, J., Ismail, T., El-Moghazy, A. N., Khan, S. A., … Oliver, S. G. (2001). Functional Analysis of six novel ORFs on the left arm of Chromosome XII of *Saccharomyces cerevisiae* reveals three of them responding to S-starvation. *Yeast*, *18*, 325–334.

Zhang, X., Teng, Y. B., Liu, J. P., He, Y. X., Zhou, K., Chen, Y., & Zhou, C. Z. (2010). Structural insights into the catalytic mechanism of the yeast pyridoxal 5-phosphate synthase Snz1. *Biochemical Journal*, *432*, 445–450.

Abbreviation: EDTA, ethylenediamine tetra-acetic acid.

Note. Protein lists were obtained through advanced search in UNIPROT

and manually curated (https://www.uniprot.org).

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