Chapter 2

Vitamin B1 (Thiamine) Metabolism and Regulation in Archaea

Julie A. Maupin-Furlow

Additional information is available at the end of the chapter

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Abstract

Thiamine is the water-soluble sulfur containing vitamin B1 that is used to form thiamine diphosphate (ThDP), an enzyme cofactor important in the metabolism of carbohydrates, amino acids and other organic molecules. ThDP is synthesized *de novo* by certain bacteria, archaea, yeast, fungi, plants, and protozoans. Other organisms, such as humans, rely upon thiamine transport and salvage for metabolism; thus, thiamine is considered an essential vitamin. The focus of this chapter is on the regulation and metabolism of thiamine in archaea. The review will discuss the role ThDP has as an enzyme cofactor and the catalytic and regulatory mechanisms that archaea use to synthesize, salvage and transport thiamine. Future perspectives will be articulated in terms of how archaea have advanced our understanding of thiamine metabolism, regulation and biotechnology applications.

Keywords: thiamine, vitamin B1, archaea, thiazole, thiazolium, pyrimidine, sulfur mobilization, riboswitch

1. Introduction

Thiamine or vitamin B1 consists of a thiazole/thiazolium ring [5-(2-hydroxyethyl)-4-methylthiazole, THZ] linked by a methylene bridge to an aminopyrimidine ring (2-methyl-4-amino-5-hydroxymethylpyrimidine, HMP) (**Figure 1A**). Thiamine diphosphate (ThDP) is the best-known form of thiamine, as it is a cofactor. Other natural thiamine phosphate derivatives include: thiamine monophosphate (ThMP), thiamine triphosphate (ThTP), adenosine thiamine triphosphate (AThTP) and adenosine thiamine diphosphate (AThDP) (**Figure 1A**) [1, 2]. These latter forms have yet to be analyzed in archaea and, thus, will not be a focus of this review.

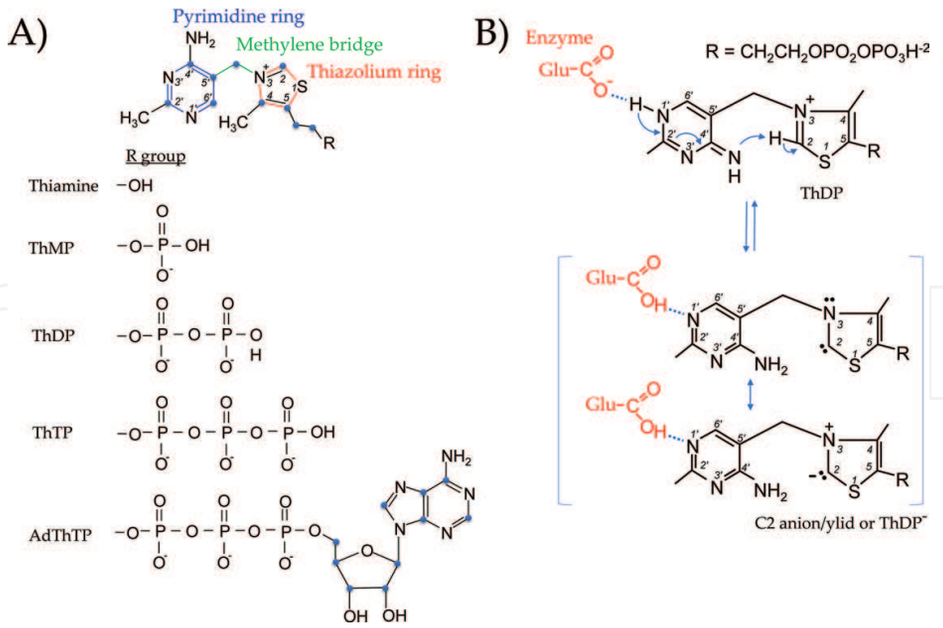

Figure 1. Thiamin (vitamin B1) and its natural forms. A) Thiamin and its natural derivatives thiamin monophosphate (ThMP), thiamin diphosphate (ThDP), thiamin triphosphate (ThTP), and adenosine thiamin triphosphate (AdThTP). The aminopyrimidine ring (blue), thiazolium ring (red) and methylene bridge (green) are highlighted with carbon indicated by C or blue balls. B) Thiamin diphosphate and its C2 anion/ylid form (ThDP-). Enzyme bound ThDP is in a V-conformation, which positions the 4′-amino group of the pyrimidine to abstract the C2-H proton of the thiazolium ring when activated by a conserved glutamate residue of the enzyme (in red). The two resonance structures of the anion/ylid are presented.

2. Thiamine diphosphate

ThDP is an enzyme cofactor found in all domains of life. In archaea and bacteria, ThDP is considered one of the eight universal cofactors along with NAD, NADP, FAD, FMN, S-adenosylmethionine (SAM), pyridoxal-5-phosphate (PLP, vitamin B6), CoA and the C1 carrier tetrahydrofolate or tetrahydromethanopterin [3]. The rare exceptions are the bacteria *Borrelia* and *Rickettsia*, which do not use ThDP as a coenzyme for metabolism [4].

ThDP-dependent enzymes catalyze the cleavage and formation of C-C, C-N, C-S and C-O bonds in a wide range of catabolic and anabolic reactions [5]. As a coenzyme, ThDP serves as an electrophilic covalent catalyst in the decarboxylation of 2-oxo acids (*e.g.*, pyruvate and 2-oxoglutarate) and in carboligation and lyase-type reactions [6–8]. The active species of ThDP is typically the C2 anion/ylid ($ThDP^-$) form, generated by dissociation of the C2-H proton from the thiazole ring (**Figure 1B**). $ThDP^-$ is the source of the catalytic power of ThDP-dependent enzymes, as it can add to unsaturated systems and serve as a sink for mobile electrons [9, 10]. ThDP typically requires Mg^{2+} or Ca^{2+} ions to bind the enzyme in a V conformation in which the 4′-amino group of the pyrimidine ring is positioned to abstract the C2-H proton from the thiazole ring (**Figure 1B**) [11–15]. This proton abstraction is often assisted by a conserved glutamate residue (Glu) of the enzyme that provides a carboxylate side chain for hydrogen bonding to the N1′ of the pyrimidine ring and for proton relay to form the $ThDP^-$ catalytic intermediate (**Figure 1B**). Thus, ThDP is fundamentally distinct among coenzymes in that both rings contribute to catalysis.

ThDP-dependent enzymes are used in pyruvate metabolism, the TCA cycle, the pentose phosphate pathway and branched chain amino acid biosynthesis (**Table 1**). Archaea commonly use ThDP-dependent 2-oxoacid: ferredoxin oxidoreductases (OFORs) to catalyze the oxidative decarboxylation of 2-oxoacids (*e.g.*, pyruvate, 2-oxoglutarate and 2-oxoisovalerate) into an energy rich CoA thioester [16–32] or the reverse reaction to fix CO_2 into cell carbon [33]. ThDP, Mg^{2+} and Fe-S cluster(s) are the intrinsic cofactors of OFORs with ferredoxin as the electron acceptor. OFORs (typically 270 kDa) are less complex than the 5-6 MDa 2-oxoacid dehydrogenases (ODHs) of mitochondria and aerobic bacteria; ODHs rely upon NAD^+ as the electron acceptor and are composed of E1p (ThDP-dependent 2-oxoacid decarboxylase), E2p (lipoate acetyltransferase) and E3p (dihydrolipoamide dehydrogenase) components [16]. While some archaea express mRNAs specific for all three ODH (E1p, E2p and E3p) homologs, ODH activity has yet to be detected in archaea [30]. Other ThDP-dependent enzymes of archaea include the non-oxidative 3-sulfopyruvate decarboxylase of coenzyme M biosynthesis [34, 35] and the acetohydroxyacid synthase of branch-chain amino acid (isoleucine, leucine and valine) biosynthesis [36, 37]. The transketolase activities of archaea [38] are presumed to be catalyzed by ThDP-dependent enzymes based on comparative genomics [39].

Archaea	Bacteria	Eukarya	EC	Enzyme (Abbreviation and Description)	
+	+	+	1.2.4.1	PDH	Pyruvate dehydrogenase (E1p component)
n.d.	+	+	1.2.4.2	OGDH	2-Oxoglutarate dehydrogenase (E1o component)
+ (rare)	+	+	1.2.4.4	BCOADH	Branched chain 2-oxoacid dehydrogenase (E1b component)
+	+	+	2.2.1.1	TK	Transketolase (glycolaldehyde transferase)
n.d.	+ (rare)	+	4.1.-.-	HACL	2-Hydroxyphytanoyl−/2-hydroxyacyl-CoA lyase
+	+	n.d.	1.2.3.3	POX	Pyruvate oxidase (phosphate-dependent)
+	+	n.d.	1.2.7.1	PFOR	Pyruvate: ferredoxin oxidoreductase
+	+	n.d.	1.2.7.3	KGOR	2-Oxoglutarate: ferredoxin oxidoreductase
+	+	n.d.	1.2.7.7	VOR	2-Oxoisovalerate: ferredoxin oxidoreductase
+	+	n.d.	1.2.7.8	IOR	Indolepyruvate: ferredoxin oxidoreductase
n.d.	+ (rare)	n.d.	1.2.7.10	—	Oxalate: ferredoxin oxidoreductase
n.d.	n.d.	+	2.2.1.3	DHAS	Dihydroxyacetone synthase (formaldehyde transketolase)
+	+	+	2.2.1.6	AHAS	Acetohydroxyacid synthase (acetylacetate synthase)
n.d.	+	+	2.2.1.7	DXPS	1-Deoxy-D-xylulose 5-phosphate synthase
+	+	+	2.2.1.9	MenD	2-Succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylic-acid synthase
n.d.	+	n.d.	2.5.1.66	CeaS	N2-(2-carboxyethyl)arginine synthase
?	+	?	3.7.1.11	—	Cyclohexane-1,2-dione hydrolase
?	+	+	4.1.1.1	PDC	Pyruvate decarboxylase

Archaea	Bacteria	Eukarya	EC	Enzyme (Abbreviation and Description)	
+	+	n.d.	4.1.1.7	BFD	Benzoylformate decarboxylase
n.d.	+	n.d.	4.1.1.8	OXC	Oxalyl-CoA decarboxylase
?	?	+	4.1.1.43	—	Phenylpyruvate decarboxylase
n.d.	+	n.d.	4.1.1.47	GCL	Glyoxylate carboligase (tartronate semialdehyde synthase)
n.d.	+	n.d.	4.1.1.71	KGD	2-Oxoglutarate decarboxylase
+	+	n.d.	4.1.1.74	IpdC	Indolepyruvate decarboxylase
+	+	n.d.	4.1.1.79	ComDE	Sulfopyruvate decarboxylase
+ (rare)	+	+	4.1.1.82	PnPyDC	3-Phosphonopyruvate decarboxylase
n.d.	+	+	4.1.2.9	PHK	Phosphoketolase (D-xylulose-5-phosphate phosphoketolase)
?	+	?	4.1.2.38	BAL	Benzaldehyde lyase (benzoin aldolase)

Table 1. Thiamin diphosphate (ThDP)-dependent enzymes and their distribution among the three domains of life. Enzyme homolog detected (+), not detected (n.d.), or low homology (?) as indicated.

3. Thiamine biosynthesis *de novo*

Thiamine is synthesized *de novo* by generating thiazole and aminopyrimidine rings separately and then joining the rings to form ThMP, the precursor of ThDP. The *de novo* pathways rely upon energy input (ATP), carbon- and nitrogen-based intermediates and a source of sulfur (the latter incorporated into the thiazole ring).

3.1. Synthesis and phosphorylation of the aminopyrimidine ring of thiamine

ThiC (HMP-P synthase; EC 4.1.99.17) is the major enzyme used by bacteria [40, 41], plant chloroplasts [42] and archaea [43] to synthesize the aminopyrimidine ring of thiamine (**Figures 2-4**). ThiC converts 5′-phosphoribosyl-5-aminoimidazole (AIR) to 4-amino-5-hydroxymethyl-2-methylpyrimidine phosphate (HMP-P), thus, diverting carbon/nitrogen skeletons of purine metabolism to thiamine biosynthesis. ThiC is a radical SAM enzyme, that initiates this catalytic reaction by use of a $[4Fe\text{-}4S]^{+}$ cluster that reductively cleaves SAM to methionine and an 5′-deoxyadenosyl radical [40], a presumed oxidizing cosubstrate of the reaction [44].

THI5 forms the aminopyrimidine ring of thiamine from the substrates PLP and histidine in yeast [45, 46] (**Figure 3**). Only a subset of THI5 family (IPR027939) proteins have the conserved histidine residue needed for HMP-P synthesis [45] and appear restricted to yeast, fungi, plants (non-chloroplast) and select γ-proteobacteria. Bacterial ABC-type solute binding proteins for HMP precursor (ThiY) [47] and riboflavin (RibY) [48] transport are structurally related to THI5. Thus, the archaeal THI5 family proteins, which are devoid of the conserved histidine residue, are suggested to serve a similar role in transport.

ThiD domain proteins are used as bifunctional HMP kinase (EC 2.7.1.49)/HMP-P kinase (EC 2.7.4.7) enzymes in thiamine biosynthesis and salvage (**Figures 2-4**). Bacterial ThiD [49, 50] and yeast THI20 and THI21 (N-terminal ThiD domain proteins) [51] phosphorylate HMP-P to HMP-PP in the *de novo* pathway and successively phosphorylate HMP to HMP-PP in the

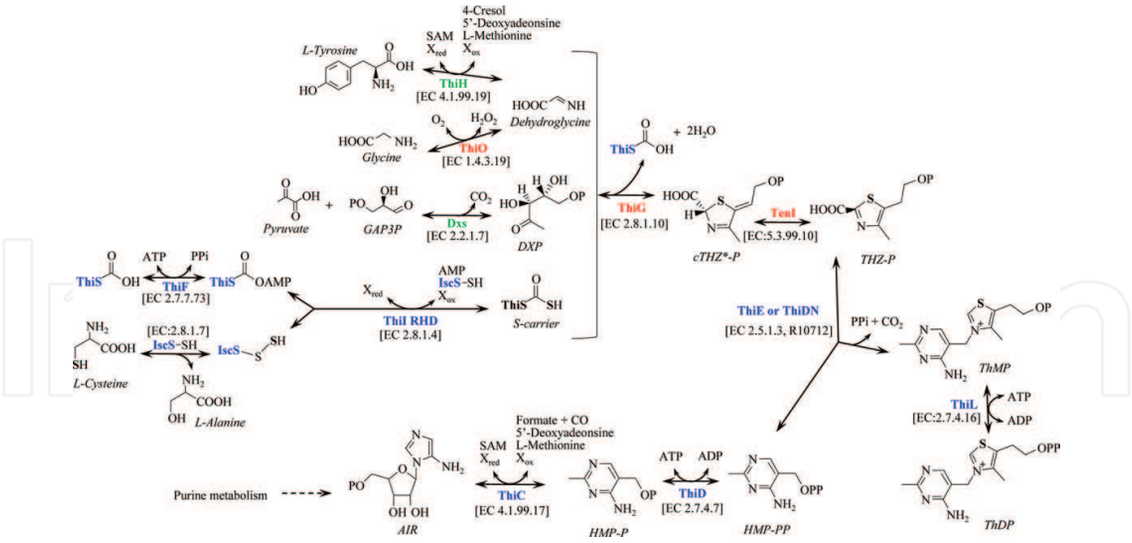

Figure 2. Thiamin (vitamin B1) biosynthesis in bacteria. Enzymes are discussed in text and colored by phylogenetic distribution (red, restricted to one domain of life; blue, found in all domains of life; green, apparent homologs in all domains of life but no direct evidence). Abbreviations: AIR, 5-aminoimidazole ribotide; SAM, S-adenosyl-methionine; GAP3P, D-glyceraldehyde 3-phosphate; HMP-P, 4-aminohydroxymethyl-2-methylpyrimidine phosphate; HMP-PP, 4aminohydroxymethyl-2-methylpyrimidine diphosphate; ThMP, thiamin monophosphate; ThDP, thiamin diphosphate; DXP, 1-deoxy-D-xylulose 5-phosphate; cTHZ-P, 2-[(2R,5Z)-2-carboxy-4-methylthiazol-5(2H)-ylidene]ethyl phosphate; THZ-P, 4-methyl-5-(β-hydroxyethyl)thiazolium phosphate; X, electron carrier.

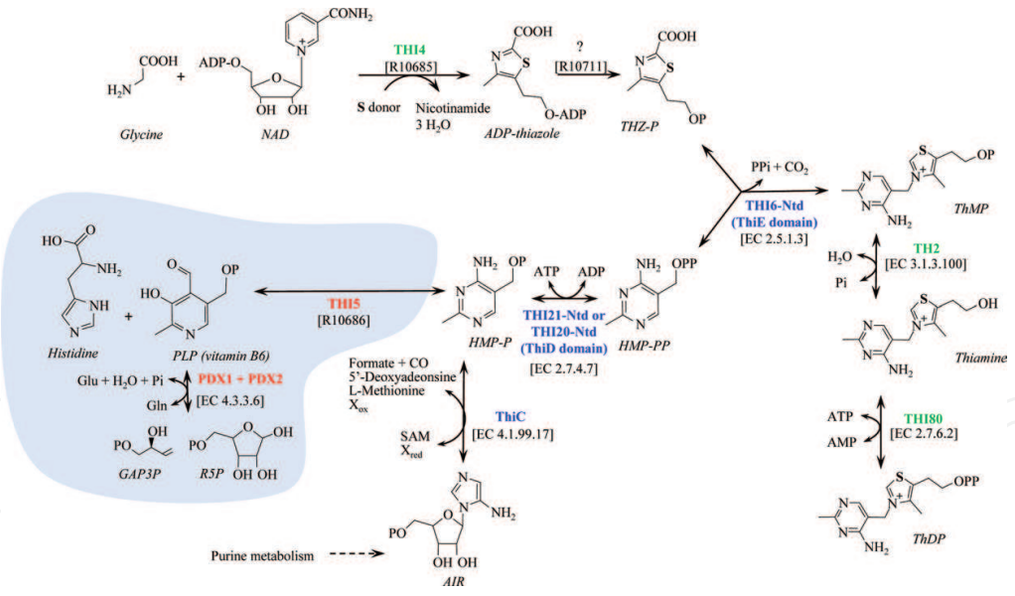

Figure 3. Thiamin (vitamin B1) biosynthesis in eukaryotes. Blue shading indicates restricted to yeast. Abbreviations: ADP-thiazole, ADP-5-ethyl-4methylthiazole-2-carboxylate; PLP, pyridoxal phosphate; R5P, D-ribose 5-phosphate.?, not determined to date. For additional abbreviations and coloring scheme see **Figure 2**.

salvage pathway. Proteins with an unusual ThiD2 domain (standalone or fused to ThiE) are identified in bacteria to catalyze only HMP-P kinase activity, potentially to avoid misincorporation of damaged and/or toxic analogs of HMP into ThDP-dependent enzymes [52]. ThiD homologs (IPR004399) are widespread in all domains of life, including organisms that only salvage HMP and do not synthesize thiamine *de novo*. Archaeal ThiD proteins are standalone or fused to a ThiN-type ThMP synthase domain (see later discussion) [43, 53, 54].

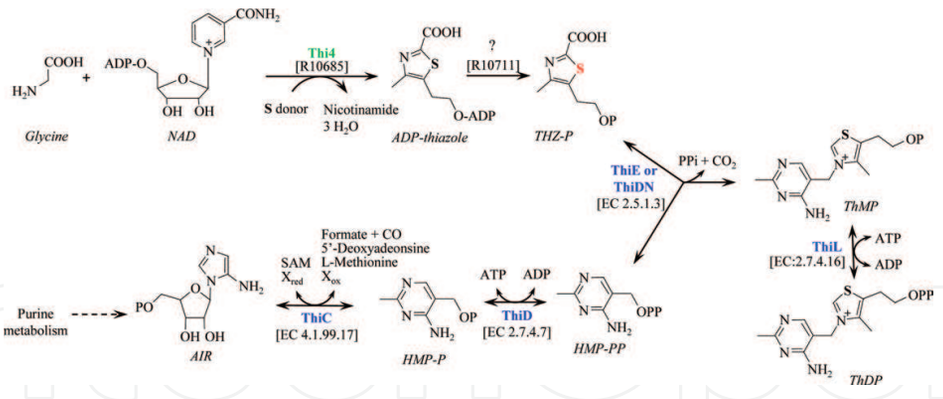

Figure 4. Thiamin (vitamin B1) biosynthesis in archaea. For abbreviations and coloring scheme see **Figures 2**, **3**.

3.2. Synthesis of the thiazole ring of thiamine

De novo biosynthesis of the thiazole ring can be classified into two fundamentally distinct pathways based on the type of thiazole synthase (ThiG vs. Thi4) used. While similar in nomenclature, the ThiG- and Thi4-type thiazole synthases differ in terms of structure and function. The ThiG-dependent pathway relies upon at least six steps to form THZ-P and appears limited to bacteria based on the phylogenetic distribution of ThiG (EC 2.8.1.10) (**Figure 2**). By contrast, the Thi4-type branch for thiazole biosynthesis is simpler in having only two steps (**Figures 3**-**4**) and appears more widespread, as Thi4-homologs (KEGG K03146) are represented in all domains of life and are demonstrated to function in thiazole ring biosynthesis in yeast [55] and archaea [56, 57].

3.2.1. Synthesis of the thiazole ring of thiamine by the ThiG-pathway

To form the thiazole ring, ThiG uses three substrates: () dehydroglycine, (ii) 1-deoxy-D-xylulose-5-phosphate (DXP) and (iii) thiocarboxylated ThiS [58–61] (**Figure 2**).

(i) Dehydroglycine is synthesized by either oxygen-dependent (ThiO; EC 1.4.3.19) or SAM radical enzymes (ThiH; EC 4.1.99.19), both of which are broadly distributed in bacteria but generally absent in archaea and eukaryotes. The ThiO glycine oxidase catalyzes the oxidative deamination of glycine to form the dehydroglycine required for thiazole ring synthesis [62–65]. By contrast, the ThiH tyrosine lyase forms a 5′-deoxyadenosyl radical that initiates cleavage of the C alpha-C beta bond of tyrosine to generate the dehydroglycine (needed for thiamine biosynthesis) and p-cresol (the byproduct) [66–68].

(ii) The 1-deoxy-D-xylulose-5-phosphate synthase (Dxs; EC 2.2.1.7) is a ThDP-dependent enzyme that condenses the (hydroxyethyl)-group derived from pyruvate with the C1 aldehyde group of D-glyceraldehyde 3-phosphate (GAP3P) to generate DXP and CO_2 [69, 70]. Dxs homologs (IPR005477) are widespread in bacteria, green algae, higher plants and protists but rare in archaea. Dxs generates the DXP precursor of thiamine, pyridoxol and non-mevalonate isoprenoid biosynthesis pathways [69, 70]. DXP is used for thiamine biosynthesis in bacteria but not in eukaryotes or archaea (**Figure 2**).

(iii) The ThiG-dependent pathway uses a protein-based relay system to mobilize sulfur to the thiazole ring. Sulfur is transferred from L-cysteine to an active site cysteine residue of a sulfurtransferase (*e.g.*, IscS-SH) [71] to form an enzyme persulfide intermediate (*e.g.*, IscS-S-SH) [72].

In a separate reaction, the E1-like ThiF adenylates the C-terminus of the ubiquitin-fold protein, ThiS, in a mechanism resembling the activation step of ubiquitination [73]. This modification step readies the C-terminus of ThiS for thiocarboxylation. The sulfur is relayed from IcsS-S-SH to ThiS through the ThiI rhodanese (RHD) domain [71, 74–76]. The resulting thiocarboxylated ThiS serves as the sulfur donor for the ThiG mediated synthesis of the thiazole ring [58–61].

3.2.2. Synthesis of the thiazole ring of thiamine by the Thi4-pathway

The Thi4-pathway used to form the thiazole ring (**Figures 3**, **4**) is distinct from that of ThiG (**Figure 2**). Key to the pathway is Thi4-mediated formation of ADP-thiazole, which is then hydrolyzed to THZ-P by a presumed NUDIX hydrolase [55]. Thi4 family (IPR002922) proteins are distributed in all domains of life and generally absent from ThiG-containing bacteria. Although initially annotated as ribose-1,5-bisphosphate isomerases (R15Pi) based on indirect assay [77], archaeal Thi4 homologs are found to be distinct from archaeal R15Pi of the e2b2 family [78, 79] and demonstrated to catalyze thiazole synthase activity [56] that is transcriptionally repressed when thiamine and THZ levels are sufficient [43] and is required for thiazole ring formation [57]. *In vitro*, yeast Thi4 operates by a suicide mechanism by mobilizing the sulfur of its active site cysteine (C205) to form ADP-thiazole from NAD and glycine [55]. By contrast, the methanogen Thi4, uses an active site histidine residue and iron to catalyze the synthesis of ADP-thiazole from NAD, glycine and sulfide [56]. Thi4 enzymes of archaea, yeast [80] and plant [81] are related based on X-ray crystal structure; in addition, yeast Thi4 modified to use an active site histidine residue can operate by a catalytic mechanism with iron similarly to the methanogen Thi4 [56, 80].

3.2.3. Condensation of the aminopyrimidine and thiazole rings to form ThMP

Once formed, the thiamine ring precursors (*i.e.,* THZ-P and HMP-PP) are condensed to ThMP by a ThMP synthase of the ThiE- or ThiN-type (EC 2.5.1.3).

ThiE-type ThMP synthases are widespread in all domains of life (IPR036206) and are found to catalyze the substitution of the diphosphate of HMP-PP with THZ-P to yield ThMP, CO_2 and diphosphate (PPi) in bacteria [82, 83], plants [84] and yeast [85]. ThiE homologs are often bifunctional, fused to an additional catalytic domain such as HMP-P kinase (EC 2.7.4.7) [52, 84, 85]. ThiE serves as a ThMP synthase in certain archaea based on its requirement for growth of haloarchaea in the absence of thiamine, HMP and/or THZ [43].

ThMP synthases of the ThiN-type are also identified in archaea and bacteria, but absent in eukaryotes. ThiN domain (IPR019293) proteins are of three major types: I) fused to an N-terminal DNA binding domain (ThiR type), II) fused to an N- or C-terminal catalytic domain (*e.g.,* ThiD) and III) standalone ThiN domains. The ThiDN proteins are ThMP synthases based on *in vitro* assay and complementation of *ΔthiE* mutants for growth in the absence of thiamine [43, 53, 54]. Fusion of the ThiN domain to the HMP/HMP-P kinase domain (ThiD) is suggested to minimize the release of HMP-PP prior to its condensation with THZ-P and, thus, channel substrate to the ThMP product [43]. ThiN domains that lack a conserved α-helix near the active site histidine are not ThMP synthases and instead can serve as apparent ligand binding sites for transcriptional regulation as in ThiR (see later discussion) [43].

3.2.4. Formation of ThDP from ThMP or thiamine

Thiamine diphosphate (ThDP), the biologically active form of thiamine, is produced from ThMP by two routes. ThMP is commonly phosphorylated to ThDP by the ATP-dependent ThiL ThMP kinase (EC 2.7.4.16 of IPR006283) in bacteria [86] and archaea [87]. Alternatively, ThMP is hydrolyzed to thiamine, and thiamine, is converted to ThDP by a Mg^{2+}-dependent thiamine pyrophosphokinase TPK (THI80) that catalyzes thiamine + ATP ⇋ ThDP + AMP (EC 2.7.6.2) in eukaryotes [88–91]. Consistent with this latter route, TPK is required for the *de novo* biosynthesis of thiamine in yeast [89, 90] and the ThMP phosphatase TH2 can hydrolyze ThMP to thiamine in plants [92]. TPK is also used to salvage thiamine to ThDP in eukaryotes [91, 93] and certain bacteria (TPK homolog YloS) [93]; by contrast, γ-proteobacteria use a thiamine kinase (ThiK, EC 2.7.1.89) to phosphorylate thiamine to ThMP [93] prior to ThiL-mediated phosphorylation of ThMP to ThDP. While TPK (IPR036759) homologs are conserved in some archaea, ThiK is not. Puzzling then is that certain archaea (*e.g.,* haloarchaea and *Pyrobaculum*) have ThiBQP thiamine transport and ThiL ThMP kinase homologs but do not have ThiK or TPK homologs or activities (*e.g., Pyrobaculum californica*) [87]. Furthermore, archaea lacking TPK and ThiK homologs can transport thiamine and generate ThDP as demonstrated by growth of a ThMP synthase mutant, *Haloferax volcanii ΔthiE*, when supplemented with thiamine but not THZ or HMP [43, 57]. These findings suggest that certain archaea use an alternative pathway to salvage thiamine to ThDP.

4. Thiamine transport

Thiamine is a micronutrient that is actively transported into cells against a concentration gradient. Transport of thiamine and its precursors alleviates the need for *de novo* biosynthesis of thiamine. Thiamine transporters are predicted in archaea based on homology to bacterial transport systems or identification of putative transporter genes that are either in genomic synteny with thiamine biosynthesis genes or downstream of ThDP-binding riboswitch (THI- box) motifs [57, 94–96].

Bacterial transporters of thiamine and thiamine precursors, conserved in archaea, can be classified into: (i) ABC-type transporters (*e.g.*, ThiBPQ and ThiYXZ) [47, 97, 98], (ii) a new ABC-type class termed energy coupling factor (ECF) importers [95, 99], (iii) NiaP transporters [100] of the major facilitator superfamily (MSF, IPR036259) that use an ion gradient [101] and (iv) PnuT transporters that mediate the facilitated diffusion of thiamine [102, 103]. ABC and ECF are primary active transporters that hydrolyze ATP in thiamine uptake by use of conserved ATPases (**Figure 5**). ECF and ABC transporters are distinguished by the type of protein used to bind solute: ECF uses a transmembrane substrate-capture protein (S component, ThiT) while ABC uses an extracytoplasmic solute binding protein (*e.g.,* ThiB or ThiY) [95, 99]. ECF systems are typically modular in that ThiT and other S-components (*e.g.,* the biotin specific BioY) interchangeably bind to the transmembrane (T) component of the system [95, 99, 104]. By comparison, ABC systems are not modular and have solute binding proteins (ThiB/Y) that bind to the extracytoplasmic domain of the transporter [47, 48, 105, 106].

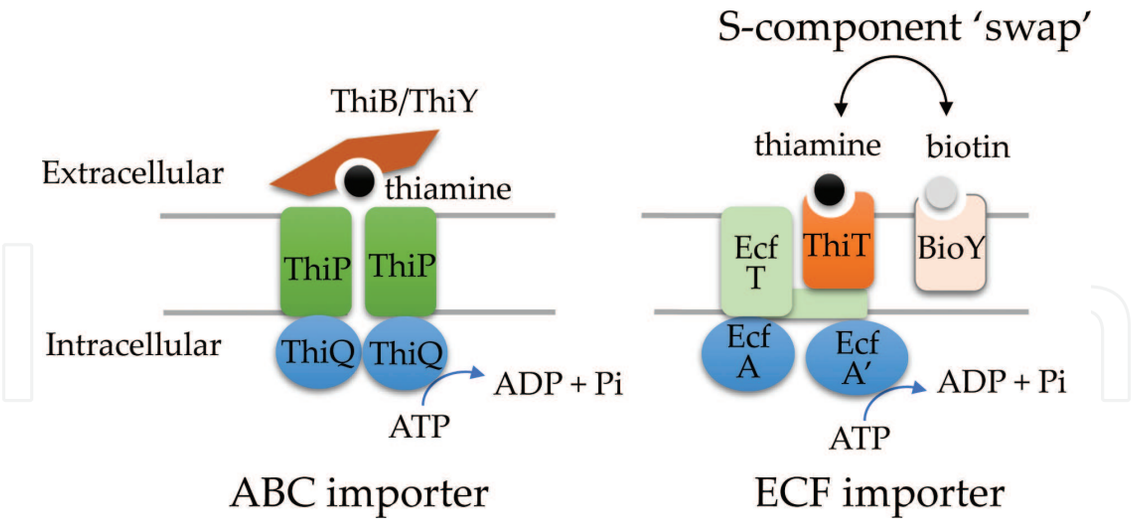

Figure 5. Comparison of thiamin transport by ABC and ECF importers. The nucleotide-binding domains that hydrolyze ATP and drive transporter are shown in blue. The ABC-type transmembrane domain protein (ThiP) and ECF-type Tcomponent (EcfT) are in shades of green. The soluble binding protein (ThiB, ThiY) of the ABC importer is in dark orange. The ECF importer S-components of thiamin (ThiT) and biotin (BioY), which can be swapped, are in shades of orange.

5. Thiamine salvage

Thiamine and its derivatives are salvaged from the outside and inside of a cell to replenish and repair the ThDP cofactor for metabolism. Thiamine salvage pathways are widespread in all domains of life and overcome the need for *de novo* biosynthesis of thiamine, minimize energy cost, and reduce the misincorporation of thiamine breakdown products into ThDP-dependent enzyme active sites [107].

Archaea are found to salvage thiamine and its derivatives (HMP and THZ) from the environment [43, 57] and repress the *de novo* biosynthesis of thiamine when thiamine levels are sufficient [43, 108]. Archaeal salvage pathways are predicted to include enzymes of *de novo* biosynthesis (*i.e.*, ThiD, ThiE or ThiDN, and ThiL) with enzymes specific for salvage such as ThiM (THZ kinase, EC 2.7.1.50), TenA (aminopyrimidine aminohydrolase, EC 3.5.99.2) and/or YlmB (formylaminopyrimidine deformylase, EC 3.5.1.-) the latter speculative as it clusters to a family of proteins (IPR010182) that includes succinyl-diaminopimelate desuccinylase and YodQ of N-acetyl-beta-lysine synthesis [57] (**Figure 6**). ThiM is a THZ kinase in bacteria [49, 109–111], protists [112], and plants [113] and is predicted in archaea (*e.g.*, UniProtKB D4GV40) based on conserved active site residues [114]. TenA homologs are subclassified into TenA_C and TenA_E [115], based on conserved active site cysteine and glutamate residues, respectively. Both types of TenA proteins are conserved in archaea. TenA_C is demonstrated to be an aminohydrolase that works in concert with the YlmB deformylase to regenerate HMP from thiamine degradation products and to function as a thiaminase II that hydrolyzes thiamine to THZ and HMP in bacteria [94, 116]. Note that thiaminase I (EC 2.5.1.2) which is secreted by certain bacteria to degrade thiamine [117, 118] is distinct from TenA. In plants, TenA_E is bifunctional in catalyzing deformylase and aminohydrolase activities to regenerate

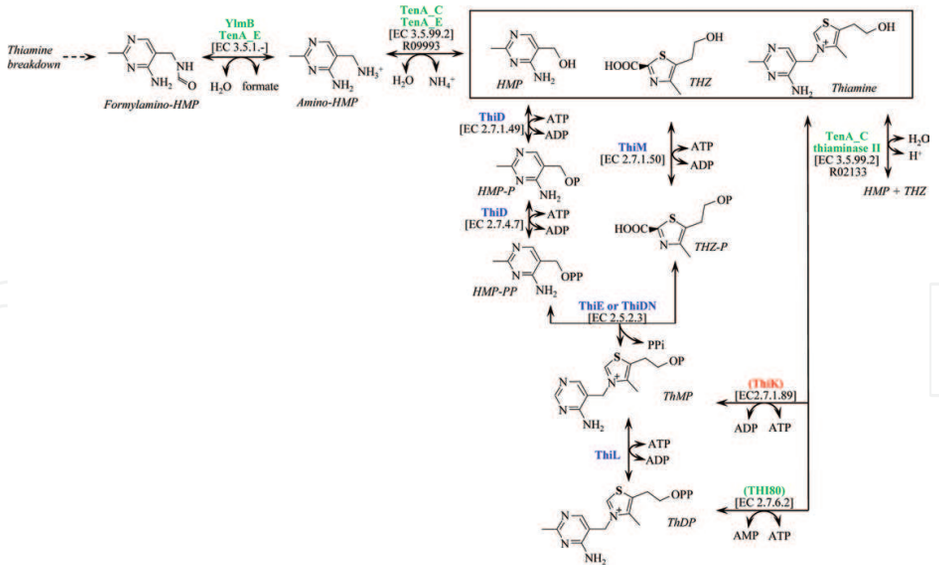

Figure 6. Thiamin (vitamin B1) salvage in archaea. Abbreviations: Formylaminio-HMP, N-formyl-4-amino5-aminomethyl-2-methylpyrimidine; amino-HMP, 4amino-5-aminomethyl-2-methylpyrimidine; HMP, 4amino-5-hydroxymethyl-2-methylpyrimidine; THZ, 4methyl-5-(2-hydroxyethyl)thiazole. For additional abbreviations and coloring scheme see **Figures 2**-**4**.

HMP from thiamine breakdown products, thus, overcoming the need for YlmB [115]. TenA_C and TenA_E are conserved in archaea and likely to function in thiamine salvage.

6. Thiamine regulation

Thiamine biosynthesis, salvage and/or transport pathways are regulated by THI-box riboswitches in bacteria [119–121], eukaryotes [122–125], and a few archaea (based on Rfam RF00059) [43, 96]. The THI-box riboswitch is a regulatory element of an mRNA/pre-mRNA aptamer that binds a thiamine metabolite and an expression platform that transduces the ligand binding to control gene expression [126]. In bacteria, when ThDP levels are sufficient, ThDP binds the 5′ untranslated region (UTR) of the THI-box and triggers the formation of a stem-loop structure that masks the Shine-Dalgarno (SD) sequence of the mRNA and inhibits translation initiation [119–121]. The major targets of this regulation are the mRNAs of the thiamine metabolic operons (*e.g.*, *thiCEFSGH* and *thiMD* in *E. coli*) [119–121] and the ABC-type thiamine transporter (*thiBPQ*), with the latter based on motif analysis (Rfam RF00059). Eukaryotes (plants, fungi, and algae) also use a THI-box riboswitch to regulate expression of thiamine metabolism but do so by modulating the alternative splicing of pre-mRNAs [42, 122–125, 127–130]. In these eukaryotic systems, ThDP or HMP-PP binds the THI-box riboswitch of an intron located in the 5′- or 3′-UTR and causes mispairing of the splice donor (GU) and acceptor (AG) of the pre-mRNA (*e.g.*, *THIC* and *THI4*). This incorrect pairing promotes alternative mRNA slicing and, thus, reduces thiamine biosynthesis.

Thiamine metabolism is also regulated by transcription factors, as exemplified by organisms that synthesize thiamine *de novo* but do not have a THI-box riboswitch motif including yeast and many archaea. In yeast, three proteins (Thi2p, Thi3p, and Pdc2p) coordinate the induction of thiamine biosynthetic (*THI*) gene expression in response to thiamine starvation [131–136].

Thi3p serves as the thiamine sensor for the two transcription factors (Thi2p and Pdc2p) that bind specific DNA sequences upstream of the *THI* genes. When thiamine is low, Thi3p forms a ternary complex with Thi2p and Pdc2p that activates transcription of the *THI* genes. Once the levels of thiamine are sufficient, Thi3p binds ThDP, triggering dissociation of Thi3p from the ternary complex and reduced expression of the *THI* genes. In archaea from the phyla *Euryarchaeota* [43] and *Crenarchaeota* [108], a novel transcription factor, ThiR, is found to repress thiamine metabolic gene (*thi4* and *thiC*) expression when the levels of thiamine are sufficient. ThiR is composed of an N-terminal DNA binding domain and C-terminal ThiN domain. The ThiN domain of ThiR is not catalytic, as it is missing an α-helix extension and conserved Met near the active-site His that are needed for the thiazole synthase activity of ThiDN proteins [43]. Instead the ThiN domain of ThiR serves as an apparent sensor of thiamine metabolites that triggers ThiR-mediated repression of *thi4* and *thiC* transcription during thiamine sufficient conditions. This type of transcriptional regulation appears common in archaea based on the widespread phylogenetic distribution of ThiR homologs vs. THI-box motifs.

7. Future perspectives and conclusions

Thiamine is an important vitamin for improving human health [137], is a strategic nutritional supplement [138, 139], is targeted for production in probiotics [140], is useful in drug discovery including developing antimetabolites to treat cancer or fungal infections [141–144], has potential for use as antitoxic agent in the food industry [145], may improve crop resistance [146], is a starting point for design of novel riboswitches [147], functions in central metabolism and unusual biocatalytic reactions [6–8, 148–151], may modulate global nutrient cycles [152], and holds promise for other applications.

Discovery of the metabolic route for the *de novo* biosynthesis of thiamine in archaea opens a new window for the use of extremophiles in thiamine-related biotechnology applications. Archaea are designated as GRAS (generally recognized as safe) by the FDA, are amenable to genetic manipulation [153], and can readily express ThDP-dependent enzymes from foreign systems (*e.g.*, bacterial pyruvate decarboxylase) [154]. Thus, archaea provide a useful resource to discover and optimize ThDP-dependent biocatalysts for the generation of renewable fuels and chemicals.

Archaea also provide an evolutionary perspective on the origins of thiamine biosynthesis pathways. The aminopyrimidine biosynthesis branch, composed of the radical SAM enzyme ThiC and the HMP/HMP-P kinase ThiD, appears ancient based on its functional conservation in all three domains of life. By contrast, thiazole biosynthesis can be divided into two major pathways: ThiG- and Thi4-dependent. Of these two divisions, the Thi4-type is suggested to be fairly ancient as Thi4 depends on Fe for catalytic activity, can use sulfide as a source of sulfur for thiazole ring formation, is functionally conserved in archaea and eukaryotes, and is predicted to function in certain bacteria (including anaerobes) based on genome sequencing.

Identification of genes needed to transport, synthesize, and salvage thiamine (from the three domains of life) improves understanding of how vitamin B1 may be trafficked in the environment. Finding that Thi4 is important for thiazole ring formation in eukaryotes and archaea provides new perspective on defining the organisms that synthesize thiamine *de novo*. Microbes that produce thiamine and thiamine precursors are suggested to be of benefit to

other microbial taxa that cannot produce thiamine yet require this vitamin as a cofactor for their metabolic activity [152]. Thus, interspecies vitamin transfer may influence the metabolism of microbial consortia and global/carbon energy cycles.

Finally, thiamine is damaged by extreme conditions such as oxidation. Plant and yeast have a hydrolase (Tnr3, YJR142W) that converts the oxy- and oxo-damaged forms of ThDP into monophosphates to avoid misincorporation of the damaged thiamine molecules into the ThDP-dependent enzymes [155]. Many archaea thrive in conditions of extreme thermal and oxidative stress suggesting these microbes use unique mechanisms to avoid and/or repair damaged ThDP for use as a cofactor.

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Conflict of interest

The author has no conflict of interest to declare.

Author details

Julie A. Maupin-Furlow

Address all correspondence to: jmaupin@ufl.edu

Department of Microbiology and Cell Science, Institute of Food and Agricultural Sciences, University of Florida, Gainesville, Florida, USA

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