

Heme and Chlorophyll Biosynthesis

How do cells synthesize heme or chlorophyll?

In the first step of heme synthesis, glycine and succinyl-CoA condense to form δ -aminolevulinate (ALA) (Figure 14.33). This reaction is catalyzed by ALA synthase (ALAS), a pyridoxal phosphate–requiring mitochondrial enzyme. Mammals have two nuclear ALAS genes: *ALAS1*, which is expressed in all nucleated cells, and *ALAS2*, which is expressed only in reticulocytes. *ALAS1* activity is regulated by free heme molecules and hematin (an oxidized derivative of heme), which prevent the transcription of the *ALAS1* gene and the translation of *ALAS1* mRNA. Heme also prevents the transport of ALAS into mitochondria.

In the next step of porphyrin synthesis, two molecules of ALA condense to form porphobilinogen. Porphobilinogen synthase, which catalyzes this reaction, is a zinc-containing enzyme that is extremely sensitive to heavy-metal poisoning. Uroporphyrinogen I synthase catalyzes the symmetric condensation of four porphobilinogen molecules. An additional protein is also required in this reaction. Uroporphyrinogen III cosynthase alters the specificity of uroporphyrinogen synthase so that the asymmetrical molecule uroporphyrinogen III is produced. When four CO_2 molecules are removed, catalyzed by uroporphyrinogen decarboxylase, coproporphyrinogen is synthesized. This reaction is followed by the removal of two additional CO_2

molecules, thus forming protoporphyrinogen IX. Oxidation of the porphyrin ring's methylene groups forms protoporphyrin IX, the direct precursor of heme. The final step in the synthesis of heme (also called *protoheme IX*) is the insertion of Fe^{2+} , a reaction that occurs spontaneously but is accelerated by ferrochelatase.

The *porphyrias*, a group of rare inherited metabolic disorders, are characterized by toxic accumulations of porphyrins and various precursor molecules. Each type of porphyria is caused by the deficient activity of a specific enzyme (with the exception of ALAS) in the heme biosynthetic pathway. The major symptoms of the porphyrias may be neurological (e.g., pain, agitation, hallucinations, and/or convulsions) and gastrointestinal (e.g., abdominal pain or vomiting). Photosensitivity, caused by high blood levels of heme precursors, may cause skin blisters. The absorption of wavelengths of UV and visible light by heme precursors generates cytotoxic ROS.

Protoporphyrin IX is also a precursor of the chlorophylls (Figure 14.33). After magnesium (Mg^{2+}) has been incorporated, the enzyme Mg-protoporphyrin methylesterase catalyzes the addition of a methyl group to form Mg-protoporphyrin IX monomethylester. This molecule is then converted to chlorophyll in several light-induced reactions.

SUMMARY: The complex molecule heme is derived from glycine and succinyl-CoA. In plants and some bacteria the synthesis of ALA, the precursor of both heme and chlorophyll, is instead derived from glutamate.



Biochemistry IN PERSPECTIVE cont.

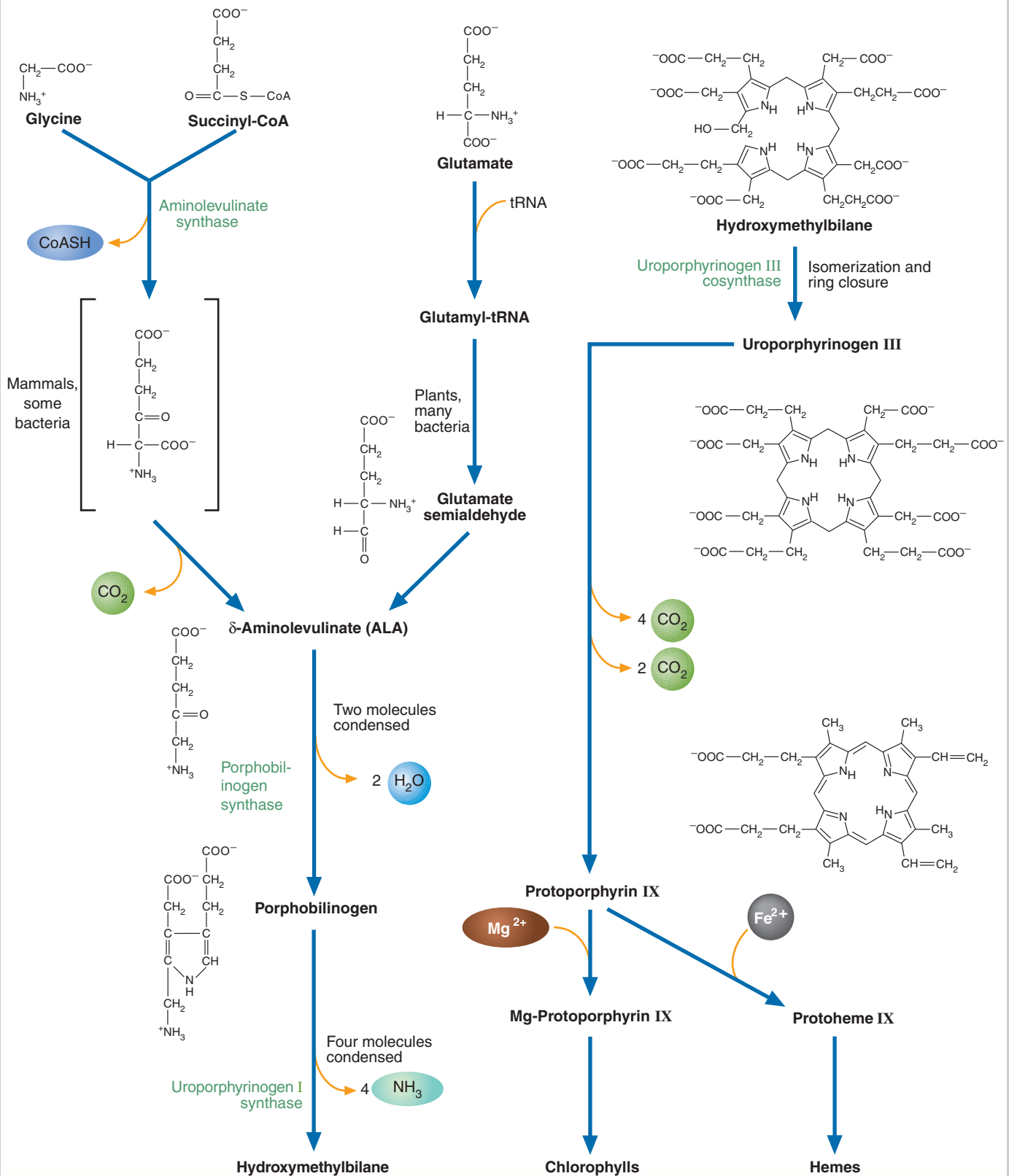


FIGURE 14D

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In animals, the first reaction and the last three reactions occur within mitochondria, whereas the remaining four reactions occur in cytoplasm. In plants, the entire chlorophyll biosynthetic pathway occurs within chloroplasts. In plants and some bacterial species, ALA is synthesized from glutamate in a process involving glutamyl tRNA. Refer to Chapter 17 for a discussion of tRNA (transfer RNA).