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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 vitamin (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 maintaining 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 ($(\text{NH}_4)_2\text{SO}_4$)	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 ($\text{FeSO}_4 \cdot 7 \text{H}_2\text{O}$)		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	
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
	<i>para</i> -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 oscillates between bioassay based on growth of an auxotroph organism (1.4–1.5 µg/g; Emery, McLeod, & Robinson, 1946), immunodetection (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 (B₂) and folic acid (B₉) that are only present in YNB will not be discussed further. *S. cerevisiae* and more generally *Saccharomycotina* yeasts are B₂ prototroph under both aerobic and anaerobic conditions (Burkholder et al., 1944). Folic acid (B₉) 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 B₆ 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 tetra-substituted 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-ribose 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 families (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

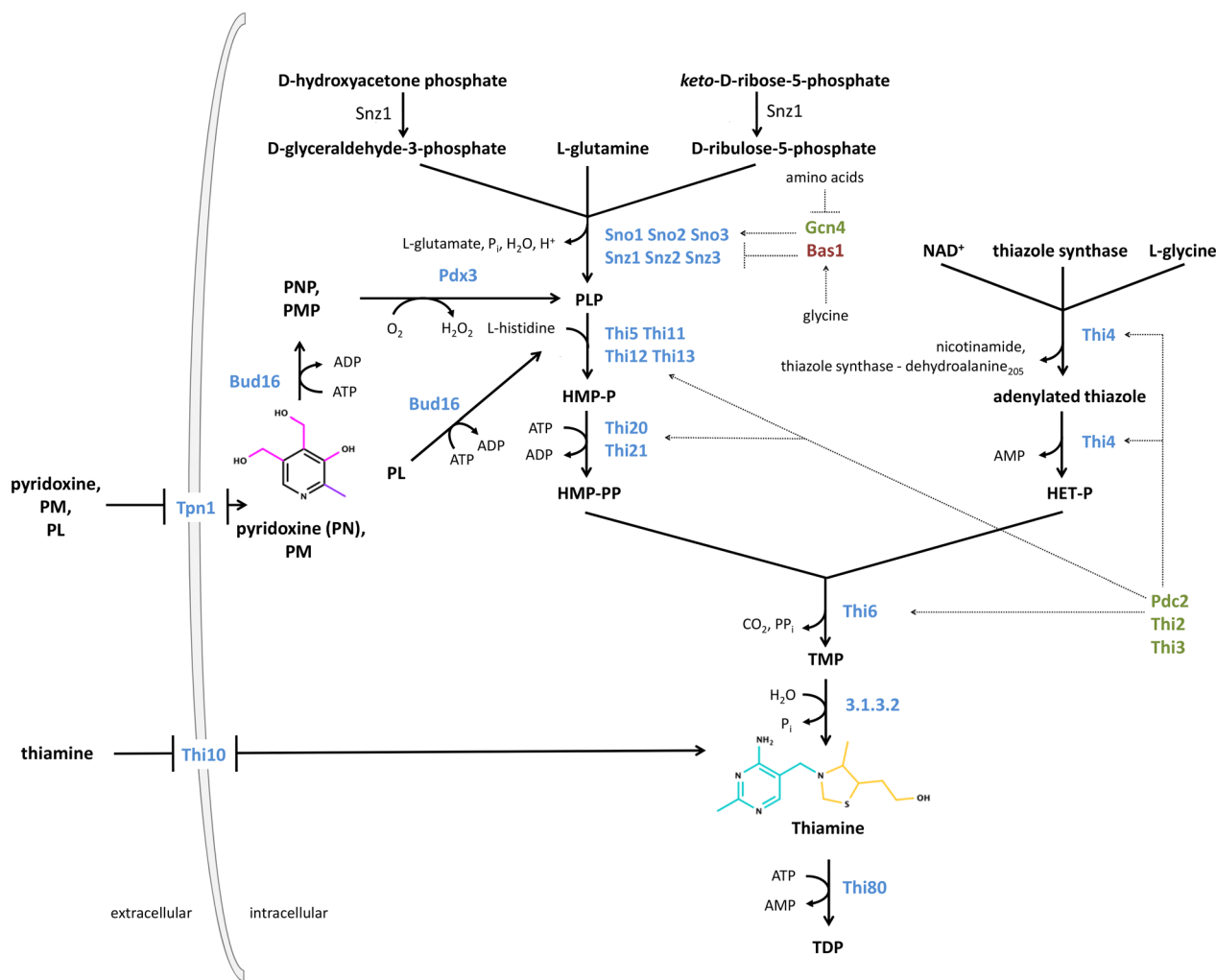


FIGURE 1 PLP and TDP *de novo* synthesis pathway in *Saccharomyces cerevisiae*. D-glyceraldehyde 3-phosphate, L-glutamine, and keto-D-ribose 5-phosphate are converted to PLP by the catalytic activity of the *SNO1,2,3* and *SNZ1,2,3* gene products. *Gcn4* acts as positive regulator of *de novo* PLP biosynthesis, 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-hydroxyethyl)-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* (Daigian-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 *Saccharomyces 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	Acetylnornithine 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 (Karashevitch & 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	<i>Saccharomyces eubayanus</i>	CBS12357 ^T	NBRC111513 ^T	(Baker et al., 2015)	NA
226127	<i>Saccharomyces uvarum</i>	CBS7001 ^T	MCYC623 ^T	(Scannell et al., 2011)	SAMN13069661
1160507	<i>Saccharomyces arboricola</i>	CBS10644 ^T	H-6 ^T	(Liti et al., 2013)	SAMN13069660
226230	<i>Saccharomyces kudriavzevii</i>	CBS8840 ^T	IFO1802 ^T	(Scannell et al., 2011)	NA
226126	<i>Saccharomyces mikatae</i>	CBS8839 ^T	IFO1815 ^T	(Scannell et al., 2011)	SAMN13069662
1987369	<i>Saccharomyces jurei</i>	CBS14759 ^T	NCYC3947 ^T	(Naseeb et al., 2017)	SAMN13069663
226125	<i>Saccharomyces paradoxus</i>	CBS432 ^T	NRRLY-17217 ^T	(Yue et al., 2017)	SAMN13069659
559292	<i>Saccharomyces cerevisiae</i>	S288C	CBS8803	(Goffeau et al., 1996)	NA
889517	<i>S. cerevisiae</i>	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 (B₁)

Thiamine, also known as vitamin B₁, 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-hydroxyethyl)-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-hydroxyethyl)-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-hydroxyethyl)-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, Luttk, 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 (B₇)

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

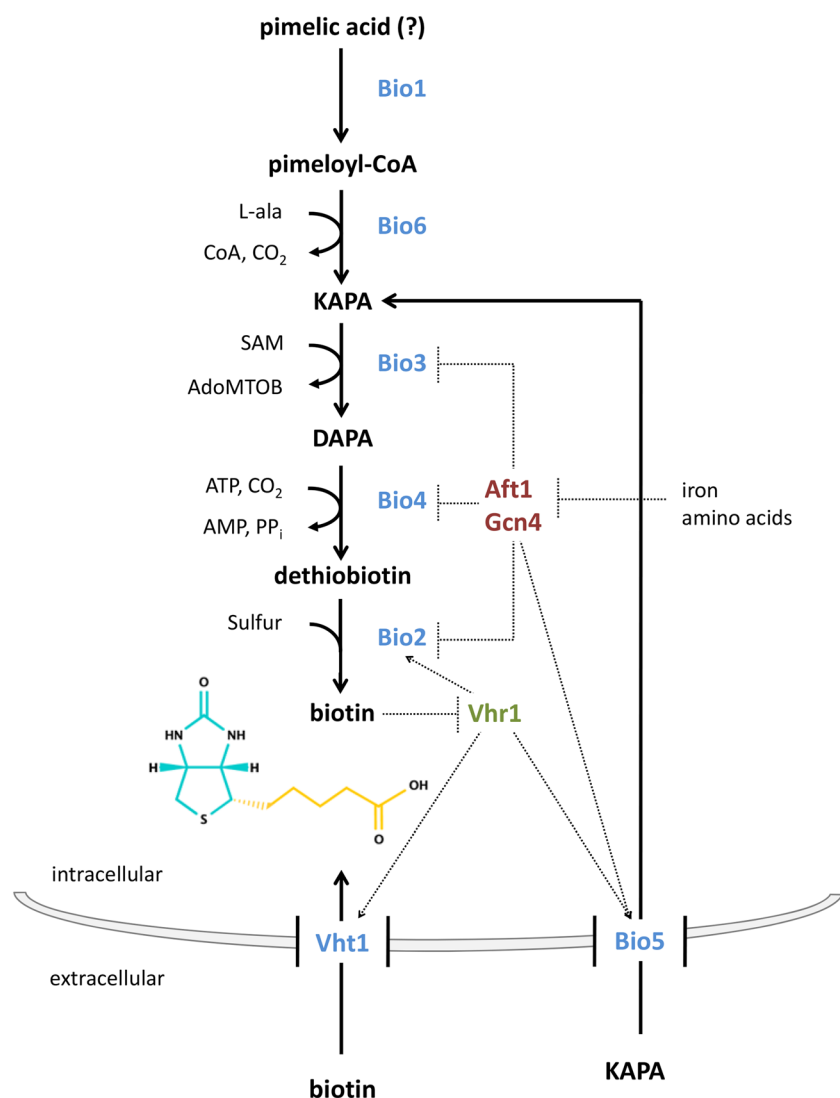


FIGURE 2 Biotin *de novo* biosynthesis pathway in *Saccharomyces cerevisiae*. Biotin is composed of an ureido and a tetrahydrothiophene ring (shown in cyan) fused to a valeric acid chain (shown in yellow). The five final steps of *de novo* biotin synthesis are carried out by Bio1, Bio6, Bio3, Bio4, and 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-oxonanote (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 strain-independent. 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 (B₅)

Vitamin B₅ 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).

Pantothenate 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).

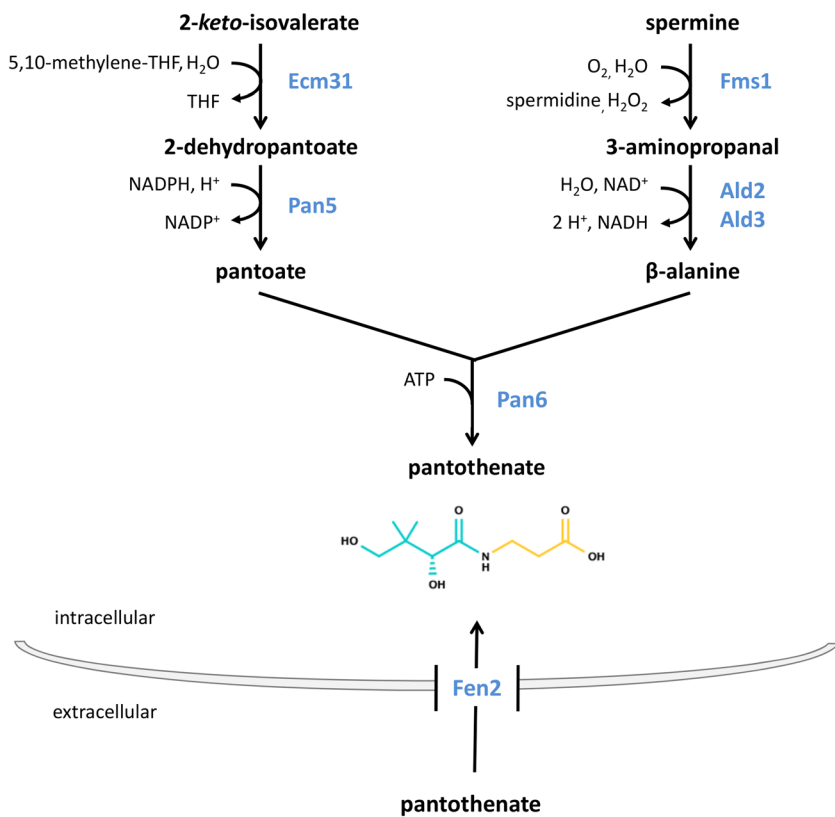


FIGURE 3 Pantothenate *de novo* synthesis pathway in *Saccharomyces cerevisiae* and transcription profiles of pantothenate biosynthetic genes under different growth conditions. Pantothenate can be imported by the proton symporter Fen2 or synthesized *de novo* by condensation of pantoate (shown in cyan) 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, constitutive, and unaffected by extracellular pantothenate 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 | pABA (B₁₀)

pABA, also known as vitamin B₁₀, 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). pABA 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 pABA (B₁₀), GTP, and glutamate, out of which pABA is the less abundant intracellularly and limit folic acid (B₉) synthesis. Additionally, growth deficiency in the presence of

pABA and absence of folic acid has not been reported before, making this vitamin dispensable for CDMY.

In *S. cerevisiae*, pABA 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) pABA and folates. Conversion of chorismate in to pABA 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 pABA (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; Luttk 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 pABA pathway, are transcribed constitutively (Ambroset et al., 2011), suggesting that any regulation of pABA 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 pABA synthesis to overall strain performance (Ambroset et al.,

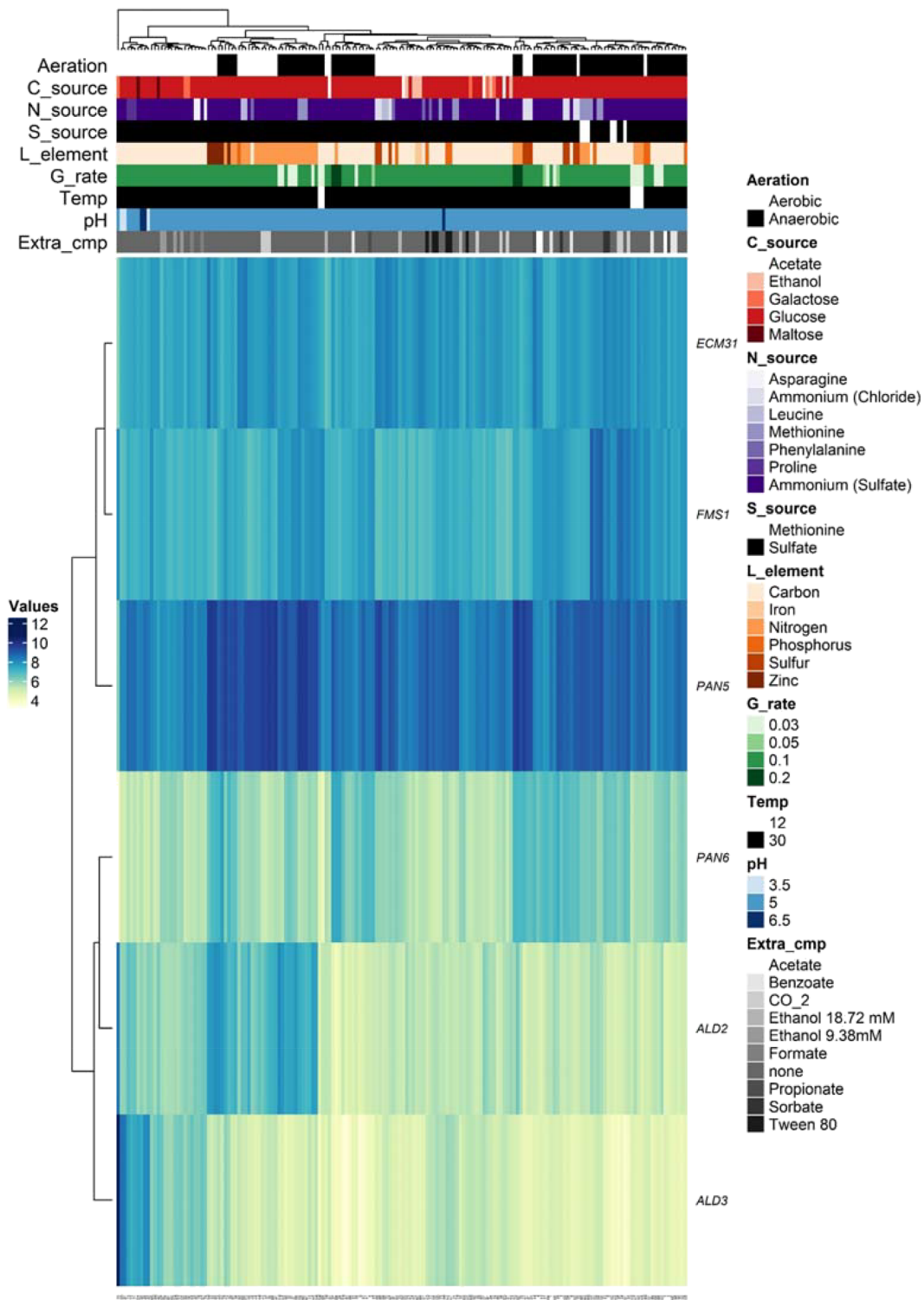


FIGURE 4 Heatmap showing mRNA levels for pantothenate biosynthetic genes measured under 70 different conditions in chemostat cultures. Each row shows a gene involved in *de novo* pantothenate biosynthesis, whereas each column represents one condition. Data are derived from (Knijnenburg et al., 2007; 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](https://onlinelibrary.wiley.com)]

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

3.3 | Nicotinic acid (B₃)

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

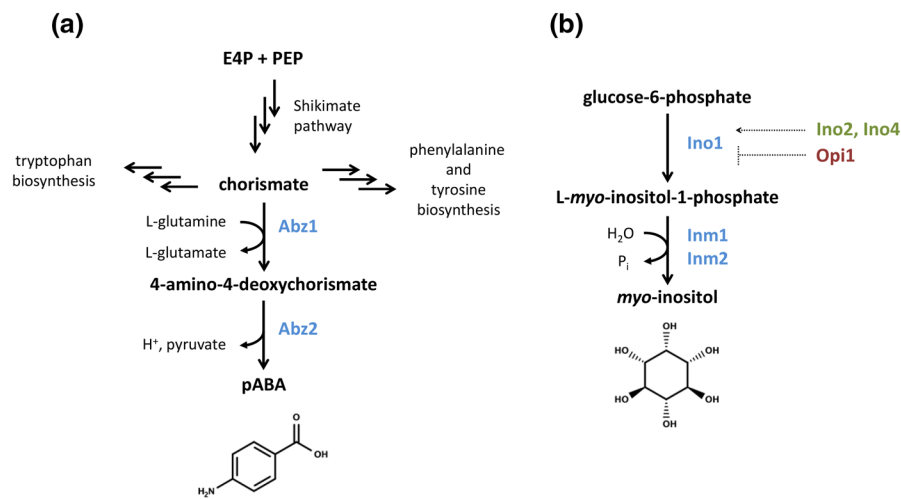


FIGURE 5 *pABA* and *myo*-inositol *de novo* synthesis pathways in *Saccharomyces cerevisiae*. (a) The genes *ABZ1* and *ABZ2* code for a two-step pathway producing *pABA* from chorismate via the intermediate 4-amino-4-deoxychorismate. Chorismate is synthesized from erythrose-4-phosphate and phosphoenolpyruvate via the shikimate pathway. In addition to being precursor for *pABA* 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*. *INO1*, *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. *pABA*, *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 B₃ complex. Nicotinic acid is an important precursor for the essential redox cofactors NAD⁺ and nicotinamide adenine dinucleotide phosphate (NADP⁺).

S. cerevisiae can either obtain 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.

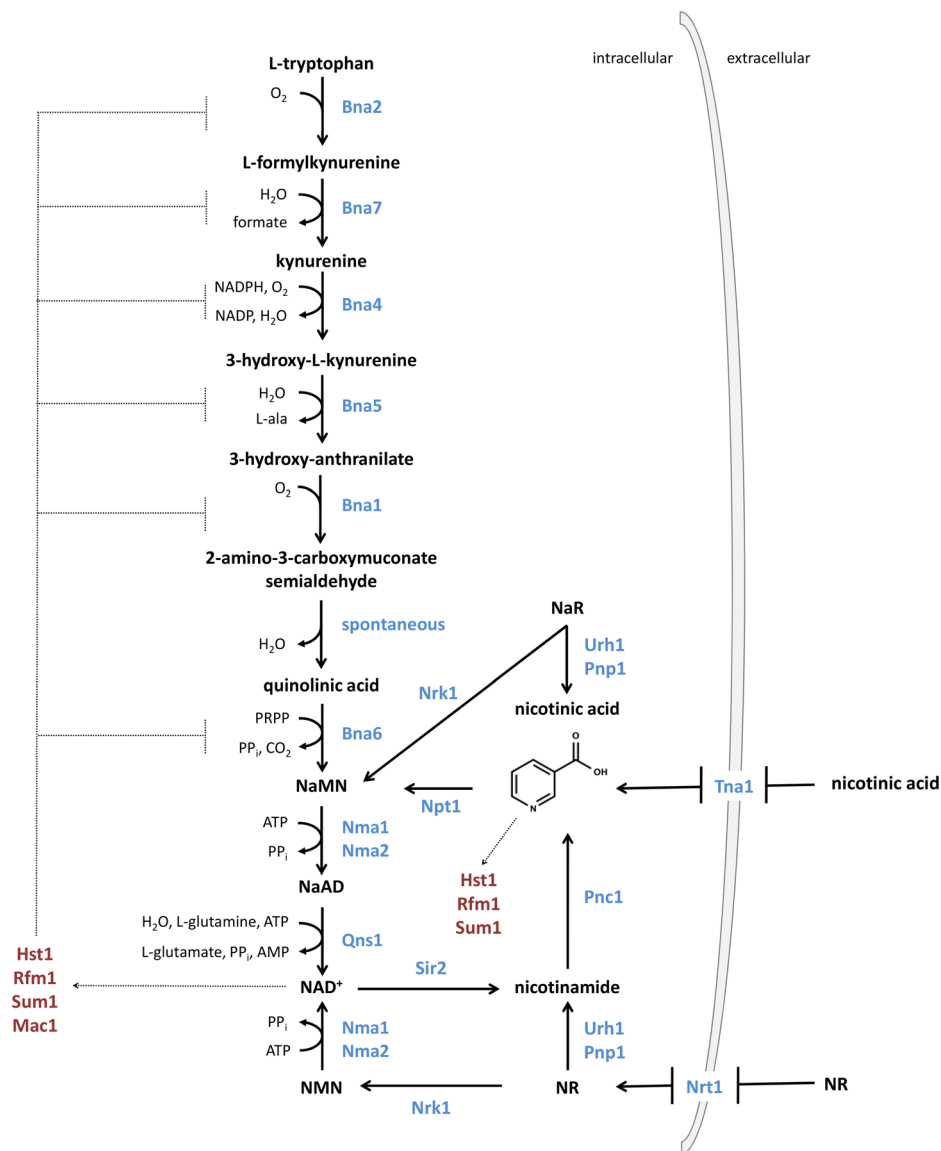
In the *de novo* biosynthesis pathway, NaMN is synthesized from L-tryptophan in a series of six enzymatic reactions (catalyzed by Bna1-2 and Bna4-7) and one spontaneous reaction (Figure 5). Three of the enzymes involved in the *de novo* biosynthesis pathway, indoleamine 2,3 dioxxygenase (Bna2), kynurenine 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 Npt1 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, nicotinic acid 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 (B₈)

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-myoinositol 1-phosphate is generated from glucose-6-phosphate by L-myoinositol 1-phosphate synthase (Ino1; Donahue & Henry, 1981). Subsequently, myo-inositol is generated by dephosphorylation of L-myoinositol 1-phosphate by the heterodimeric enzyme inositol 3-phosphate monophosphatase (Inm1/Inm2 Murray & Greenberg, 2000).

Lipid metabolism in eukaryotic cells, including yeasts, is rigorously 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 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* pan-genome harbors all necessary genetic information to synthesize inositol, biotin, thiamine, nicotinic acid, panthotenate, pyridoxine, and *pABA*. 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, *pABA*, 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.

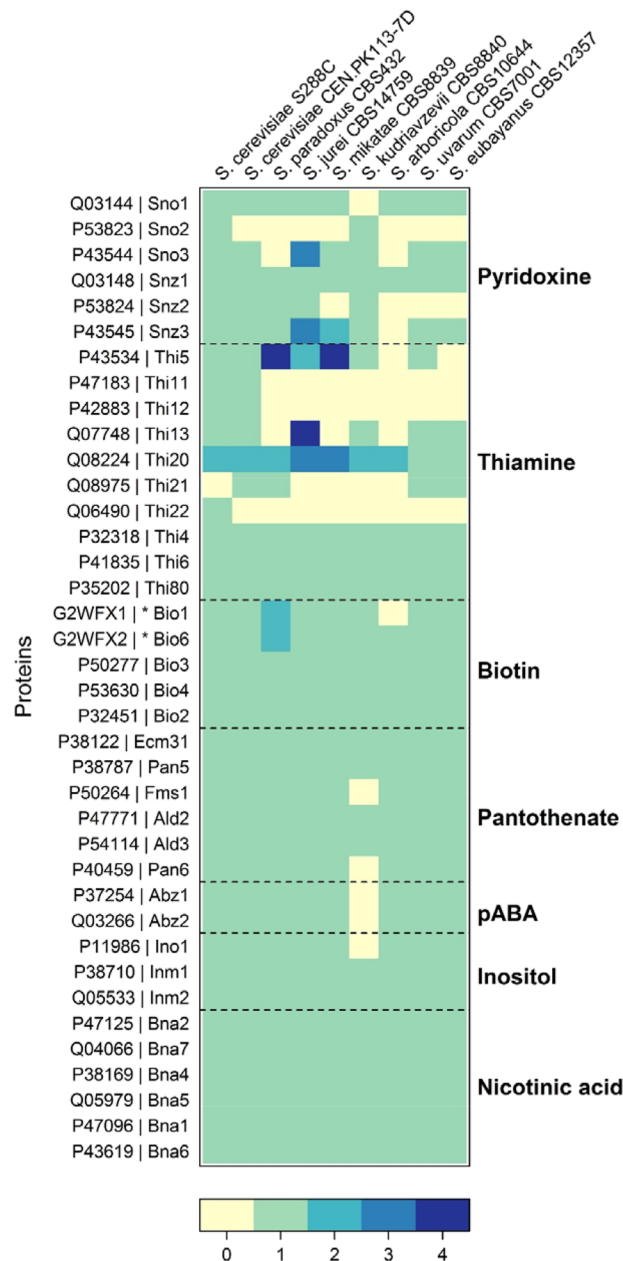


FIGURE 7 Occurrence of vitamin biosynthesis annotated genes in *Saccharomyces* species. A homology search was conducted using HMMER v3 (Eddy, 2011) with *Saccharomyces cerevisiae* S288C proteins as queries (left side row names) against a database of annotated proteins from the *Saccharomyces* species 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 (formerly 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](https://onlinelibrary.com)]

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CONFLICT OF INTEREST

Authors declare that they have no conflict of interests.

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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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