Subsystem: Ubiquinone Biosynthesis

Olga Zagnitko, Fellowship for Interpretation of Genomes

Introduction

Quinones are widely distributed in nature. They are best known as lipid-soluble components of membrane-bound electron-transport chains, but in animal cells ubiquinone is found not only in the inner mitochondrial membrane but also in the endoplasmic reticulum, Golgi apparatus, lysosomes, peroxisomes, and in the plasma membrane. This distribution suggests that ubiquinones may be involved in a number of biological processes beyond the respiratory electron transport (ref. 3, 5, 6).

Bacterial respiratory quinones can be divided into two groups. The first one comprises a benzoquinone termed ubiquinone or coenzyme Q (UQ). The second group contains naphthoquinones - menaquinone (MK) and demethylmenaquinone (DMK). Animal cells synthesize only UQ, but MK is obtained from the diet. Most Gram-positive bacteria and anaerobic Gram-negative bacteria contain only MK, whereas the majority of strictly aerobic Gram-negative bacteria contain exclusively UQ. Both types of isoprenoid quinones are found only in facultatively anaerobic Gram-negative bacteria. Archaea lack ubiquinone. A nearly complete set of orthologs of the ubiquinone biosynthesis genes is apparent in all cyanobacterial genomes, in spite of the apparent absence of ubiquinone in these organisms. The possibility for these genes to be involved in plastoquinone (rather than ubiquinone) biosynthesis in cyanobacteria has been proposed.

The biosynthesis of UQ is studied in great detail in bacteria and yeast but only to a limited extent in animal tissues (ref.1, 3, 4). The UQ biosynthetic enzymes may constitute a complex that is tightly bound to the membrane. In the biosynthetic pathway the " nucleus" of UQ is derived from the shikimate pathway via chorismate in bacteria or tyrosine in higher eukaryotes. Our subsytem analysis suggests that many bacteria lacking UbiC may also depend on an alternative (and yet unknown) source of 4-hydroxybenzoate. The prenyl side chain of UQ is derived from prenyl diphosphate and methyl groups are derived from S-adenosylmethionine.

The biosynthesis of UQ includes at least nine reactions. The formation of 4-hydroxybenzoate from chorismate is the first committed step in the biosynthesis of UQ in bacteria. Three hydroxylation reactions introduce hydroxyl groups at positions C-6, C-4, and C-5 of the benzene nucleus of Q (genes *ubiB, ubiH,* and *ubiF*). The same O-methyltransferase with dual specificity (UbiG in *E. coli* and Coq3 in yeast) catalyzes both O-methylation steps in UQ biosynthesis (ref.1, 2).

Subsystem: Ubiquinone Biosynthesis

Functional roles (A) and a Spreadsheet (B) for selected species representing functional variants

(A)

Abbrev	Functional Role
UbiC	Chorismate--pyruvate lyase (EC 4.-.-.-)
UbiA	4-hydroxybenzoate polyprenyltransferase (EC 2.5.1.-)
UbiD	3-polyprenyl-4-hydroxybenzoate carboxy-lyase (EC 4.1.1.-)
UbiB	Ubiquinone biosynthesis monooxygenase UbiB
UbiG	Ubiquinone biosynthesis SAM-dependent O-methyltransferase (EC 2.1.1.-)
UbiH	Ubiquinone biosynthesis monooxgenase UbiH/COQ6 (EC 1.14.13.-)
UbiE	Ubiquinone/menaquinone biosynthesis methyltransferase UbiE/COQ5 (EC 2.1.1.-)
UbiF	Ubiquinone biosynthesis monooxgenase UbiF/COQ7 (EC 1.14.13.-)

(B)

Genome ID	Organism	Variant Code	UbiC	UbiA	UbiD	UbiB	UbiG	UbiH	UbiE	UbiF
83333.1	Escherichia coli K12 [B]	1	3949	3950	3769	3762	2205	2859	3760	2858, 663
12149.1	Salmonella bongori 12149 [B]	1	4179	4180	2839, 3983	3976	2325, 4456	2971	3974	2970, 638
216599.1	Shigella sonnei 53G [B]	1	3490	3491	4349	4355	2339	3892, 961, 962	4357	3893, 513
257311.1	Bordetella parapertussis 12822 [B]	1	1382	97	1107	3772	2945	3356	3775	3918
235.1	Brucella abortus [B]	2		2060	135, 136, 417	2718	84	894	2719	1724
955.1	Wolbachia pipientis quinquefasciatus [B]	2		10	474	1242	803	1114	1009	394
4932.1	Saccharomyces cerevisiae [E]	2		4813	1403	1939, 3794, 5554	4918	2294	4017	5129
263.2	Francisella tularensis (Livermore) [B]	28		381	?	434	1772	778	432	779
155920.1	Xylella fastidiosa Ann-1 [B]	28		2000		574	1301	1102	1930	1101
4896.1	Schizosaccharomyces pombe [E]	28		3189		2103, 2449, 3235	577	1267	172	1282
Genome ID	**Organism**	**Variant Code**	**UbiC**	**UbiA**	**UbiD**	**UbiB**	**UbiG**	**UbiH**	**UbiE**	**UbiF**
9606.2	Homo sapiens (Human) [E]	28		24096	?	16249, 29286, 2990, 30646	35069	9670, 9671	4393, 4395	11597
10090.2	Mus musculus (House mouse) [E]	28		20884		1670, 22089, 23883	18222	6110	14089, 21173	25418
74547.1	Prochlorococcus marinus str. MIT 9313 [B]	3		1322	397	2073, 2263	1424, 1468	811	1168, 612	?
167540.1	Prochlorococcus marinus MED4 [B]	3		1909		1171, 238, 458		1477	1957	
1148.1	Synechocystis sp. PCC 6803 [B]	3		2880	298	1093, 2237, 2677, 568	2604, 333	271	2700	
171101.1	Streptococcus pneumoniae R6 [B]	-1							1435, 1586	
282458.1	Staphylococcus aureus subsp. aureus MRSA252 [B]	-1					1568		1400	

Variant codes:

(1) - ubiquinone from chorismate, "bacterial pathway" (containing UbiC gene, as in E.coli and many other bacteria);

(2) - ubiquinone from tyrosine or phenylalanine, no UbiC gene (as in S.cerevisiae and some bacteria);

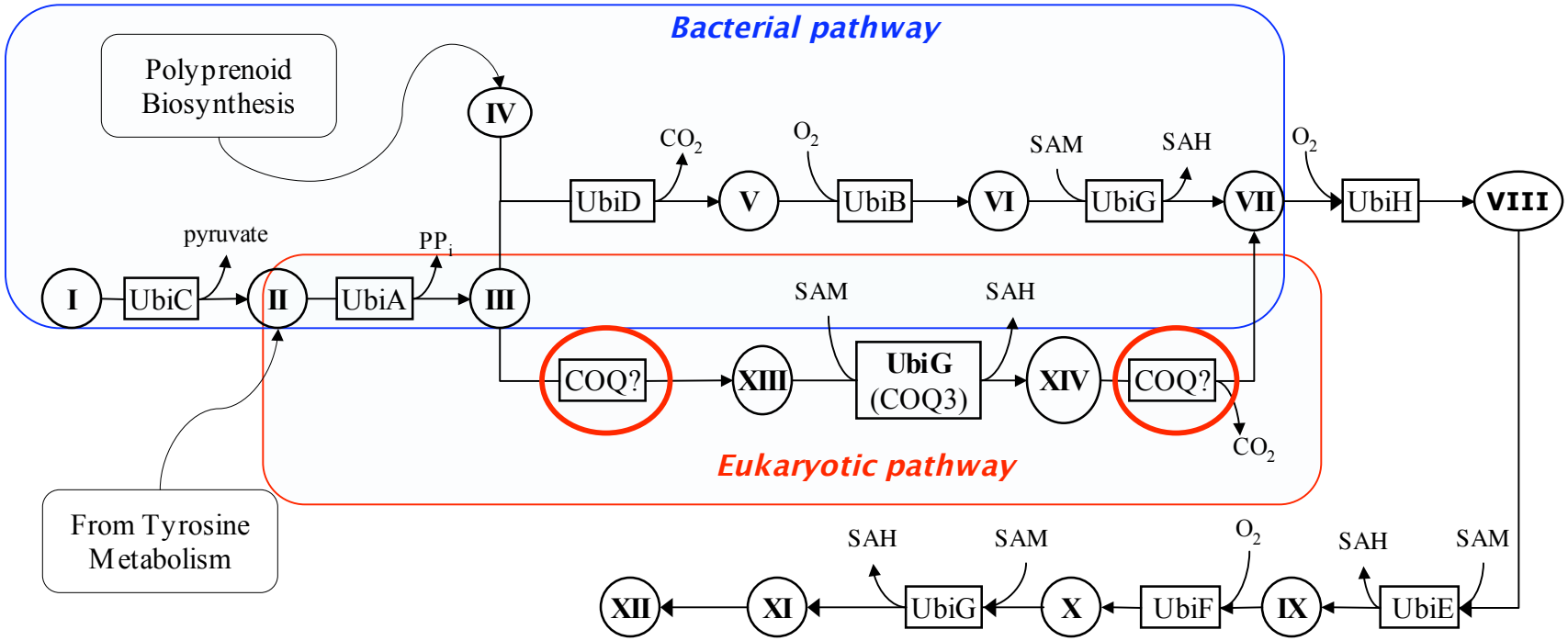
(28) - "UbiD-independent" variant. In eukaryotes it may include an alternative and incompletely understood "eukaryotic" pathway. For example, S.cerevisiae is believed to have a second (alternative) pathway. It includes at least two uncharacterized enzymes (marked as" COQ?" in the "eukaryotic pathway" of the subsystem diagram (see next slide). Interestingly the same pattern of genes is observed in a number of bacteria, such as Xylella ssp. or Francisella tularensis;

(3) – "incomplete pathways", lacking some of the Ubi-genes. For example, many cynaobacteria (eg Synechocystes sp.) contain all genes of the functional variant 2, except UbiF. According to experimental data, these organisms do not produce ubiquinone, and the physiological role of other Ubi-genes is unclear;

(-1) – no ubiquinone biosynthesis. UbiE is often present due to its participation in Menaquinone biosynthesis, such as in Staphylococci that do not produce ubiquinone but produce menaquinone.

Subsystem: Ubiquinone Biosynthesis

Subsystem diagram, functional roles and intermediates



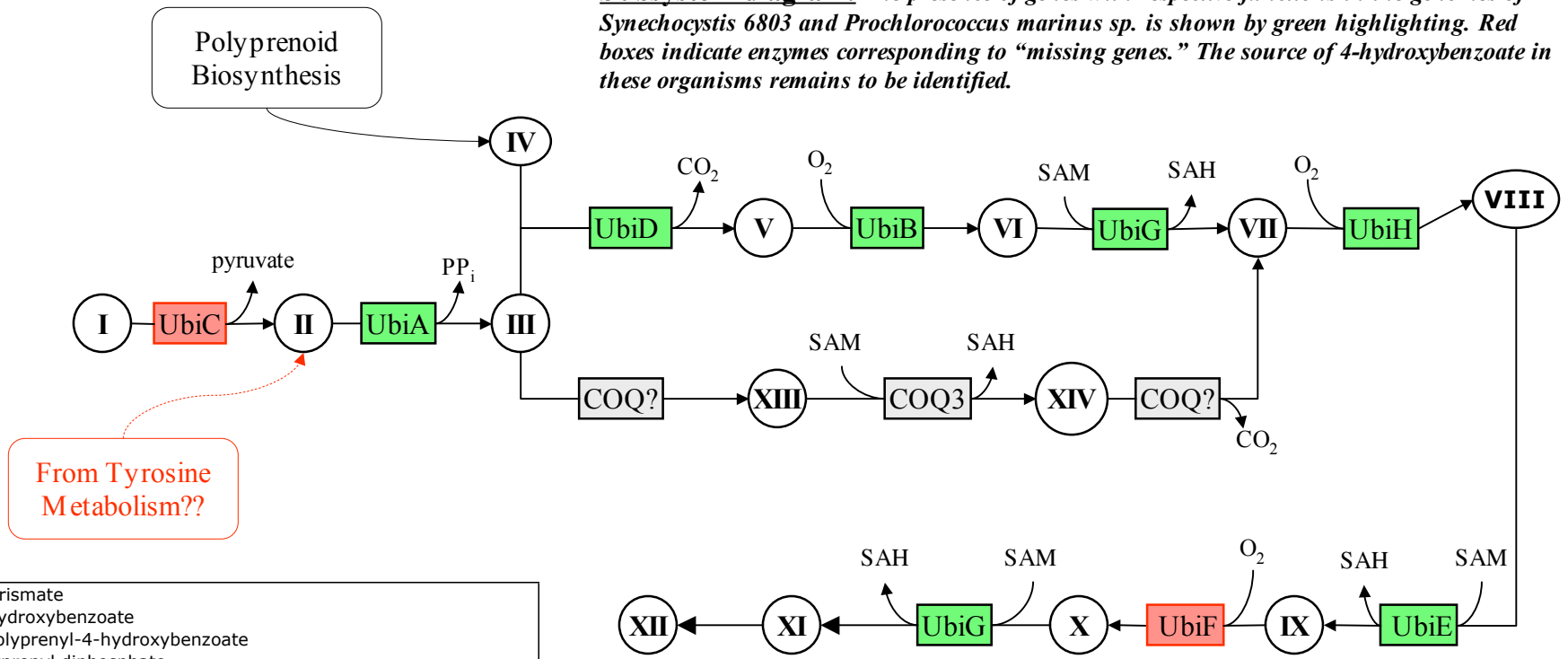
I	Chorismate
II	4-Hydroxybenzoate
III	3-polyprenyl-4-hydroxybenzoate
IV	Polyprenyl diphosphate
V	2-polyprenylphenol
VI	2-polyprenyl-6-hydroxyphenol
VII	2-polyprenyl-6-methoxyphenol
VIII	2-polyprenyl-6-methoxy-1,4-benzoquinone
IX	2-polyprenyl-3-methyl-6-methoxy-1,4-benzoquinone
X	2-polyprenyl-3-methyl-5-hydroxy-6-methoxy-1,4-benzoquinone
XI	Ubiquinole
XII	Ubiquinone
XIII	3,4-dihydroxy-5-polyprenilbenzoate
XIV	3-methoxy-4-hydroxy-5-polyprenilbenzoate
SAM	S-Adenosyl-L-methionine
SAH	S-Adenosyl-L-homocysteine

Abbrev	Functional Role
UbiC	Chorismate--pyruvate lyase (EC 4.-.-.-)
UbiA	4-hydroxybenzoate polyprenyltransferase (EC 2.5.1.-)
UbiD	3-polyprenyl-4-hydroxybenzoate carboxy-lyase (EC 4.1.1.-)
UbiB	Ubiquinone biosynthesis monooxygenase UbiB
UbiG	Ubiquinone biosynthesis SAM-dependent O-methyltransferase (EC 2.1.1.-)
UbiH	Ubiquinone biosynthesis monooxgenase UbiH/COQ6 (EC 1.14.13.-)
UbiE	Ubiquinone/menaquinone biosynthesis methyltransferase UbiE/COQ5 (EC 2.1.1.-)
UbiF	Ubiquinone biosynthesis monooxgenase UbiF/COQ7 (EC 1.14.13.-)

Open problem: Ubiquinone Biosynthesis in cyanobacteria

An almost complete set of ubiquinone biosynthesis genes is present in the majority of cyanobacterial genomes available to date (see Spreadsheet on slide 2), in spite of the absence of ubiquinone in these organisms. The overwhelming co-occurrence of these genes and the fact that this pathway is largely preserved even in the "minimal" Prochlorococcal genomes (7) argues for its physiological significance in cyanobacteria. It's function is a mystery.

Subsystem diagram: ***The presence of genes with respective functions in the genomes of Synechocystis 6803 and Prochlorococcus marinus sp. is shown by green highlighting. Red boxes indicate enzymes corresponding to "missing genes." The source of 4-hydroxybenzoate in these organisms remains to be identified.***



I	Chorismate
II	4-Hydroxybenzoate
III	3-polyprenyl-4-hydroxybenzoate
IV	Polyprenyl diphosphate
V	2-polyprenylphenol
VI	2-polyprenyl-6-hydroxyphenol
VII	2-polyprenyl-6-methoxyphenol
VIII	2-polyprenyl-6-methoxy-1,4-benzoquinone
IX	2-polyprenyl-3-methyl-6-methoxy-1,4-benzoquinone
X	2-polyprenyl-3-methyl-5-hydroxy-6-methoxy-1,4-benzoquinone
XI	Ubiquinole
XII	Ubiquinone
XIII	3,4-dihydroxy-5-polyprenilbenzoate
XIV	3-methoxy-4-hydroxy-5-polyprenilbenzoate
SAM	S-Adenosyl-L-methionine
SAH	S-Adenosyl-L-homocysteine

Abbrev	**Functional Role**
UbiC	Chorismate--pyruvate lyase (EC 4.-.-.-)
UbiA	4-hydroxybenzoate polyprenyltransferase (EC 2.5.1.-)
UbiD	3-polyprenyl-4-hydroxybenzoate carboxy-lyase (EC 4.1.1.-)
UbiB	Ubiquinone biosynthesis monooxygenase UbiB
UbiG	Ubiquinone biosynthesis SAM-dependent O-methyltransferase (EC 2.1.1.-)
UbiH	Ubiquinone biosynthesis monooxgenase UbiH/COQ6 (EC 1.14.13.-)
UbiE	Ubiquinone/menaquinone biosynthesis methyltransferase UbiE/COQ5 (EC 2.1.1.-)

References:

1. Meganathan R. Ubiquinone biosynthesis in microorganisms. FEMS Microbiology Letters. 2001; v. 203(2):131-139.

2. Szkopinska A. Ubiquinone. Biosynthesis of quinone ring and its isoprenoid side chain. Intracellular localization. Acta Biochim Pol. 2000; v.47(2):469-80. Review.

3. Makoto Kawamukai. Biosynthesis, bioproduction and novel roles of ubiquinone. Journal of Bioscience and Bioengineering. 2002; v.94(6):511-51.

4. Poon WW, Davis DE, Ha HT, Jonassen T, Rather PN, Clarke CF. Identification of Escherichia coli ubiB, a gene required for the first monooxygenase step in ubiquinone biosynthesis. J Bacteriol. 2000; v.182(18):5139-46.

5. Turunen M, Olsson J, Dallner G. Metabolism and function of coenzyme Q. Biochim Biophys Acta. 2004; v.1660(1-2):171-99. Review.

6. Soballe B, Poole RK. Microbial ubiquinones: multiple roles in respiration, gene regulation and oxidative stress management. Microbiology. 1999; v.145 (Pt 8):1817-30. Review.

7. Dufresne, A., M. Salanoubat, et al. (2003). Genome sequence of the cyanobacterium Prochlorococcus marinus SS120, a nearly minimal oxyphototrophic genome. PNAS, 100(17): 10020-10025.