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1 **Advances in bacterial pathways for the biosynthesis of ubiquinone**

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17
18
19 **Keywords**

20 Ubiquinone, biosynthesis, evolution, isoprenoid quinone, bacteria, respiration, anaerobiosis, pathway

21
22
23 **Highlights**

- 24
- 25 • Ubiquinone is a crucial component of bacterial bioenergetics
 - 26 • The bacterial pathways to produce ubiquinone are highly diverse
 - 27 • Ubiquinone is produced in anoxic conditions by a dioxygen-independent pathway
 - 28 • Ubi-, mena- and plasto-quinone biosynthetic pathways are evolutionary related

29 **Abstract**

30 Ubiquinone is an important component of the electron transfer chains in proteobacteria and
31 eukaryotes. The biosynthesis of ubiquinone requires multiple steps, most of which are common to bacteria
32 and eukaryotes. Whereas the enzymes of the mitochondrial pathway that produces ubiquinone are highly
33 similar across eukaryotes, recent results point to a rather high diversity of pathways in bacteria. This review
34 focuses on ubiquinone in bacteria, highlighting newly discovered functions and detailing the proteins that
35 are known to participate to its biosynthetic pathways. Novel results showing that ubiquinone can be
36 produced by a pathway independent of dioxygen suggest that ubiquinone may participate to anaerobiosis,
37 in addition to its well-established role for aerobiosis. We also discuss the supramolecular organization of
38 ubiquinone biosynthesis proteins and we summarize the current understanding of the evolution of the
39 ubiquinone pathways relative to those of other isoprenoid quinones like menaquinone and plastoquinone.

40

41 1) Introduction

42 Isoprenoid quinones are central to bioenergetics as they constitute obligate electrons and protons
43 shuttles in the respiratory chains of most organisms. These molecules are composed of a quinone head
44 group (in most cases a naphtho- or a benzo- ring) to which is attached a polyprenyl tail with a length that
45 varies depending on the organisms (from 4 to 14 isoprene units, indicated as subscript, Q_{4-14}) (Figure 1) ¹.
46 A specific number of isoprene units characterizes the quinone pool (Q_n) of a given species, but several
47 lower abundance isoprenologs, typically Q_{n-1} and Q_{n+1} , are also usually produced ^{2,3}. The polyprenyl tail is
48 hydrophobic and localizes isoprenoid quinones inside membranes. The polar head group is the functional
49 part of the molecule and undergoes a two-steps redox chemistry between quinone (oxidized) and quinol
50 (reduced) forms ¹. Historically, isoprenoid quinones have been used as chemotaxonomic markers ^{2,3} and
51 more recently, quinone profiles served as markers of bacterial communities in complex ecosystems ^{4,5}.

52 Isoprenoid quinones are classified based on the nature of the head group and also according to
53 their midpoint redox potential. Menaquinone (MK) belongs to naphthoquinones, whereas ubiquinone
54 (UQ), plastoquinone (PQ) and rhodoquinone (RQ) are benzoquinones (Figure 1). Classically, MK and RQ
55 are considered low potential quinones ($E' \sim -70$ mV), whereas UQ and PQ are high potential quinones (E'
56 $\sim +100$ mV) ⁶. The redox potential of quinones determines the protein partners with which they
57 functionally interact in respiratory chains. For example, complex II reduces UQ in the oxidation of succinate
58 into fumarate, and it oxidizes RQ in the reduction of fumarate into succinate ⁷; the related
59 quinol:fumarate reductase oxidizes MK ⁸. Excellent reviews have covered the taxonomic distribution, the
60 functions and the biosynthesis of isoprenoid quinones ^{1,9} and the case of RQ is discussed in detail by
61 Shepherd and colleagues in this issue of BBA-Bioenergetics ¹⁰.

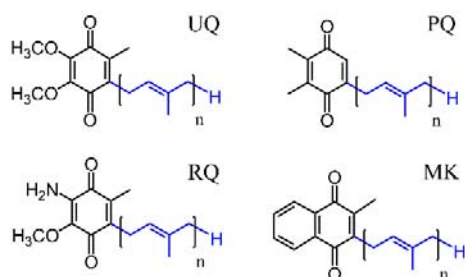


Figure 1: Chemical structures of common isoprenoid quinones. The polyprenyl chain of various lengths are in blue and the polar head groups are in black. The molecules are represented in their oxidized form. However, in this review, the abbreviations used for quinones (UQ, RQ, MK, PQ) refer to the molecules irrespective of their redox state, which will be specified in the text, when necessary.

69
70 MK, which is present in most bacterial phyla and in archaea, was proposed to have been a
71 component of the bioenergetic toolbox of the last universal common ancestor (LUCA) ^{6,11}. In contrast, UQ
72 evolved later and is restricted to specific classes of proteobacteria (α , β , γ) and to eukaryotes, in which UQ
73 participates to oxidative phosphorylation in mitochondria. Much attention has been paid to the

74 biosynthesis and functions of UQ (also called coenzyme Q) in eukaryotes, and these topics - including the
75 pathologies resulting from coenzyme Q deficiencies in humans - have been covered recently in
76 authoritative reviews^{9,12-15}.

77 In contrast, an update is needed for UQ in bacteria. The historical model to study bacterial UQ
78 biosynthesis has been *Escherichia coli* and several recent discoveries advanced our understanding of the
79 UQ pathway in this species. At the same time, studies on other bacterial models revealed substantial
80 differences with the *E. coli* pathway and highlighted an unsuspected diversity of solutions evolved by
81 bacteria to synthesize UQ. The numerous sequences of bacterial genomes now available in public
82 databases also appear to be a very relevant source of information with this respect. In this review, we
83 summarize the recent results obtained on bacterial UQ biosynthesis and functions, and we emphasize how
84 they advanced our current understanding of the field.

85

86 **2) New functions for UQ in bacteria**

87 The functions of UQ related to respiration, gene regulation and oxidative stress have been
88 reviewed elsewhere^{16,17} and will not be covered here. In 2014, Sevin and Sauer reported that UQ promotes
89 tolerance to osmotic stress in *E. coli*¹⁸. The authors showed that the growth of a UQ-deficient strain was
90 impaired when the medium contained high concentrations of salt. Furthermore, they observed a ~100
91 fold increase of the UQ content in response to osmotic stress¹⁸. In such conditions, UQ represented ~1%
92 of the lipids constituting the plasma membrane of *E. coli*. UQ and structural analogs had a stabilizing effect
93 on liposomes, which led the authors to propose that the polyprenyl tail of UQ mediates a mechanical
94 stabilization of the plasma membrane that likely explains the osmoprotective effect observed *in vivo*¹⁸.
95 However, these results have been challenged recently¹⁹. Indeed, a new study suggests that the impaired
96 growth of UQ-deficient *E. coli* cells at high osmotic pressure was simply caused by the compromised
97 function of the respiratory chain, which affected the proton-solute symporter ProP¹⁹. ProP mediates the
98 uptake of zwitterionic osmolytes such as proline and glycine betaine, and requires high proton-motive
99 force for function. As the proton gradient is compromised in the absence of UQ, the function of ProP is
100 impaired, impacting osmotic regulation¹⁹. The authors also found that UQ amounted to ~1% of the total
101 lipids, but the UQ content was not significantly modulated by the osmotic pressure of the growth medium
102¹⁹, consistent with unpublished results from several laboratories (personal communications of David
103 Pagliarini and Gilles Basset) and ours. Overall, it appears that UQ levels do not respond to osmotic stress

104 and that the decreased tolerance to osmotic stress observed in UQ-deficient *E. coli* cells results from an
105 indirect effect of the inactivation of the respiratory chain¹⁹. Even though multiple *in vitro* studies reported
106 that UQ modifies the mechanical and physical properties of liposomes (^{18,20} and references therein),
107 sometimes at UQ concentrations hardly compatible with biological levels, the direct impact of UQ on the
108 properties of membranes does not seem relevant for protection against osmotic stress *in vivo*.

109 A new contribution of UQ to cell metabolism was described by Chaba and colleagues who showed
110 that UQ is required by *E. coli* to grow on medium containing long-chain fatty acids (LCFAs) as a carbon
111 source²¹. Interestingly, mutants with intermediate UQ levels (15-20% compared to wild-type) grew
112 normally on various non-fermentable carbon sources but not on the LCFA oleate. Thus, in addition to its
113 role as an electron shuttle in the respiratory chain, UQ has another function in oleate metabolism. The
114 authors suggested that the antioxidant function of the reduced form of UQ was important based on the
115 observations that the level of reactive oxygen species (ROS) increased in cells metabolizing oleate, and
116 that supplementation with antioxidants improved growth and decreased ROS levels of UQ-deficient
117 mutants in oleate-containing medium²¹. Remarkably, UQ levels increased ~1.8 fold in cells metabolizing
118 oleate. Overall, the authors proposed that UQ is the preponderant antioxidant system during LCFA
119 degradation and acts to mitigate ROS production by the acyl-CoA dehydrogenase FadE. In this regard, UQ
120 might be particularly important for pathogenic bacteria that use LCFAs derived from host tissues as their
121 main nutrient²¹.

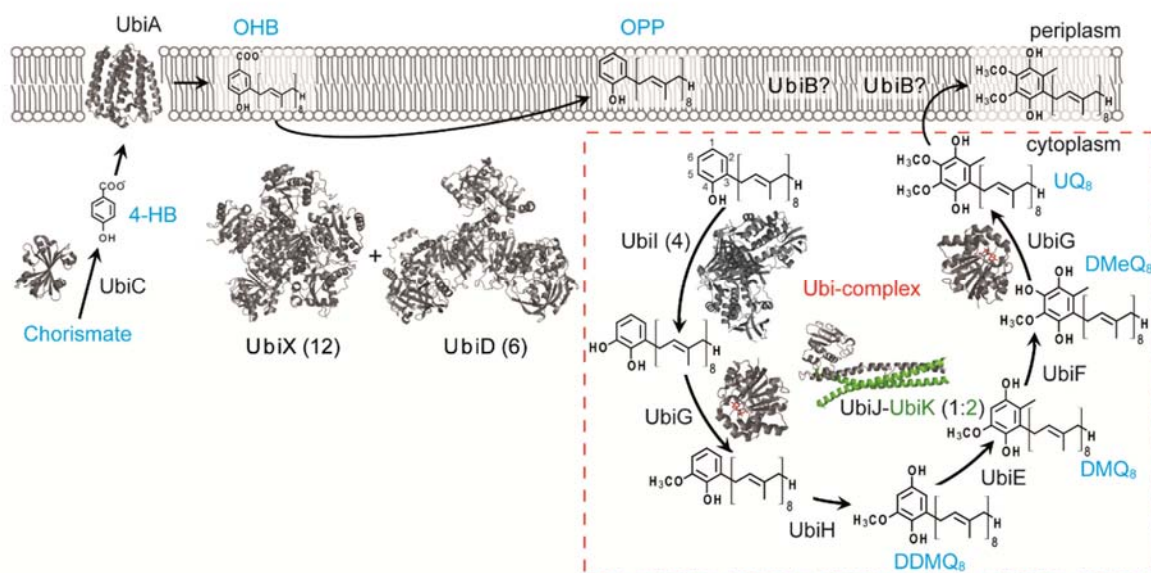
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123 **3) UQ biosynthesis in *E. coli***

124 **3.1 Biochemical steps of the classical pathway and enzymes involved**

125 Over a period of several decades, the UQ biosynthetic pathway has been extensively studied in *E.*
126 *coli*, a bacterium that synthesizes UQ₈ as its main isoprenolog. Nowadays, the pathway is known to require
127 twelve proteins (UbiA to UbiK and UbiX), most of them being involved in reactions that modify the
128 aromatic ring originating from 4-hydroxybenzoic acid (4-HB) (Figure 2). UbiC is the first committed enzyme
129 in the biosynthesis of UQ₈, catalyzing the removal of pyruvate from chorismate to produce 4-HB²². Then,
130 the membrane-bound UbiA prenylates 4-HB using octaprenyl diphosphate (a molecule with 40 carbon
131 atoms) as a side chain precursor²³. The octaprenyl diphosphate synthase IspB synthesizes the C₄₀ chain by
132 successive condensation of five isopentenyl diphosphate units onto a C₁₅ precursor formed by the
133 diphosphate synthase IspA²⁴. The length of the octaprenyl diphosphate moiety is controlled by bulky

134 residues at the bottom of the active site tunnel, Met 123 and Met 135 in *E. coli* IspB²⁵. Recent three
 135 dimensional (3D) structures of two members in the UbiA superfamily^{26,27} revealed an all α -helical structure
 136 that is completely different from the α/β barrel structure of soluble aromatic prenyltransferases, in
 137 agreement with a catalysis that occurs in lipid bilayers. Both UbiA homologs contain nine transmembrane
 138 helices arranged counterclockwise in a U-shape presenting a large central cavity with an opening
 139 assimilated to a lateral portal that is largely buried in the membrane. It was proposed that this lateral
 140 portal may facilitate the binding of long-chain isoprenyl diphosphate substrates, the prenylated products
 141 being directly released into membranes through this portal^{26,27}. We note that the two crystallized UbiA
 142 homologs belong to archaeal species and as such do not participate to UQ biosynthesis. However, given
 143 the conservation of important catalytic residues with *E. coli* UbiA²⁷, we believe that the structural insights
 144 provided by these structures are largely applicable to UbiA family members involved in UQ biosynthesis.



145
 146 **Figure 2:** Model of UQ₈ biosynthesis in *E. coli* and supramolecular organization of the pathway. The names
 147 of precursors and intermediates are indicated in blue and the molecules are represented in their reduced
 148 forms. The red dotted rectangle delimits the Ubi-complex, which is composed of UbiE to UbiK proteins and
 149 encompasses the last six reactions of the pathway. The numbering of the aromatic carbon atoms is shown
 150 on OPP. Abbreviations used are: 4-HB, 4-hydroxybenzoate; OHB, octaprenyl-4-hydroxybenzoate; OPP,
 151 octaprenyl phenol; DDMQ₈, C2-demethyl-C6-demethoxy-ubiquinone 8; DMQ₈, C6-demethoxy-ubiquinone
 152 8; DMeQ₈, 6-demethyl-ubiquinone 8; UQ₈, ubiquinone 8. The 3D-structures of UbiC (PDB ID: 1G81), UbiI
 153 (PDB ID: 4K22), UbiD (PDB ID: 5M1B) and UbiG (PDB ID: 4KDR) correspond to the proteins from *E. coli* and
 154 the 3D-structures of UbiX (PDB ID: 4RHE) and UbiA (PDB ID: 4TQ5) correspond to the proteins from
 155 *Pseudomonas aeruginosa* and *Archaeoglobus fulgidus*, respectively. The UbiJ monomer is colored grey and
 156 the UbiK dimer is colored green in the model of the *E. coli* UbiK–UbiJ 2:1 heterotrimer complex²⁸. The

157 oligomerization state of the 3D-models is indicated in brackets when it is greater than one. The ribbon
158 diagrams were drawn using PyMOL (DeLano Scientific LLC).

159
160 Following its prenylation by UbiA, 4-HB is decarboxylated by the UbiD-UbiX system, which consists
161 of the decarboxylase UbiD and its associated flavin prenyltransferase UbiX that produces the prenylated
162 FMN (pFMN) used as a cofactor by UbiD²⁹. Recent studies have provided structural insights into the
163 mechanism of both enzymes, detailing unusual chemistry in each case^{30–32}. Crystal structures of UbiD from
164 *E. coli* in complex or not with pFMN have been solved, showing the quaternary structure as
165 homohexamers³¹. The 3D-structure of UbiX from *Pseudomonas aeruginosa* is organized as a
166 homododecamer²⁹. Interestingly, Blue Native-PAGE of *E. coli*'s soluble extracts showed a co-migration of
167 UbiD and UbiX at ~700 kDa, compatible with a UbiD₆-UbiX₁₂ complex (theoretical mass of 582 kDa)
168 suggested by the individual 3D-multimeric structures³³. The apparent difference in mass may reflect
169 aberrant migration in native gels or the presence of additional proteins in the complex.

170 Both *O*-methylation reactions in the biosynthesis of UQ₈ are catalyzed by the *S*-adenosyl-L-
171 methionine (SAM)-dependent UbiG protein (Figure 2). Crystal structures of UbiG in complex with *S*-
172 adenosyl-L-homocysteine have been determined, with the proteins organized as monomers^{34,35}.
173 Interestingly, the conserved region from amino acid 165 to 187 was identified in UbiG as essential for *in*
174 *vivo* UQ production and for *in vitro* interaction with liposomes. The authors hypothesized that, upon
175 interaction with membrane lipids, this region may promote the entrance of SAM into the protein^{34,35}.
176 However, whether or not the membrane association of UbiG contributes to its catalytic activity has not
177 yet been investigated. Moreover, UbiG purified from *E. coli* extracts exhibits *in vitro* methyltransferase
178 activity³⁶ and a large part of UbiG is detected in the soluble fraction³³. Thus, the relevance of the lipid
179 binding region of UbiG remains unclear, especially when considering that UbiG is part of the soluble Ubi
180 complex³³ (see 3.3). The *C*-methylation reaction of the pathway is catalyzed by UbiE, a SAM-dependent
181 methyltransferase that is involved in the biosynthesis of UQ and MK³⁷. UbiE, for which no structural
182 information is yet available, converts DDMQ₈ to DMQ₈ (2-octaprenyl-6-methoxy-1,4-benzoquinone to 2-
183 octaprenyl-3-methyl-6-methoxy-1,4-benzoquinone, Figure 2) and demethyl-menaquinone to MK³⁷.

184 Finally, three related class A flavoprotein monooxygenases (FMOs) – UbiH, UbiI and UbiF - catalyze
185 hydroxylation reactions on the aromatic ring at carbon atoms C-1, C-5, and C-6, respectively^{38,39} (Figure
186 2). These FMOs use dioxygen as a source of hydroxyl⁴⁰ and use the flavin adenine dinucleotide (FAD) to

187 activate O₂. UbiI and UbiH seem specific of the position that they modify, whereas UbiF has a broader
188 regio-selectivity since it has a limited ability to hydroxylate C-5 in addition to C-6³⁹. The 3D-structure of a
189 truncated form of UbiI revealed an association as a tetramer, with each monomer containing a typical FAD-
190 binding domain with a Rossmann-like $\beta/\alpha/\beta$ -fold³⁹. It is important to note that *in vitro* assays have still not
191 been developed for most Ubi enzymes, owing in part to the difficulty to obtain isolated purified proteins
192 and to manipulate highly hydrophobic substrates.

193 3.2 Accessory proteins in UQ biosynthesis

194 Besides the enzymes discussed above, accessory proteins are also involved in UQ biosynthesis.
195 UbiB is an important accessory factor given the nearly complete absence of UQ in *E. coli* mutants lacking
196 a functional *ubiB* gene⁴¹. UbiB was originally assigned to the C5-hydroxylation step⁴¹, which is now known
197 to depend on UbiI³⁹. The UbiB family, composed of bacterial UbiB proteins and of the eukaryotic homologs
198 Coq8-ACDK3/4, belongs to the atypical protein kinase-like family⁴². Biochemical studies of Coq8 and
199 ADCK3 showed that these proteins interact with UQ intermediates and possess ATPase activity but lack
200 kinase activity *in trans*^{42,43}. Furthermore, the ATPase activity is stimulated by the interaction with
201 membranes containing cardiolipin and by compounds that resemble UQ intermediates⁴⁴. Overall, UbiB
202 family members were hypothesized to couple the hydrolysis of ATP to the extraction of UQ precursors out
203 of the membrane in order to make them available for UQ biosynthetic enzymes⁴⁴, but this hypothetical
204 role remains to be confirmed.

205 Two other accessory factors, UbiJ and UbiK (formerly YigP and YqiC), were identified recently^{28,45}.
206 Cells lacking *ubiJ* show a complete absence of UQ, while *ubiK* mutants retain ~ 20% UQ compared to wild-
207 type. The UQ deficiency is apparent only when the cells are grown in oxic conditions, suggesting that UbiJ
208 and UbiK do not play important functions for UQ biosynthesis under anoxic conditions^{28,45,46}. Purified UbiJ
209 and UbiK interact and form an elongated UbiJ₁:UbiK₂ complex²⁸ (Figure 2). UbiJ is able to bind UQ
210 biosynthetic intermediates via its Sterol Carrier Protein 2 (SCP2) domain, which crystal structure was
211 solved recently³³. The current hypothesis is that UbiJ and UbiK assist several steps of UQ biosynthesis by
212 presenting UQ intermediates to Ubi enzymes inside the Ubi complex (see 3.3)³³. In addition to producing
213 a protein, the *ubiJ* locus was proposed to encode a small non-coding RNA (sRNA) termed EsrE^{47,48}. EsrE is
214 composed of 252 nucleotides and resides in the 3' half of the *ubiJ* gene⁴⁸. Our group showed that the C-
215 terminal part of the UbiJ protein is sufficient to maintain a minimal level of UQ biosynthesis and we
216 provided evidence to rule out the implication of a sRNA⁴⁵. In contrast, another group reported that both
217 the UbiJ protein and the sRNA EsrE are involved in UQ biosynthesis^{48,49}. While some controversy remains,

218 data from both groups agree that the main contribution of the *ubiJ* locus to UQ biosynthesis is carried out
219 by the UbiJ protein rather than by the sRNA EsrE^{45,49}.

220 Finally, a new *E. coli* gene (named *pasT* in the uropathogenic strain CFT073, and *ratA* in the
221 MG1655 laboratory strain) was very recently connected to aerobic respiration and UQ functioning in ETC
222⁵⁰. CFT073 cells lacking PasT exhibited a mild defect for *de novo* UQ biosynthesis in early exponential
223 growth phase but had normal steady state levels of UQ. The *pasT/ratA* mutant cells displayed several
224 phenotypes consistent with impaired aerobic respiration, among which decreased membrane potential,
225 sensitivity to H₂O₂ and small colony size⁵⁰. These phenotypes were complemented with Coq10, the
226 eukaryotic homolog of PasT/RatA, which was proposed to function as a lipid chaperone that facilitates the
227 implementation of UQ in the electron transport chain^{51,52}. Overall, PasT/RatA do not seem important for
228 UQ biosynthesis, but rather act to promote the function of UQ in aerobic respiration⁵⁰.

229 3.3 Supramolecular organization of the *E. coli* UQ biosynthetic pathway

230 Since UbiA adds the polyprenyl tail onto 4-HB early on (Figure 2), most biosynthetic intermediates
231 of the UQ pathway contain the octaprenyl tail and are therefore highly hydrophobic. Surprisingly, Ubi
232 proteins acting downstream of UbiA are mostly soluble and the last six reactions of the pathway take place
233 in soluble extracts, and not in the membrane fraction as the hydrophobicity of the biosynthetic
234 intermediates would predict³³. In fact, we showed that a ~1 MDa Ubi complex composed of seven proteins
235 (UbiE-K) exists in the soluble fraction of *E. coli* extracts³³. This complex contains the five enzymes (UbiE-I)
236 that catalyze the reactions downstream of OPP (Figure 2) and the accessory factors UbiJ and UbiK, the
237 former being essential to the stability of the Ubi complex³³. We also demonstrated that the biosynthetic
238 intermediates OPP and DMQ₈ are bound in the Ubi complex and we proposed that the N-terminal SCP2
239 domain of UbiJ mediates the interaction³³. Altogether, the current model is that the Ubi complex forms a
240 soluble metabolon that synthesizes UQ from OPP (Figure 2). The trafficking of these two hydrophobic
241 molecules between the membrane and the Ubi complex might involve the UbiB protein with its ATPase
242 activity and its predicted C-terminal transmembrane domain^{33,44}.

243 Interestingly, a similar organization of the UQ pathway has also been described in eukaryotes with
244 complex Q (also termed the 'CoQ-synthome'). Complex Q groups the enzymes of the late steps^{12,53}, but it
245 is associated to the membrane, contrary to the Ubi complex which is soluble. Outstanding questions
246 remain regarding the supramolecular assembly of the UQ pathway, notably the conservation of the Ubi
247 complex in other bacterial species, the exact composition and stoichiometry of the complexes, their 3D

248 structures, their potential dynamic nature and their cellular localization. A recent study began to address
249 the two latter points in yeast ⁵⁴.

250 3.4 Discovery of a conserved O₂-independent pathway

251 Based on the observation that *E. coli* was able to synthesize UQ under anoxic conditions, the
252 existence of a UQ biosynthesis pathway independent from O₂ had long been hypothesized ⁵⁵. This pathway
253 remained uncharacterized until 2019, when we identified three genes, *ubiT*, *ubiU* and *ubiV* which are
254 required for UQ biosynthesis under anoxic conditions but are dispensable under oxic conditions ⁴⁶. The
255 only reactions that differ between the O₂-dependent and O₂-independent pathways are the three
256 hydroxylation steps catalyzed by the O₂-consuming flavin hydroxylases UbiI, UbiH and UbiF ⁴⁶. UbiU and
257 UbiV, which belong to the U32 peptidase family, form a heterodimer that is required for the hydroxylation
258 of DMQ₈ *in vivo*. This result is in line with the demonstration that UbiU from *P. aeruginosa* co-purifies with
259 UQ₈ and DMQ₈ ⁵⁶. Besides obtaining evidence for a role of UbiU and UbiV in the hydroxylation of DMQ₈ ⁴⁶,
260 we also hypothesized that UbiU and UbiV may participate in the two other hydroxylation steps of the
261 anaerobic UQ pathway, thus substituting for UbiI and UbiH of the O₂-dependent pathway (Figure 3A) ^{46,56}.
262 A role for UbiU and UbiV in O₂-independent hydroxylation reactions is supported by recent studies showing
263 that two other U32 peptidase family members - RlhA and TrhP – are required for the hydroxylation of
264 C2501 on 23S rRNA ⁵⁷ and of U34 on some tRNAs ^{58,59}, respectively. The source of oxygen used in the
265 hydroxylation reactions involving U32 peptidase family members is unknown at this stage but prephenate,
266 a metabolite of the shikimate pathway, is a candidate since it is required for the function of RlhA and TrhP
267 ^{57,59}. The presence of an iron-sulfur cluster might be another feature common to U32 proteins. Indeed, we
268 showed that UbiU and UbiV each carry a 4Fe-4S cluster ligated by a motif of conserved cysteine residues,
269 which is found in most U32 peptidase family members ⁴⁶. Interestingly, the function of RlhA and TrhP
270 depends on these Cys residues and on the genes of the *isc* operon that catalyze the biogenesis of Fe-S
271 clusters ^{57,59}. Some additional players may also be involved in the function of UbiU and UbiV, like the low
272 potential ferredoxin YhfL, which is required for the hydroxylation of tRNAs by TrhP ⁵⁸. Overall, the U32
273 peptidase family emerges as a new class of O₂-independent hydroxylases and additional work is required
274 to elucidate the mechanism of these enzymes and the precise function of UbiU and UbiV in UQ
275 biosynthesis.

276 The role of UbiT in the O₂-independent UQ biosynthetic pathway is still unclear. Yet, the presence
277 of a SCP2 domain in the sequence of UbiT and the demonstration that UbiT binds the lipid phosphatidic

278 acid ⁶⁰ suggests that UbiT's function is linked to lipids. Moreover, we recently showed that UbiT from *P.*
279 *aeruginosa* binds UQ₈ by recognizing its isoprenoid tail ⁵⁶, suggesting that UbiT may perform a role similar
280 to UbiJ in presenting the hydrophobic intermediates of the UQ pathway to Ubi enzymes. Interestingly, UbiJ
281 is important for UQ biosynthesis only in oxic conditions, whereas the role of UbiT is limited to anoxic
282 conditions ^{45,46}. The possibility that UbiJ and UbiT may functionally replace each other depending on
283 environmental conditions is an appealing hypothesis, given that both SCP2 proteins need to assist different
284 sets of UQ biosynthetic enzymes, the O₂-dependent hydroxylases (UbiI, UbiH, UbiF) in one case, and the
285 O₂-independent hydroxylases (likely UbiU and UbiV) in the other case.

286 The *ubiT*, *ubiU* and *ubiV* genes are widespread in proteobacterial genomes that possess the O₂-
287 dependent UQ pathway, suggesting that numerous bacteria have the previously unrecognized capacity to
288 synthesize UQ over the entire O₂ range ⁴⁶. The low potential quinones MK and RQ are typically involved in
289 transferring electrons in anaerobic respiratory chains, thus the physiological function(s) of UQ synthesized
290 in anoxic conditions remains to be clarified in proteobacteria possessing both UQ and MK pathways.
291 Whether bacteria synthesizing RQ possess or not the O₂-independent UQ biosynthesis pathway is an
292 interesting question, which has not been investigated yet. Several gram-negative bacteria, such as *P.*
293 *aeruginosa*, contain UQ as sole quinone ². We found that the *ubiT*, *ubiU* and *ubiV* genes are essential for
294 UQ production by *P. aeruginosa* in anoxic conditions and that these genes are required for denitrification
295 ⁵⁶, a metabolism on which *P. aeruginosa* heavily relies to develop in the lungs of cystic fibrosis patients.
296 Overall, the discovery of a widespread UQ pathway independent of O₂ certainly changes our perspective
297 of the relative contribution of various quinones to bacterial metabolism under hypoxic and anoxic
298 conditions. Interestingly, substantial amounts of UQ were reported lately in the anoxic zone of the water
299 column of the Black Sea ⁵, suggesting that an O₂-independent pathway could have been at work in this
300 ecosystem. It remains to be investigated whether or not bacteria containing *ubiT*, *ubiU* and *ubiV* genes are
301 found in this ecological niche. By extension, assessing the contribution of the O₂-independent UQ pathway
302 to anaerobiosis constitutes an exciting new research avenue.

303

304 **4) Variations in UQ biosynthesis pathways across bacteria**

305 Our current view of the biosynthesis of UQ in bacteria is mostly based on the *E. coli* pathway ¹⁷.
306 Even though numerous discoveries on *E. coli* are applicable to other bacterial species, recent studies using

307 other bacterial models revealed an unsuspected diversity in the composition of the UQ biosynthesis
308 pathway across bacteria.

309 4.1 Synthesis of the aromatic ring precursor

310 So far, only 4-HB has been described as an aromatic ring precursor for UQ in bacteria. In contrast,
311 the eukaryote *Saccharomyces cerevisiae* is able to use additional molecules like para-aminobenzoic acid
312 (pABA)^{61,62}. Note that pABA was shown to be processed through several steps of the UQ pathway in *E. coli*
313 ⁶². However, the amino-substituted intermediates were not converted into UQ ⁶², thus pABA is not
314 considered a precursor for UQ in *E. coli*. The first gene identified to synthesize 4-HB for bacterial UQ
315 biosynthesis was *ubiC*, which encodes a chorismate pyruvate-lyase ²². The *xanB2* gene of *Xanthomonas*
316 *campestris* was later shown to encode a chorismatase that produces 4-HB for UQ biosynthesis and 3-
317 hydroxybenzoic acid for the biosynthesis of pigments from the xanthomonadin family ⁶³. Even though UbiC
318 and XanB2 use the same substrate – chorismate, the end product of the shikimate pathway – they do not
319 share sequence or structural identities and belong to different protein families, chorismate pyruvate-lyase
320 and chorismatase, respectively ⁶³. *xanB2* is present in several proteobacterial genera that do not contain
321 *ubiC* ⁶³, supporting a strong anti-occurrence of the two genes, although this has not been analyzed in detail.
322 It is currently unclear if all UQ producing bacteria contain UbiC or XanB2 or if additional unidentified 4-HB
323 generating systems might also be involved in some species. Interestingly, a new subfamily of chorismatase
324 (type IV) was shown to produce only 4-HB (and not a mixture of 3-HB and 4-HB as the type III chorismatase
325 XanB2) ⁶⁴ and may therefore represent a new candidate to produce 4-HB for UQ biosynthesis.

326 4.2 Hydroxylases

327 Three hydroxylation reactions on contiguous positions of the aromatic ring are required during
328 the biosynthesis of UQ. The enzymes (UbiI, UbiH and UbiF) involved in the O₂-dependent *E. coli* pathway
329 each hydroxylate one position and belong to the same family of flavin monooxygenases. An unrelated di-
330 iron monooxygenase Coq7 is implicated in the C-6 hydroxylation instead of UbiF in some bacterial species
331 ⁶⁵⁻⁶⁷. In 2016, a search for these four monooxygenases over representative proteobacterial genomes led
332 to the identification of two new flavin monooxygenases, UbiL and UbiM ⁶⁸. This study revealed an
333 astonishing diversity of combinations of monooxygenases used by bacteria to synthesize UQ (19
334 combinations in 67 species) ⁶⁸. Interestingly, some genomes contained less than three UQ
335 monooxygenases ⁶⁸. We demonstrated that the UbiL protein from *Rhodospirillum rubrum* hydroxylates
336 two positions (C-1 and C-5) and that the UbiM protein from *Neisseria meningitidis* hydroxylates three

337 positions, rationalizing the presence of respectively two and one UQ monooxygenase genes in these
338 species. Some genes are restricted to specific classes (*ubiL* to α - and *ubiF* to γ -proteobacteria), while the
339 distribution of *ubiM* across α , β , γ -proteobacteria is likely the result of horizontal gene transfer ⁶⁸.
340 Intriguingly, some species such as *Xanthomonas campestris* or *Alteromonas macleodii* contain four UQ
341 monooxygenases ⁶⁸. The reason as to why bacteria evolved such a diversity of O₂-dependent UQ
342 monooxygenases is still unknown. Of note, the putative hydroxylases of the O₂-independent pathway
343 show probably less diversity since a very high co-occurrence of UbiU and UbiV was observed ⁴⁶.

344 4.3 Incomplete UQ biosynthesis pathways

345 The decarboxylation step of the pathway seems also variable. Indeed, the only enzyme implicated
346 so far is the UbiD decarboxylase assisted by the prenyl-transferase UbiX ⁶⁹. However, several authors
347 recently noticed the absence of *ubiX-ubiD* genes from genomes containing most of the other *ubi* genes,
348 suggesting that another enzymatic system could be involved in the decarboxylation reaction ^{67,70,71}. A
349 candidate gene *ubiZ* was proposed based on its co-localization with *ubiE* and *ubiB* in the genomes of
350 *Acinetobacter spp.* and *Psychrobacter sp.* PRwf-1 ⁷¹. However, the sequence of UbiZ is quite short (~ 160
351 aa) and does not resemble any known decarboxylases, so a careful investigation of its potential role as a
352 decarboxylase is needed. In any case, the fact that the *ubiZ* gene is not conserved in all the genomes lacking
353 *ubiD* and *ubiX* suggests the existence of yet another decarboxylation system in UQ biosynthesis (Table 1).

354 Another intriguing possibility is that incomplete quinone biosynthesis pathways might
355 nevertheless be functional. Indeed, organisms with incomplete pathways might be able to scavenge
356 particular metabolites from their environment rather than to synthesize them intracellularly. As such,
357 genetic gaps in *Wolbachia* for the biosynthesis of 4-HB and of isopentenyl diphosphate (one of the building
358 blocks of the polyprenyl tail of UQ), led the authors to propose that these compounds might be acquired
359 exogenously in order to support UQ biosynthesis ⁷². Remarkably, *Streptococcus agalactiae* synthesizes its
360 demethylmenaquinone thanks to a partial MK biosynthesis pathway and the uptake of the late
361 intermediate 1,4-dihydroxy-2-naphthoic acid (DHNA) from the extracellular environment ⁷³. Several
362 *Lactobacillus* species also contain a partial MK pathway ⁷¹, suggesting that these bacteria might also rely
363 on the import of exogenous intermediates to synthesize MK. Exchanges of metabolites between species
364 are common in bacterial communities as in the gut of vertebrates, and small soluble components like
365 DHNA are likely exchanged more easily than the large hydrophobic intermediates of the UQ pathway.
366 Therefore, this strategy of complementing a partial pathway by importing extracellular intermediates is

367 certainly more applicable to quinone pathways with a prenylation reaction occurring at a late stage (like
 368 the MK pathway in which most intermediates are small and hydrophilic ⁹) rather than to UQ and PQ
 369 pathways with early prenylation steps, and consequently large and hydrophobic intermediates.

370 Overall, the large diversity of combination of enzymes used to synthesize UQ in various
 371 environmental conditions (Table 1) leads us to refer to UQ biosynthesis pathways and not anymore to a
 372 single pathway, as already proposed by Degli Esposti ⁷⁰. We envision that even more UQ pathways will be
 373 revealed by systemic bioinformatic approaches aimed at studying the variations of UQ biosynthesis in the
 374 ever expanding diversity of bacterial genomes available. Let's mention here that the task faces several
 375 difficulties, one of which is that only some *ubi* genes tend to group into operonic structures whereas others
 376 are dispersed around the chromosome ¹⁷.

377 **Table 1:** Protein composition of the bacterial UQ biosynthetic pathways. green: proteins involved only in
 378 the O₂-independent pathway; red: proteins involved only in the O₂-dependent pathway, ?: suspected
 379 existence of unidentified alternative proteins

380

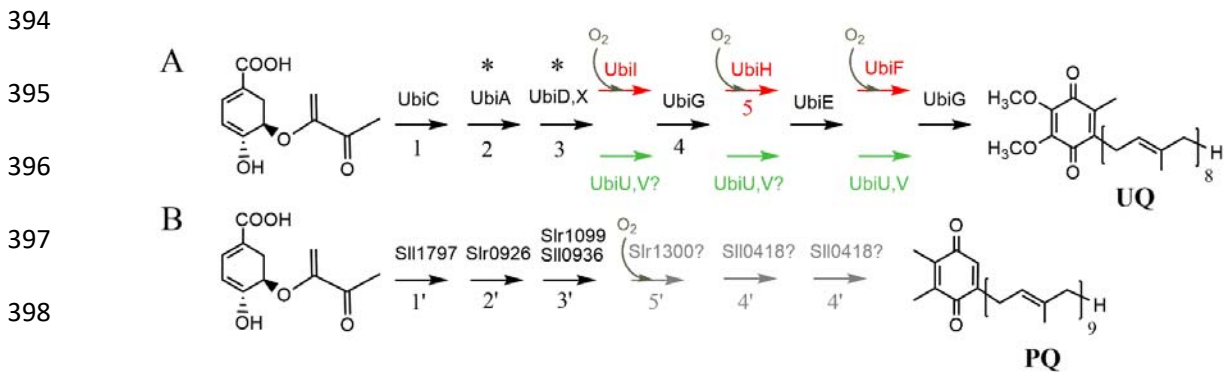
| Step or function | <i>E. coli</i> pathways | | Alternative proteins in other bacteria |
|---------------------------------------|---|-----------------------------|---|
| | O ₂ -dependent | O ₂ -independent | |
| Synthesis of polyprenyl-pyrophosphate | IspA, IspB | IspA, IspB | |
| Synthesis of 4-HB | UbiC (chorismate lyase) | UbiC | XanB2 (chorismatase) |
| Polyprenyl transferase | UbiA | UbiA | |
| Decarboxylation | UbiD (decarboxylase) UbiX (flavin prenyltransferase) | UbiD UbiX | UbiZ?, ? |
| Methylation | UbiG, UbiE | UbiG, UbiE | |
| Hydroxylation | UbiH, UbiF, UbiI (flavin cofactor) | UbiU, UbiV (Fe-S cofactor) | UbiL, UbiM (flavin cofactor) Coq7 (di-iron cofactor) |
| SCP2 protein | UbiJ | UbiT | |
| ATPase | UbiB | UbiB | |
| Accessory factor | UbiK | | |

381

382 **5) An evolutionary perspective on (ubi)quinone biosynthetic pathways**

383 The rise of O₂ concentrations on Earth caused a shift from globally reducing to oxidizing conditions
 384 around 2.4 billion years ago ⁷⁴. This transition had far-reaching consequences, notably for quinones.
 385 Indeed, the low potential MK, which was present at the time of the great oxidation event, is readily
 386 oxidized by O₂ ⁷⁵. Thus, it was proposed that microorganisms had to evolve higher potential quinones, like
 387 UQ and PQ, to sustain electron transport in bioenergetic chains operating under oxidizing conditions ⁷⁵.

388 This scenario is in line with the presence of O₂-requiring steps, respectively three and one, in the
 389 biosynthetic pathways for UQ and PQ (Figure 3). However, our recent discovery of an O₂-independent
 390 pathway for UQ production, widespread across proteobacterial lineages, suggests that UQ biosynthesis
 391 might have emerged in a less favorable O₂ context than previously thought ⁴⁶. One way to tackle the
 392 question of the relative origins of the quinone pathways is to study the evolution of the involved enzymes
 393 provided homologs are shared between pathways.



400 **Figure 3:** Homology between bacterial UQ- and cyanobacterial PQ- pathways. A) Biosynthetic pathway of
 401 UQ in *Escherichia coli* with enzymes specific of the O₂-dependent and O₂-independent pathways in red and
 402 green respectively. B) Biosynthetic pathway of PQ in the cyanobacterium *Synechocystis sp.* PCC 6803.
 403 Reactions 1-3 in the UQ pathway and 1'-3' in the PQ pathway are catalyzed by homologous enzymes.
 404 Proposed candidates for the PQ pathway (Slr1300? and Sll0418?) are homologous to UbiH and UbiG (see
 405 text). Enzymes with homologs in MK pathways are designated with (*).

406

407 5.1 Evolution of the UQ and PQ pathways

408 It should be possible to address the relative appearance of the UQ and the PQ pathways since they
 409 share several homologs. Here, we consider only the cyanobacterial PQ pathway which consist of six
 410 reactions (Figure 3), as opposed to the pathway found in plants which is entirely different ⁷⁶. In the
 411 cyanobacterium *Synechocystis sp.*, the first three steps of PQ biosynthesis involve homologs to UbiC, UbiA,
 412 and UbiD – UbiX of the UQ pathway: respectively, the chorismate lyase Sll1797, the 4-HB prenyltransferase
 413 Slr0926, and the decarboxylase - flavin prenyltransferase Sll0936 - Slr1099 ^{77,78} (Figure 3). The following
 414 hydroxylation and methylation steps are still to be experimentally validated, but candidates have been
 415 proposed (Slr1300 and Sll0418) based on their homology to UbiH and UbiG enzymes of the UQ pathway
 416 ⁷⁹. Degli Esposti conducted a phylogenetic analysis of the UbiA, -C, -D, -H homologs and proposed that the
 417 UQ pathway derived from the PQ pathway and appeared twice independently in Alphaproteobacteria and

418 in Zetaproteobacteria⁷⁰. Yet the trees built in this study are missing outgroups to root the phylogenies and
419 as such do not definitively address the question of the relative origins of the UQ and PQ pathways⁷⁰.

420

421 5.2 Relationships between the UQ and the MK pathways

422 Two pathways are known for the biosynthesis of MK⁹: a fully characterized, long-known “classical MK
423 pathway” and a still incomplete, more recently identified “futalosine pathway”⁸⁰. The classical MK
424 pathway has only two steps related to the UQ pathway: the prenylation step catalyzed by the
425 prenyltransferase MenA (homologous to UbiA) and the methylation of the aromatic ring catalyzed by the
426 literally shared enzyme MenG/UbiE. The characterized *mqnA-E* genes are specific to the futalosine
427 pathway⁸¹, but the still putative MqnP, MqnL, MqnM, and UbiE/MenG have homologs in the UQ pathway
428 (UbiA, UbiD and UbiX, respectively)^{71,80}. These later *mqnP*, *-L*, *-M* genes were found to strictly co-occur
429 with *mqnA-E* in many bacterial genomes, which reinforces their potential to participate in the futalosine
430 pathway⁷¹. In 2014, Zhi and colleagues observed that the futalosine pathway was found in more phyla of
431 Bacteria and Archaea than the classical MK pathway¹¹. Furthermore, phylogenies of MenB, -C, -F
432 suggested that the classical MK pathway was acquired in Archaea, specifically in Halobacteriaceae, as a
433 result of lateral gene transfers from bacteria. In contrast, phylogenies for the MqnA, -D, and -C enzymes
434 (specific to the futalosine pathway) globally retrieved the delineation of major bacterial and archaeal
435 lineages, suggesting a vertical inheritance of the futalosine pathway and an early emergence predating
436 that of the classical pathway¹¹.

437 In 2016, Ravcheev and Thiele built phylogenies for genes of the two MK, and the UQ pathways⁷¹. Their
438 trees showed that homologs from the different pathways separated well (including those of the candidate
439 MqnP, -L and -M, homologs of UQ enzymes). Interestingly, the only enzyme supposedly shared by the
440 three pathways, the prenyltransferase UbiA/MenA/MqnP family, had a phylogeny displaying a dichotomy
441 between the classical MK pathway on one side, and the futalosine and UQ pathways on another side⁷¹.
442 However, in the tree of the methyltransferase family (UbiE/MenG), candidate enzymes of the futalosine
443 pathway positioned within those of the classical MK pathway, and apart from those of the UQ pathway.
444 The authors therefore suggested that the likely younger pathway of UQ evolved from parts of the two pre-
445 existing MK pathways, with some enzymes being more closely related to the futalosine pathway, and
446 others to the classical pathway.

447 Future studies in the context of recent discoveries, including that of new pathways (e.g. the O₂-
448 independent UQ pathway) or new taxonomic groups of Archaea and Bacteria⁸², are very likely to further
449 enlighten the origins of quinones. Elucidating the evolutionary relationships of the quinone pathways is
450 indeed important as it bears strong implications for understanding the evolution of bioenergetics and
451 adaptation to extant oxidizing environments.

452

453 **6) Conclusion and Perspectives**

454 Recent results have significantly expanded our view of the biosynthesis of UQ in bacteria. Several
455 functional homologs have now been identified at various steps (Table 1) and a pathway independent from
456 O₂ has been characterized⁴⁶. The first proof of a supramolecular structuration of the *E. coli* O₂-dependent
457 UQ pathway was recently provided with the characterization of the Ubi complex³³. Whether such
458 multiprotein complexes exist or not in other bacterial species and how they accommodate the variability
459 of the constituting proteins (notably the hydroxylases) remains to be investigated. Understanding the
460 regulation of the various UQ pathways and establishing their cellular localization will also be of interest.
461 Indeed, we may expect the UQ biosynthesis apparatus to localize close to active bioenergetic enzymes,
462 and some of them adopt a specific localization, as recently observed for the fumarate dehydrogenase and
463 nitrate reductase in respiring *E. coli*⁸³. Whether the UQ pathways indeed originated from the MK pathways
464⁷¹ and how they evolved in the past 2 billion years is also a challenging and interesting question.

465 To obtain a satisfactory understanding of the composition, regulation and evolution of the UQ
466 pathways across bacteria, it will certainly be fruitful to combine biochemical and bioinformatic approaches
467 in order to extract information from the multiple genomes now available in public databases. Besides
468 increasing our basic knowledge of UQ pathways, such studies will also benefit bioengineering projects
469 aimed at increasing the production of UQ⁸⁴ or that of related natural products like anthraquinone, a
470 molecule currently in clinical trials for non-small-cell lung cancer⁸⁵. In addition, a better understanding of
471 the UQ pathways may refine possible strategies to target them in order to develop novel antibiotics, and
472 may also provide valuable information to help pinpoint the nature of the bacterial ancestor of
473 mitochondria⁸⁶.

474

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