be explained by differing sensitivities of nicotine and cotinine clearances to changes in hepatic blood flow. As a drug with a high extraction ratio, the clearance of nicotine is influenced by changes in hepatic blood flow, whereas clearance of cotinine with low extraction ratio is more dependent on changes in intrinsic clearance, i.e., amount and activity of metabolic enzymes. Studies in newborn animals, mainly sheep, have shown that hepatic blood flow is low immediately after delivery because of the loss of the umbilical venous blood supply and the patency of ductus venosus. Hepatic blood flow rises to adult levels within the first week, due to increased blood flow in the portal vein and gradual closure of ductus venosus, which is complete by the eighteenth day in human neonates. This would mean that nicotine clearance should rise and the nicotine half-life shorten within the first couple of weeks as hepatic blood flow increases. Another explanation could be that nicotine and cotinine are metabolized mainly by enzymes other than CYP2A6 in neonates. However, neonates have only slightly lower amounts of CYP2A6, CYP2D6, and CYP2E1 protein in liver microsomes, whereas the CYP2B6 amount is clearly diminished in neonates compared to adults and older children [5].

References:

1. Hukkanen J. et al. Effect of grapefruit juice on cytochrome P_{450} 2A6 and nicotine renal clearance. *Clin Pharmacol Ther.* 2006; 80(5):522–530.
2. Benowitz N.L. et al. Mentholated cigarette smoking inhibits nicotine metabolism. *J Pharmacol Exp Ther.* 2004; 310:1208–1215.
3. Benowitz N. et al. Genetic Influences in the Variation in Renal Clearance of Nicotine and Cotinine. *Clin Pharmacol Ther.* 2008b;84(2):243–247.
4. Florescu A, Ferrence R, Einarson TR, Selby P, Kramer M, Woodruff S, Grossman L, Rankin A, Jacqz-Aigrain E, Koren G. Reference values for hair cotinine as a biomarker of active and passive smoking in women of reproductive age, pregnant women, children, and neonates: systematic review and meta-analysis. *Ther Drug Monit.* 2007;29(4):437–446.
5. Benowitz N, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal Serum Cotinine Levels to Distinguish Cigarette Smokers and Non-Smokers within Different Racial/Ethnic Groups in the United States Between 1999–2004. *Am J Epidemiol.* 2008a (in press).

BIOCHEMICAL SYNTHESIS OF COENZYME Q IN PLANTS

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Introduction. Coenzyme Q (CoQ), also known as ubiquinone, is an essential electron transporter in the oxidative respiratory chain that generates adenosine triphosphate (ATP). CoQ is synthesized by nearly all eukaryotes and some proteobacteria. Structurally, CoQ is composed of a benzoquinone head group attached to a polyisoprenoid tail whose number of isoprene units varies among species: 10 (CoQ10) in humans and some crops (such as tomato and soybean), CoQ9 in *Arabidopsis* thaliana and rice, CoQ8 in *Escherichia* coli, and CoQ6 in yeast (*Saccharomyces cerevisiae*). The quinone head group of CoQ can exist in three oxidation states: the fully oxidized form

(CoQ, ubiquinone), the semi-oxidized form with one electron (CoQH·, ubisemiquinone), and the fully reduced form (CoQH2, ubiquinol).

Materials and methods. A literature review of scientific articles on ubiquinone biosynthesis in plant organisms was carried out.

Results and discussion. The CoQ biosynthetic pathway can be divided into three parts: formation of the aromatic ring precursor, biosynthesis of the polyisoprenoid tail, and modifications of the aromatic ring. Although the eukaryotic CoQ biosynthetic pathway has not been fully defined to date, some components have been found to be conserved across fungi, metazoans, and plants [1]. Most plants are photo-autotrophic; although photophosphorylation in the chloroplast is the major source of ATP supply, the mitochondrial oxidative respiratory chain is indispensable for plant survival. In recent years, plants have been reported to have special routes for generating the head group and a unique enzyme in the terminal stage. Here, we outline the CoQ biosynthetic pathway in plants and summarize progress in plant CoQ enhancement.

In plants, the isoprene subunits for the CoQ side chain are generated through the mevalonate (MVA) pathway, which also produces precursors for sesquiterpene, triterpene, sterol, and brassinosteroid biosynthesis [2, 3]. The mechanism underlying the import of isoprene units into the mitochondria remains uncharacterized. The aromatic head is decorated into a fully substituted benzoquinone ring in mitochondria by one prenylation, one decarboxylation, three hydroxylations, and three methylations. First, the isoprene tail is attached to 4-HB, and then the ring is hydroxylated at C5, followed by O-methylation. After sequential decarboxylation and hydroxylation at C1, the ring is further modified via C2 methylation, C6 hydroxylation, and O methylation. The order of these reactions in eukaryotes is still debatable. Among the enzymes characterized, four (Coq2, Coq3, Coq5, and Coq6) are conserved across plants, fungi, and mammals. The recently identified CoqF is a unique flavin-dependent monooxygenase prevalent in plants and green algae but distinct from its counterpart in fungi and *Metazoa*. Besides these enzymes, a number of proteins without a clear catalytic role are also involved in CoQ biosynthesis.

Plants have evolved the unique ability to synthesize 4-HB from phenylalanine via two parallel routes. The phenylpropanoid pathway also serves as a starting point for the production of a variety of metabolites such as lignin, flavonoids, coumarins, and lignans. A recent analysis of the evolutionary history of key enzymes in the phenylpropanoid pathway showed that the enzymes involved in making p-coumaroyl-CoA from phenylalanine (PAL, C4H, and 4CL), are generally present across *Embryophyta* [4]. Homologs of the genes encoding PAL and 4CL can even be found in streptophyte algae, the algal sisters of land plants. The main route that opens up after the synthesis of p-coumaroyl-CoA is β-oxidative metabolism in the peroxisomes. In *Arabidopsis*, two peroxisomal 4CLs (AT4G19010 and 4CL8) have been identified to participate in this pathway. In the acyl-activating enzyme superfamily, AT4G19010 and 4CL8 belong to clade V, which also contains several members that exhibit high activities toward fatty acids. A phylogenetic analysis showed that the clade V members of *Arabidopsis* fell into a clade that included sequences from major lineages of land plants. It would be interesting to see whether peroxisomal 4CLs are widely distributed in plants. The second route is the conversion of p-coumaric acid into kaempferol. Among flavonoids,

kaempferol is a flavonol that is widely present in land plant species ranging from bryophytes and ferns to seed plants, often in the form of glycosides. Notably, mammalian cells also have the ability to use exogenous kaempferol as a precursor for CoQ biosynthesis. The mechanism of release of a CoQ ring precursor from kaempferol is likely to be conserved between plants and mammals [5].

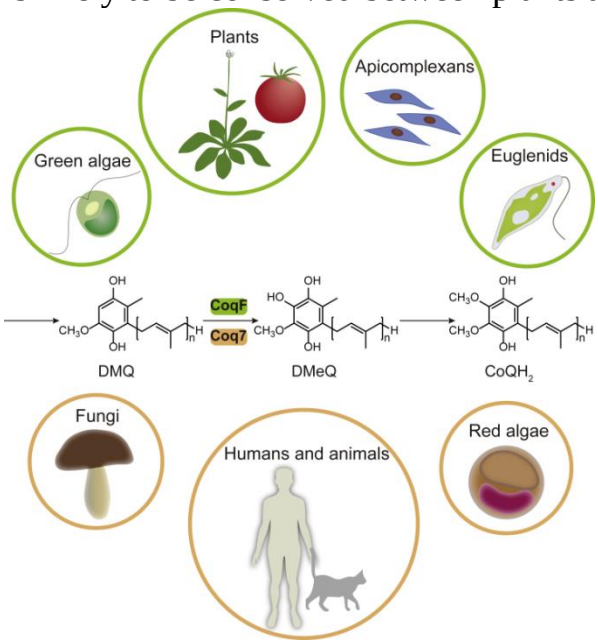

Fig. 1. The diversity of CoQ biosynthesis in eukaryotes: Two different enzymes catalyze the penultimate step.

Unlike animals and fungi, in which the C6 hydroxylation is catalyzed by Coq7, plants use CoqF (Fig. 1). Coq7, a di-iron monooxygenase, occurs in major lineages of eukaryotes, including *Metazoa* (animals), fungi, red algae, etc. The recently discovered flavin-dependent monooxygenase CoqF catalyzes this reaction in land plants, green algae, apicomplexans, euglenids, and some other.

Recent investigations in plants have identified several unique enzymes in the plant CoQ biosynthetic pathway. It will be of great interest to search for the enzymes and cofactors that act in the steps that have not been identified in plants, and this should help us to understand the evolution of oxidative respiration from bacteria to eukaryotes.

References:

1. Toda T. et al. Functional conservation of coenzyme Q biosynthetic genes among yeasts, plants, and humans. *PLoS One.* 2014;9:e99038.
2. Zhou F., Pichersky E. More is better: the diversity of terpene metabolism in plants. *Curr. Opin. Plant Biol.* 2020;55:1–10.
3. Pu X. et al. An update on the function and regulation of methylerythritol phosphate and mevalonate pathways and their evolutionary dynamics. *J. Integr. Plant Biol.* 2021;63:1211–1226.
4. de Vries S. et al.The evolution of the phenylpropanoid pathway entailed pronounced radiations and divergences of enzyme families. *Plant J.* 2021;107:975–1002.
5. Fernandez-Del-Rio L. et al. Metabolism of the flavonol kaempferol in kidney cells liberates the B-ring to enter coenzyme Q biosynthesis. *Molecules*. 2020;25:2955.