News in Ubiquinone Biosynthesis

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Ubiquinone (named because of its ubiquitous presence in organisms) functions as an electron carrier in the mitochondrial respiratory chain. Pierrel et al. (2010) have described the presence of new actors in the biosynthesis of this venerable molecule.

Coenzyme Q (CoQ, ubiquinone) is a lipophilic component of the inner mitochondrial membrane. CoQ is an electron carrier in the respiratory chain, but also functions as an antioxidant. It consists of a benzoquinone ring, 4-hydroxybenzoic acid (4-HB), and a polyprenyl chain. After the formation of a covalent bond between the benzoquinone group and the polyprenyl tail, the resulting 3-polyprenyl-4-hydroxybenzoate (HHB) then undergoes several modifications such as hydroxylation, methylation and decarboxylation to yield ubiquinone (Figure 1). In *Saccharomyces cerevisiae*, the prenyl chain contains six isoprene groups, and ubiquinone is designated as CoQ_6. While the exact order of these reactions is speculative, ten genes (COQ1-COQ10) have been identified that encode proteins involved in CoQ_6 biosynthesis (Tran and Clarke, 2007).

4-HB was the only confirmed precursor of CoQ for more than 40 years, with no hints as to the existence of other precursors. The paper published in this issue by Pierrel et al. (2010) reports the discovery of a new precursor of CoQ, para-aminobenzoic acid (pABA). This discovery results from the observation that ferredoxin and ferredoxin reductase, encoded by *YAH1* and *ARH1* in yeast, are required for CoQ biosynthesis, probably for the first hydroxylation reaction in the pathway. The Yah1 and Arh1 proteins are located inside the mitochondrion and function as an electron transport intermediate for mitochondrial cytochromes P450. *Yah1* and *Arh1* are also involved in the biogenesis of Fe-S clusters (Lill and Muhlenhoff, 2006) and of heme A (Barros et al., 2002). They are two of the few mitochondrial proteins essential for viability.

The starting point of this work was to check if *Yah1/Arh1* were the in vivo source of electrons for the two mono-oxygenases Coq6p and Coq7p responsible for hydroxylation of the benzoquinone ring, and thereby involved in CoQ_6 synthesis. Repression of *YAH1* or *ARH1* in *S. cerevisiae* indeed resulted in a strong depletion of CoQ_6 content. Moreover, this also promoted accumulation of a novel compound that was identified as 3-hexaprenyl-4-aminophenol (HAB), differing from HHB only by the amine group. HAB was found to originate from para-aminobenzoic acid (pABA), also differing from 4-HB by a single amine group.

How could the involvement of *Yah1/Arh1* in CoQ_6 synthesis have been ignored so long and pABA not been known as a CoQ_6 precursor? First of all, *YAH1* and *ARH1* are essential genes in yeast, which hampered a rapid and systematic survey of their functions. Only the targeted repression of their expression, as done by Pierrel et al. (2010), allowed for study of the resulting phenotype. Thus,

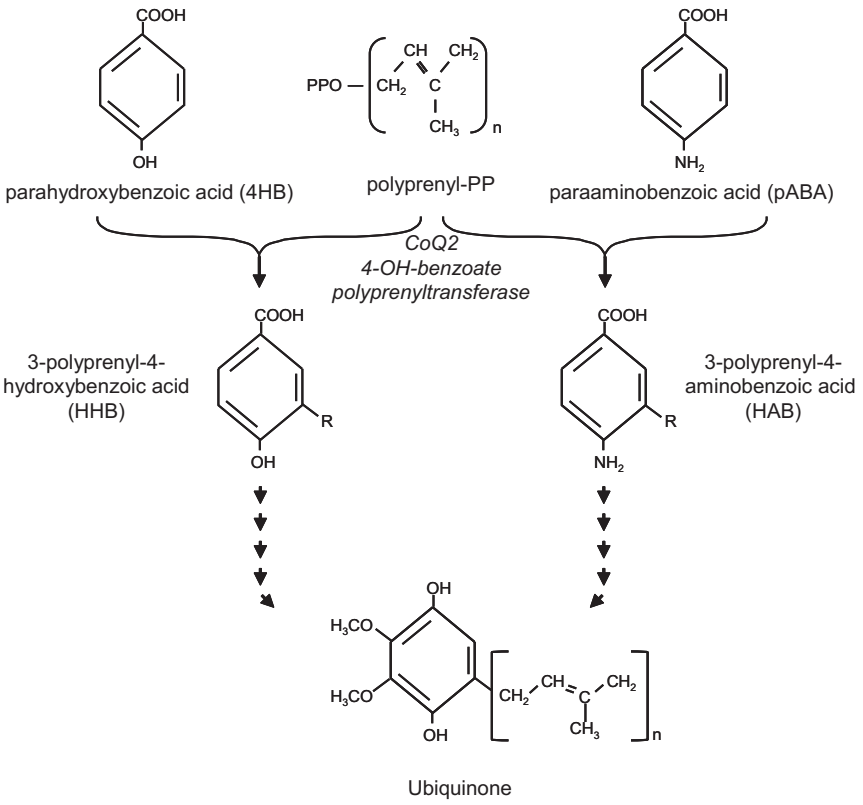

Figure 1. Precursors of Ubiquinone Biosynthesis
Parahydroxybenzoic acid (4-HB) or paraaminobenzoic acid (pABA) is condensed with the prenyl chain. The resulting molecules (HHB or HAB) then undergo hydroxylation, methylation, and decarboxylation to yield ubiquinone.

YAH1/ARH1 had escaped previous rapid and systematic screens for the identification of genes involved in ubiquinone biosynthesis. The answer to the second part of the question is relatively ironic. Glucose synthetic medium contains pABA; therefore, whenever a precursor is unknown but provided unwittingly by the scientist, the scientist will never identify it as a precursor.

This work not only describes original data, but also addresses several new questions. Indeed, Coq6p has been proposed to catalyze the C5 and/or C1 hydroxylation of the quinone ring (Tran and Clarke, 2007). However, the results of Pierrel et al. (2010) suggest that Coq6p only catalyzes the C1 hydroxylation. Therefore, another yet unknown oxygenase catalyzing the C5 hydroxylation remains to be identified. Moreover, as the only constituents of the final CoQ_6 are C, H, and O atoms, an additional step in CoQ_6 synthesis should be the replacement of the amine by a hydroxyl group at C4. The enzyme in charge of this modification must now be identified.

Mammalian homologs of the yeast COQ genes have been identified via sequence homology. All the known yeast genes have human homologs, indicating that the yeast CoQ biosynthesis pathway is conserved in humans. Primary CoQ deficiency in humans is a rare, clinically heterogeneous disorder of the respiratory chain. This form of mitochondrial dysfunction seems to respond well to oral CoQ administration (Quinzii et al., 2007; Rötig et al., 2007). The systematic study of CoQ synthesis genes in patients has led to the identification of several mutations responsible for this class of diseases (Duncan et al., 2009; Lagier-Tourenne et al., 2008; Lopez-Martin et al., 2007; Mollet et al., 2007, 2008). Nevertheless, further genes involved in CoQ synthesis may remain to be identified in human pathology, since the sequencing of all known genes still did not lead to any mutation discovery for some patients. The data presented by Pierrel et al. (2010) clearly demonstrates that new enzymes and therefore new genes involved in ubiquinone biosynthesis continue to be identified in yeast. Their human counterparts will obviously represent additional candidate genes for patients with ubiquinone deficiency.

The yeast Yah1/Arh1 proteins are highly homologous to human ferredoxin/ferredoxin reductase and adrenodoxin/adrenodoxin reductase (Adx/AdxR). Whether the Adx/AdxR system is also involved in ubiquinone biosynthesis in humans remains to be investigated, as well as if the human pABA is a precursor of ubiquinone. If this is the case, new knowledge budding off from basic research conducted in yeast will once again result in the improvement of diagnoses for human genetic disorders.

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